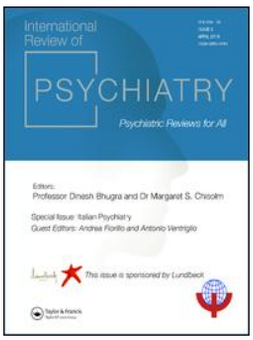

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REVIEW ARTICLE

Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress

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ABSTRACT

Cancer is highly prevalent and one of the leading causes of global morbidity and mortality. Psychological and existential suffering is common in cancer patients, associated with poor psychiatric and medical outcomes. Promising early-phase clinical research (1960s to early 1970s) suggested a therapeutic signal for serotoninergic psychedelics (e.g. psilocybin, LSD) in treating cancer-related psychiatric distress. After several decades of quiescence, research on psychedelic-assisted therapy to treat psychiatric disorders in cancer patients has resumed within the last 2 decades in the US and Europe. This review article is based on a systematic search of clinical trials from 1960–2018 researching the therapeutic use of psychedelic treatment in patients with serious or terminal illnesses and related psychiatric illness. The search found 10 eligible clinical trials, with a total of 445 participants, with the vast majority of the patients having advanced or terminal cancer diagnoses. Six open label trials, published between 1964 and 1980 ($n = 341$), suggested that psychedelic therapy (mostly with LSD) may improve cancer-related depression, anxiety, and fear of death. Four RCTs trials were published between 2011 and 2016 ($n = 104$), mostly with psilocybin treatment ($n = 92$), and demonstrated that psychedelic-assisted treatment can produce rapid, robust, and sustained improvements in cancer-related psychological and existential distress.

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Hallucinogen; cancer; anxiety; depression; psilocybin; LSD; psychedelic

Introduction

This article will systematically review the literature on the clinical use of the classic or serotoninergic psychedelics (e.g. psychoactive drugs such as psilocybin or LSD that exert their psychedelic or consciousness-altering effects primarily through activation of serotonin 2A [5HT2A] receptors) to treat cancer-related psychiatric distress. Although the classic hallucinogens have been used by humans for thousands of years, known to science for more than a century, and subjected to extensive basic science research for decades, systematic study of their clinical application in humans is still in its incipiency. Promising early-phase clinical research conducted from the 1960s through the mid-1970s was halted before any definitive conclusions could be reached concerning the efficaciousness of psychedelic therapy for any psychiatric disorder. However, clinical research conducted in that era strongly suggested therapeutic signals of psychedelic treatment (in conjunction with psychotherapy), with the data strongest for the treatment of alcoholism, followed by cancer-related psychological and existential distress (Bogenschutz & Ross, 2018).

In the past decade, clinical trials have resumed investigating the effects of classic hallucinogens in the treatment of various psychiatric illnesses (i.e. cancer-related psychiatric disorders, treatment-resistant depression, OCD) and addictive disorders (i.e. alcohol, nicotine, cocaine). The studies that have been completed to date are small open label or randomized controlled trials (RCTs), and, although the results have been very promising, they are not sufficient to definitively establish treatment efficacy. The most studied indication and the one with the most robust data from phase II randomized controlled trials (RCTs) is the use of classic hallucinogens (psilocybin and LSD) to treat cancer-related psychiatric disorders.

This review will focus on the prevalence and adverse psychological, existential, and medical impact of a cancer diagnosis, the history and resumption of clinical trials using serotoninergic hallucinogens to treat cancer-related psychiatric distress, and will end by looking into the future of clinical research in this

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area and making predictions about the clinical availability and utility of the classic psychedelics to treat emotional and existential distress in this vulnerable patient cohort.

Search methodology

This review article is similar to a recently published systematic review of the use of the serotoninergic psychedelics to treat depression and anxiety in patients with a life-threatening illness (Reiche et al., 2018). This review uses a similar methodology as the Reiche et al. review, but extends the search period until 1 February 2018, and focuses on the use of classical hallucinogens to treat patients with cancer diagnoses, since the vast majority of the historical and recent clinical trials have included patients with cancer-related psychiatric distress. Reiche et al. (2018) was a systematic literature review that searched articles from 1 January 1960 to 31 January 2017 on several electronic databases (PubMed, Cochrane, Embase, Google Scholar), and adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). The search (see Reiche et al. (2018) for more in-depth details of the search methodology) was restricted to peer-reviewed clinical trial publications where participants with advanced or terminal illnesses were treated with a classical psychedelic (i.e. LSD, psilocybin, DPT).

Our search identified 10 clinical trials ($n = 445$): six open-label trials ($n = 341$) published between 1964 and 1980, and four randomized controlled trials (RCTs) ($n = 104$) published between 2011 and 2016. All but two (Gasser et al., 2014; Kast & Collins, 1964) of the clinical trials were conducted exclusively in patients with cancer-related psychiatric distress. Across the 11 trials, six explored the therapeutic use of LSD ($n = 323$) (Gasser et al., 2014; Grof, Goodman, Richards, & Kurland, 1973; Kast, 1966; 1967; Kast & Collins, 1964; Pahnke, Kurland, Goodman, & Richards, 1969), three investigated treatment with psilocybin ($n = 92$) (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), and one examined the use of dipropyltryptamine (DPT) ($n = 30$) (Richards, 1980).

Prevalence and impact of psychiatric disorders (depression, anxiety, adjustment disorder) in cancer

Cancer is one of the leading causes of global morbidity and mortality, with ~14 million new cancer diagnoses per annum worldwide; it is the second leading cause of death globally (accounting for almost one out of six deaths), responsible for close to 9 million deaths per year (Ferlay et al., 2013). In the US, ~15.5 million Americans have a current or prior diagnosis of the illness (American Cancer Society, 2018), and ~40% of the population will be diagnosed with cancer at some point in their lives (Ries et al., 2007). In 2018, ~1.7 million new cancer cases are expected to be diagnosed, and ~610,000 individuals are expected to die of cancer in the US (American Cancer Society, 2018).

The most common psychiatric disorders in patients with cancer are depressive and anxiety spectrum disorders, as well as adjustment disorders, with rates of any psychiatric disorder in cancer patients as high as 30–40% (Mitchell et al., 2011; Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Clinically significant psychiatric distress in cancer patients is associated with a variety of poor outcomes, including: lower quality-of-life, decreased social function, increased disability, medication non-adherence, increased emergency room visits and hospital stays, hastened desire for death, increased rates of suicide, adverse medical outcomes, and decreased survival rates from the cancer (Brown, Levy, Rosberger, & Edgar, 2003; Bultz & Holland, 2006; Katon, 2003; Kissane, 2000; Partridge, Wang, Winer, & Avorn, 2003). Completed suicide is the worst mental health outcome in patients with cancer diagnoses, and a diagnosis of cancer increases the risk of suicide, by double in some estimates (Allebeck & Bolund, 1991; Levi, Bulliard, & la Vecchia, 1991; Storm, Christensen, & Jensen, 1992; Yousaf, Christensen, Engholm, & Storm, 2005)

Although pharmacologic and psychosocial treatments are commonly used to treat depressive and anxiety spectrum disorders in cancer patients, their effectiveness is limited and mixed (Grassi, Caruso, Hammelef, Nanni, & Riba, 2014; NCCN, 2014). Significant side-effects adversely affect treatment compliance, the onset of clinical improvement with anti-depressants is delayed, and relapse rates are high (Freedman, 2010; Li, Frye, & Shelton, 2012). Moreover, several meta analyses of placebo controlled trials of anti-depressants (ADs) to treat cancer-related depression have failed to demonstrate a clear effect of AD treatment over placebo (Iovieno, Tedeschini, Ameral, Rigatelli, & Papakostas, 2011; Laoutidis & Mathiak, 2013; Ostuzzi, Matcham, Dauchy, & Barbui, 2015). In one of the meta-analyses of ADs to treat major depressive disorder (MDD) in patients with co-occurring medical disorders (including cancer) ADs were more efficacious than placebo in some medical conditions (e.g. post-stroke, HIV/AIDS), but no more

effective than the ~40% placebo response rate in the cancer cohort (Iovieno et al., 2011).

Impact of spiritual/existential distress in cancer patients, and existentially-based psychosocial treatment interventions

Dame Cicely Saunders (the founder of the modern hospice movement in England) and Victor Frankl, MD (a holocaust survivor and American psychiatrist) were mental health pioneers who emphasized the importance of existential and spiritual domains, both as symptoms of mental distress and as treatment targets, in individuals with terminal cancer diagnoses (Frankl, 1984; Saunders, 1988). Existential distress has been described variably by psycho-oncologists as mental distress experienced by those facing death associated with demoralization, hopelessness, powerlessness, absence of purpose or meaning, loss of dignity, a sense of futility, and isolation (Kissane, 2000; Murata, 2003).

When patients with advanced or terminal cancer experience clinical symptoms of existential distress, it is associated with a variety of adverse outcomes, including: increased anxiety and depressive symptoms, increased desire for hastened death, increased suicidal ideation and behaviours, increased pain perception, increased healthcare visits, and decreased quality-of-life (Lemay & Wilson, 2008; Puchalski, 2012). A growing body of data has linked improved existential/spiritual well-being in cancer patients with improved quality-of-life in the face of death, decreased depression, decreased hopelessness, decreased desire for hastened death, and increased gratitude (Breitbart et al., 2000, 2010; McClain, Rosenfeld, & Breitbart, 2003; Nelson, Rosenfeld, Breitbart, & Galietta, 2002; Taylor, 2003). Several empirically supported, manualized, existentially-oriented psychosocial interventions have been developed to address the existential and spiritual distress of cancer patients (Lemay & Wilson, 2008). However, there are currently no medications or evidence-based combined pharmacologic-psychosocial interventions to treat this type of distress and poorly addressed clinical need in cancer patients (Bogenschutz & Ross, 2018).

History of psychedelic therapy in death and dying, and the treatment of cancer-related psychological and existential distress

Mid 1950s to early 1960s

Valentina Wasson and Aldous Huxley were the first westerners to suggest therapeutic effects of serotoninergic hallucinogens to alleviate emotional suffering associated with the dying process (Grof & Halifax, 1977). Valentina Wasson, a mycologist and pediatrician, was responsible (in collaboration with her husband Gordon Wasson), for introducing psilocybin into western culture and medicine. The first known westerners to participate in an indigenous psilocybin ritual in Mexico with the Mazatec curandera Maria Sabina, the Wassons wrote about their experience in *Life Magazine* in the late 1950s (Wasson, 1957). Valentina Wasson made the prediction that psilocybin would ultimately be used within medicine to treat a variety of illnesses, including psychological and existential distress associated with terminal illnesses. The writer Aldous Huxley also believed in the power of psychedelics and altered states of consciousness to aid the dying. Huxley used a hypnosis technique on his first wife, Maria, as she lay on her death bed in 1955, in an attempt to help occasion a 'good' death, and then, in 1963, while dying of cancer himself, Huxley's 2nd wife Laura administered 100 mcg of LSD to Huxley a few hours before his death, with the intention to ease the process of dying (Grof & Halifax, 1977).

1960s to early 1970s

The first scientific study and publication of classic hallucinogens as medication treatments to help the dying in an academic medical setting occurred in the 1960s with Eric Kast MD, a psychiatrist and internist at the University of Chicago's School of Medicine. Kast specialized in pain medicine in the terminally ill, and worked predominantly with cancer patients. After hearing about LSD's discovery in Switzerland in the mid-1940s, he became interested in researching LSD as a novel analgesic agent in terminally ill cancer patients with severe pain syndromes. In his first published paper in 1964, Kast conducted a comparative efficacy trial of LSD (100 mcg orally) compared to two oral opioids (Dilaudid 2 mg or Demerol 100 mg) in a sample of 50 severely medically ill patients, mostly with terminal cancer, but also those with other medical illnesses (i.e. infectious illnesses, severe burns) (Kast & Collins, 1964). The trial demonstrated that the LSD group had statistically significant reductions in pain compared to the two opioid groups, lasting from 3 h post-dosing to up at 19 h post-dose administration. He theorized that LSD's analgesic effects related to its ability to alter pain attention and perception (Kast, 1967). He also noted that the patients in the LSD group appeared to display a decreased fear of death. Kast extended his research by administering

oral LSD 100 mcg to 208 patients ($n = 80$ in Kast (1966); $n = 128$ in Kast (1967)) with terminal cancer and pain syndromes in an open-label design and, in addition to studying the anti-pain effects of LSD, he also examined psychological, existential, and behavioural outcomes such as affective changes (i.e. depression, anxiety), attitudes towards death and dying, and sleep (Kast, 1966; 1967). It is important to note that Dr Kast initially viewed LSD treatment in his patients essentially as a type of chemo-therapeutic or pharmacologic-only intervention and did not significantly account for or introduce the now well-known components of set, setting, dose titration, and psychotherapeutic preparation and integration in relation to the dosing sessions (Grof & Halifax, 1977). In Kast's later studies, more attention was paid to rapport building, psychological preparation, setting, and attitudes towards disease and death—a harbinger of the later model developed by Stanislav Grof at Spring Grove that paid careful attention to set, setting, preparation, and integration. In these later open-label studies with LSD, Kast confirmed his earlier findings and reported on: diminished pain perception acutely and lasting up to 2 weeks post-dosing, decreased depressed mood, improved morale and outlook on life, decreased fear of cancer diagnoses and death, improved sleep, reports of mystical-type experiences ('oceanic feelings'), and enhanced philosophical and spiritual states (Kast, 1966; 1967).

The other significant historical research exploring serotoninergic psychedelics to treat psychological and spiritual distress associated with advanced or terminal cancer occurred from the mid-1960s to the mid-1970s at the Spring Grove State Hospital in Maryland. Beginning in 1963, a multi-disciplinary group of psychiatrists, psychologists, social workers, nurses, and art therapists began researching LSD-assisted psychotherapy to treat patients with alcoholism. In 1965, when one of the nurses on the research team became ill with advanced breast cancer, one of the team members suggested that a course of psychedelic therapy might diminish the anxiety associated with her cancer. After the nurse underwent LSD-assisted treatment and reported relief, the researchers at Spring Grove decided to shift the research focus towards LSD-assisted psychotherapy to help patients with terminal cancer-related psychological and existential distress (Grof & Halifax, 1977). The treatment model used was significantly different from the chemo-therapeutic model developed by Dr. Kast in his initial study (Kast & Collins, 1964) of LSD as an analgesic. It was derived from Dr Grof's extensive LSD research in Prague, administering moderate-to-high doses of LSD to normal volunteers and paying careful attention to set, setting, as well as session preparatory psychotherapy and post-session integrative psychotherapy. The treatment paradigm was based on elements drawn from the indigenous use of psychedelics by various cultures, psychoanalytic theory, and transpersonal psychology (Davis, 2003). A total of 83 patients participated in the open-label trials, of which 53 received high-dose oral LSD (200–500 mcg orally) (Grof et al., 1973; Pahnke et al., 1969) and 30 were administered intramuscular dipropyltryptamine (DPT) (75–128 mg) (Richards, 1980). Longitudinal analyses performed on 31 participants in one of the LSD trials found statistically significant pre–post improvements in the following domains: anxiety, depression, fear of death, and isolation; in addition, a global index of improvement demonstrated that 71% of participants were assessed as either dramatically improved or moderately improved (Grof et al., 1973). Furthermore, two of the trials (Pahnke et al., 1969; Richards, Rhead, DiLeo, Yensen, & Kurland, 1977) demonstrated a positive correlation between the occurrence of the 'mystical experience' and clinical improvements.

In response to the enormous cultural upheaval of the 1960s in the US and the harms associated with widespread and reckless use of psychedelics in the population, all clinical research utilizing hallucinogens (including treatment models for psychological and existential distress in terminal cancer) ceased in the early 1970s with the passage of the controlled substance act of 1970, which placed all of the classic psychedelics into Schedule I of the DEA's classification of regulated psychoactive substances. Although clinical research came to an abrupt halt at this point in time, basic neuroscience research continued over the last 40 years, and has contributed considerably to understanding basic mechanistic processes of the classic hallucinogens such as structure–activity relationships and regional brain activation/de-activation patterns (Nichols, 2016).

Resumption of clinical research using psychedelics to treat cancer-related psychiatric illnesses (early 2000s–present)

After a quiescence of about 2 decades, human research with the serotoninergic psychedelics resumed in the early 1990s with Rick Strassman's studies of the physiological and subjective effects of intravenous dimethyltryptamine (DMT) on normal volunteers (Strassman & Qualls, 1994). Since the beginning of the 21st century, there has been a steady and growing

interest in academic research in this area in both the US and Europe. A significant amount of human research has characterized the acute effects of classic psychedelics on brain physiology, regional brain activity, cognition, and affect (Bogenschutz & Ross, 2018). The safety of classic psychedelics (particularly psilocybin) in human research settings (including clinical research) has been well documented when participants are carefully screened (e.g. ruling out underlying psychotic spectrum illness) with careful attention to set, setting, preparation, and integration (Johnson, Richards, & Griffiths, 2008). All of these factors have led to a surging interest in taking another look at the potential therapeutic application of using psychedelics to treat a variety of psychiatric disorders with the most extensive body of data collected thus far on the study of psychedelic-assisted psychotherapy to treat cancer-related psychiatric illnesses.

Phase II trial: LSD-assisted psychotherapy for anxiety and depression associated with life-threatening disease

Clinical research utilizing LSD-assisted psychotherapy to treat psychological distress associated with life-threatening illnesses resumed with a small RCT recently completed in Switzerland. In this randomized, double-blind, active placebo-controlled, cross-over (at 2-months) trial, 12 participants with anxiety and depression in the context of a variety of life-threatening illnesses (including but not limited to cancer diagnoses) were randomized to receive a single dose of the experimental condition (LSD 200 mcg orally) and a single dose of the active control (LSD 20 mcg orally), in conjunction with preparatory and post-dosing integrative psychotherapy. Safety of LSD was reported in this small cohort, with no reported serious adverse events (SAEs). Compared to the active control (prior to the cross-over), the experimental group had significant short-term (2 month follow-up) reductions in anxiety as measured by the State-Trait Anxiety Inventory (STAI) in both the STAI-state ($d = 1.1$; $p = .033$) and STAI-trait ($d = 1.2$; $p = .021$) sub-scales (Gasser et al., 2014). A 12-month follow-up study of participants from the trial documented sustained reductions in anxiety (as measured by the STAI), improvements in quality-of-life, and no reports of any adverse serious medical or psychological outcomes related to LSD administration (Gasser, Kirchner, & Passie, 2015).

Phase II trials: psilocybin-assisted psychotherapy for cancer-related psychiatric disorders

RCTs utilizing psilocybin-assisted psychotherapy to treat psychological (e.g. anxiety, depression) and existential (e.g. death anxiety) distress associated with advanced or terminal cancer have resumed in the US at academic medical centres within the last 2 decades at the University of California Los Angeles (UCLA), Johns Hopkins University (JHU), and New York University (NYU) Langone Medical Center. At all three sites, the treatment methodology was similar to and modelled after the Spring Grove psychedelic psychotherapy technique developed by Grof et al. (1973).

Important similarities among the three RCTs were as follows: (1) double-blind design methodology; (2) randomization among groups; (3) active placebo control; (4) use of validated outcome measures (i.e. HAM-D, HAM-A, Hospital Anxiety and Depression Scale [HADS]); (5) administration of single dose of moderate-to-high-dose psilocybin; (6) cross-over methodology; (7) important psychiatric exclusion criteria relating to major mental illness, in particular psychotic spectrum illnesses (e.g. schizophrenia, bipolar I with psychotic features) or a family history of these disorders; (8) careful preparation of the participants for the experimental sessions by trained psychotherapists (as part of a dyad team of treatment providers) after a thorough life review and review of their cancer diagnosis and its negative psychological and existential impact; (9) dosing sessions conducted in a comfortable living room like setting designed for optimal safety and comfort; (10) instruction set to participants designed to increase the likelihood of inducing mystical states of consciousness (i.e. participants instructed to lie supine on a couch with eyeshades on to reduce external visual distractions, and to focus on their inner experiences while a preselected music programme played throughout the dosing session); and (11) integration of the experience after the dosing sessions as part of post-integrative psychotherapy.

The three studies differed in the following characteristics: (1) dose of psilocybin- UCLA (0.2 mg/kg) vs NYU (0.3 mg/kg) and JHU (0.31 mg/kg); (2) the active control—niacin at UCLA and NYU vs low dose psilocybin at JHU; and (3) inclusion of non-terminally ill cancer patients at NYU and JHU vs only terminally ill cancer patients at UCLA; (4) typology of cancer-related psychiatric distress—mostly anxiety at UCLA and NYU vs a mix of depression and anxiety at JHU.

The first RCT to assess the efficacy of psilocybin-assisted psychotherapy in patients with cancer-related

psychiatric distress occurred at UCLA in a small cross-over (at 2-weeks) trial that recruited 12 participants with advanced-stage cancer and a DSM-IV diagnosis of adjustment disorder with anxiety, generalized anxiety disorder, acute stress disorder or anxiety disorder due to cancer (Grob et al., 2011). The primary outcome measures were the State-Trait Anxiety Inventory (STAI), the Beck Depression Inventory (BDI), and the Profile of Mood States, while mystical/altered states of consciousness were measured by the 5-dimension altered states of consciousness (5D-ASC) profile. The trial demonstrated feasibility of recruitment and safety in that there were no psilocybin-related serious psychiatric or medical adverse events. There were marked subjective differences between the psilocybin and placebo experiences as measured by the 5D-ASC, particularly oceanic boundlessness ($F_{1,11} = 33.12$; $p < .001$) and visionary restructuralization ($F_{1,11} = 18.95$; $p = .001$). The study failed to demonstrate statistically significant between-group differences between the single-dose psilocybin-1st vs single-dose niacin-1st groups (prior to the cross-over at 2-weeks) in terms of reduction of anxiety and depressive measures. There were, though, acute trends for reductions in anxiety and depression in the psilocybin-1st group over the niacin-1st group prior to the crossover. Also, there were significant pre–post differences in anxiety (as measured by the STAI trait anxiety sub-scale that was statistically significant at 1 and 3 months post-treatment) and depression (as measured by the BDI with significance at 6-months post-treatment). However, it is not possible to attribute these longer-term improvements to psilocybin, since the time points were after the cross-over. It is likely that this trial failed to demonstrate between-group differences (prior to the cross-over) between psilocybin and the active control, because the trial was underpowered both in terms of sample size ($n = 12$) and dose (0.2 mg/kg).

The JHU (Griffiths et al., 2016) and NYU Langone (Ross et al., 2016) trials were recently published contemporaneously and accompanied by 11 editorials by international leaders in psychiatry, palliative care, addiction, and drug policy (Nutt, 2016). The JHU trial compared a single high-dose of psilocybin (0.31 mg/kg) vs an active control (single very low-dose of psilocybin [1 or 3 mg/70 kg]) to treat a combination of cancer-related depression and anxiety. The trial employed a cross-over design (at 5-weeks post session-1) with the final outcome assessment at 6 months. Fifty-one participants with life-threatening cancers were treated with the following breakdown of psychiatric disorders: Major depressive disorder (MDD) ($n = 14$; 27%); Adjustment disorder with anxiety ($n = 11$, 22%); Adjustment disorder with anxiety and depression ($n = 11$, 22%); Generalized Anxiety Disorder (GAD) ($n = 5$, 9.8%); MDD and GAD ($n = 4$, 7.8%); GAD and dysthymic disorder ($n = 1$, 1.9%). The primary therapeutic outcome variables measuring cancer-related depression and anxiety were the clinician-rated GRID-HAM-D-17 and HAM-A, respectively. There were no SAEs in this trial attributable to psilocybin. The most scientifically robust findings were demonstrated prior to the cross-over in comparing the High-Dose psilocybin-1st group to Low-Dose psilocybin-1st control group, where high-dose psilocybin produced large and sustained (up to 5-weeks post-single dosing) improvements in depressive and anxiety symptoms associated with cancer (see Figure 1a). These improvements were highly clinically significant. For example, at 5-weeks post-session-1: 92% of participants in the High-Dose-1st group demonstrated a clinically significant anti-depressant response (i.e. $\geq$50% improvement relative to baseline scores) on the GRID-HAM-D-17 compared to a 32% response rate in the Low-Dose-1st group, and similarly 76% of participants in the High-Dose-1st group met criteria for a clinically significant anxiolytic response rate (as measured with the HAM-A) compared to 24% in the Low-Dose-1st group (see Figure 2a). At the final 6-month follow-up assessment, collapsed across the two dose sequence groups, the overall clinical response rate for anxiety and depression was 83% and 78%, respectively, and the overall rate of symptom remission for anxiety and depression was 57% and 65%, respectively. In addition, the study demonstrated that, prior to the cross-over (at 5-weeks post session-1), high dose psilocybin produced improvements in quality-of-life, death acceptance, life meaning, and optimism. These effects were sustained at the final 6-month follow-up assessment. Subjects rated the psilocybin experience as being one of the most significant events of their lives: 67% and 70% rated the experience as the singular or top 5 most personally meaningful or spiritually significant experience of their entire lives, respectively. Compared to the placebo group, psilocybin produced mystical-type experiences consistent with prior trials of psilocybin administration in terminally ill cancer patients (Grob et al., 2011) and normal volunteers (Griffiths, Richards, Johnson, McCann, & Jesse, 2008; Griffiths, Richards, McCann, & Jesse, 2006; Griffiths et al., 2011). Moreover, the psilocybin induced mystical experience was found to both correlate with and to

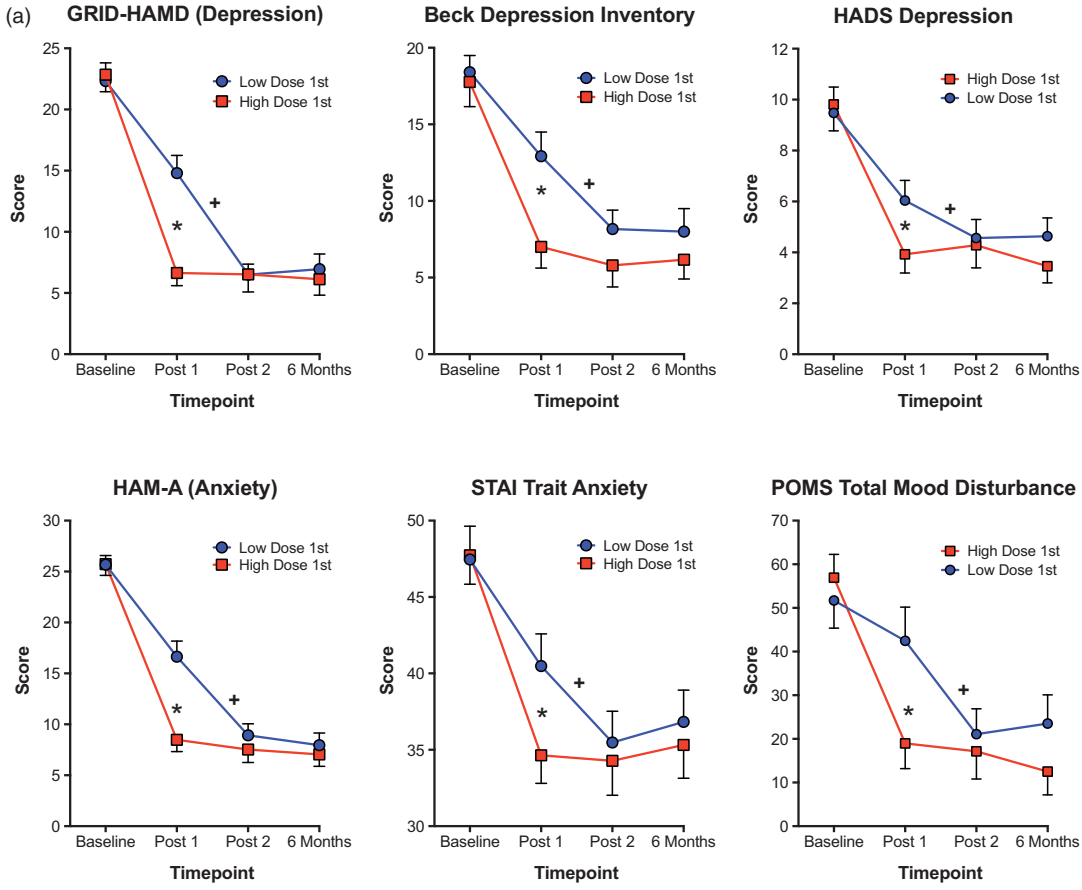

Figure 1. (a) Effects of psilocybin on cancer-related anxiety and depression. Effects of psilocybin on selected outcome measures that were assessed at baseline, post-session 1 (5 weeks after session 1), post-session 2 (5 weeks after session 2), and 6-month follow-up. Data points show means; brackets 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 the 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). The star symbol indicates a significant difference between the two groups at the post-session 1 time-point ($p < .05$, planned comparison). The 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 ($p < .05$, planned comparison). Figure 1a was originally published under a CC-BY 3.0 Creative Commons License (http://www.creativecommons.org/licenses/by/3.0/) in Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P. & Klinedinst, M.A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *J Psychopharmacol*, 30(12), 1181-1197. Available at: http://journals.sagepub.com/doi/10.1177/0269881116675513 (b) Primary outcome variables: cancer-related anxiety and depression (post-crossover). Means (±SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first $n = 14$, niacin first $n = 15$), 1-day pre dose-1 (psilocybin first $n = 14$, niacin first $n = 15$), 1 day post-dose 1 (psilocybin first $n = 14$, niacin first $n = 15$), 6 weeks post-dose 1 (psilocybin first $n = 14$, niacin first $n = 14$), 7 weeks post-dose 1 (1 day pre-dose 2) (psilocybin first $n = 12$, niacin first $n = 14$), 1 day post-dose 2, 6 weeks post-dose 2 (psilocybin first $n = 12$, niacin first $n = 11$), 26 weeks post-dose 2 (psilocybin first $n = 11$, niacin first $n = 12$). Asterisks indicate the significance level of between-group *t*-tests. Closed points represent significant within-group differences relative to scores at baseline. Figure 1b was originally published under a CC-BY 3.0 Creative Commons License (http://www.creativecommons.org/licenses/by/3.0/) in Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzi, Kl, Babb, J., Su, Z., Corby, P. & Schmidt, B.L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*, 30(12), 1165-1180. Available at: http://journals.sagepub.com/doi/pdf/10.1177/0269881116675512

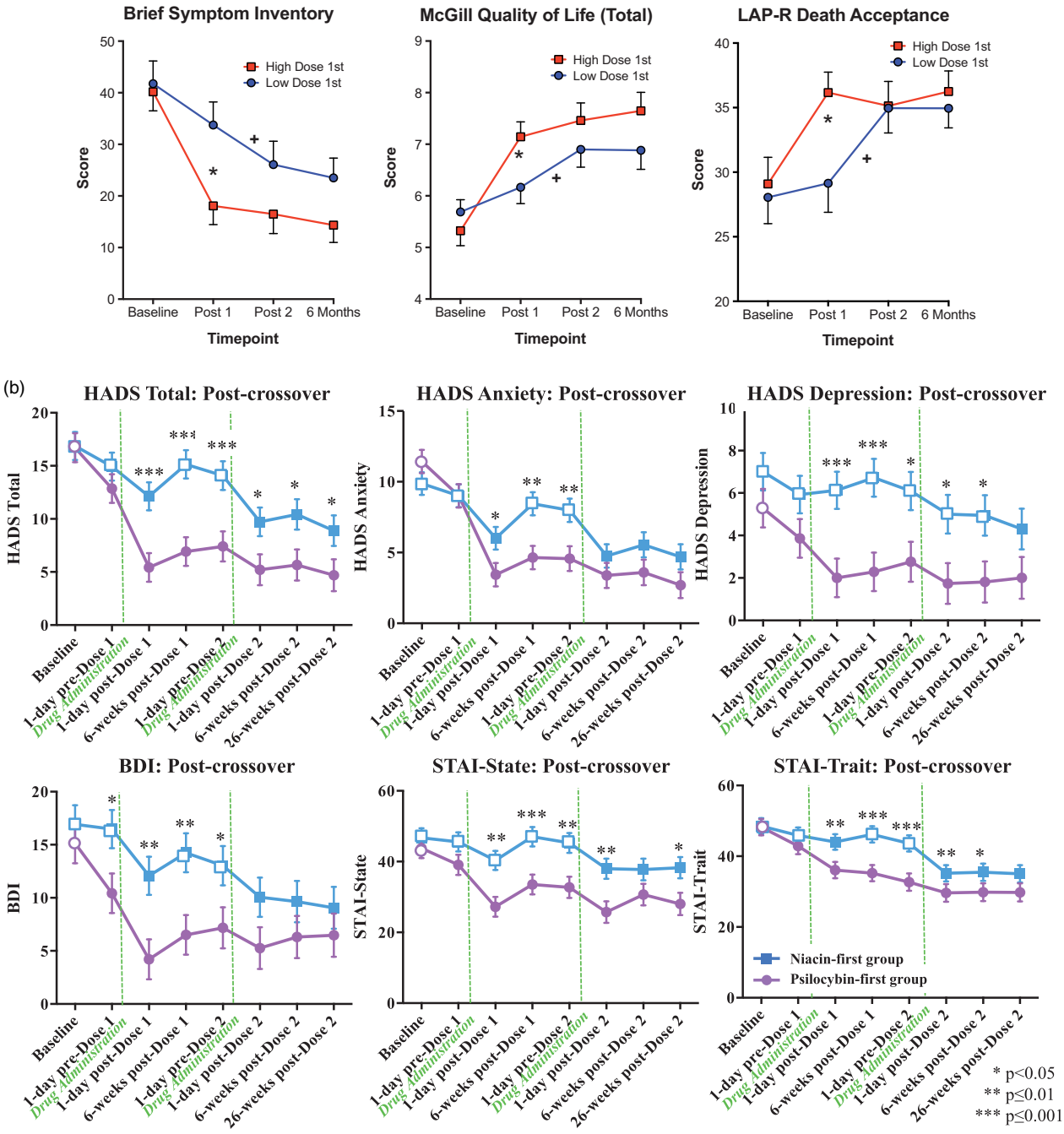

Figure 1. Continued.

partially mediate the anxiolytic and anti-depressant effects of psilocybin.

The NYU Langone trial compared a single dose of psilocybin (0.3 mg/kg) vs single dose niacin (250 mg), administered in conjunction with psychotherapy. The trial employed a cross-over design (at 7-weeks post dose-1) with the final outcome assessment at 6.5 months post dose-2 (i.e. after the cross-over). It recruited 29 individuals with life-threatening cancers with the following breakdown of psychiatric disorders: Adjustment disorder with anxiety ($n = 18$, 62%); Adjustment disorder with anxiety and depression ($n = 8$, 28%); Generalized Anxiety Disorder ($n = 3$, 10%). The main therapeutic outcome variables measuring cancer-related anxiety and depression were the following self-rated measures: STAI, HADS, BDI. Similar to the Grob et al. (2011) and Griffiths et al. (2016) trials, there were no SAEs, either psychiatric or medical, that were attributable to psilocybin, further demonstrating the safety of administering psilocybin to a cohort of patients with advanced cancer diagnoses. The most scientifically rigorous findings were

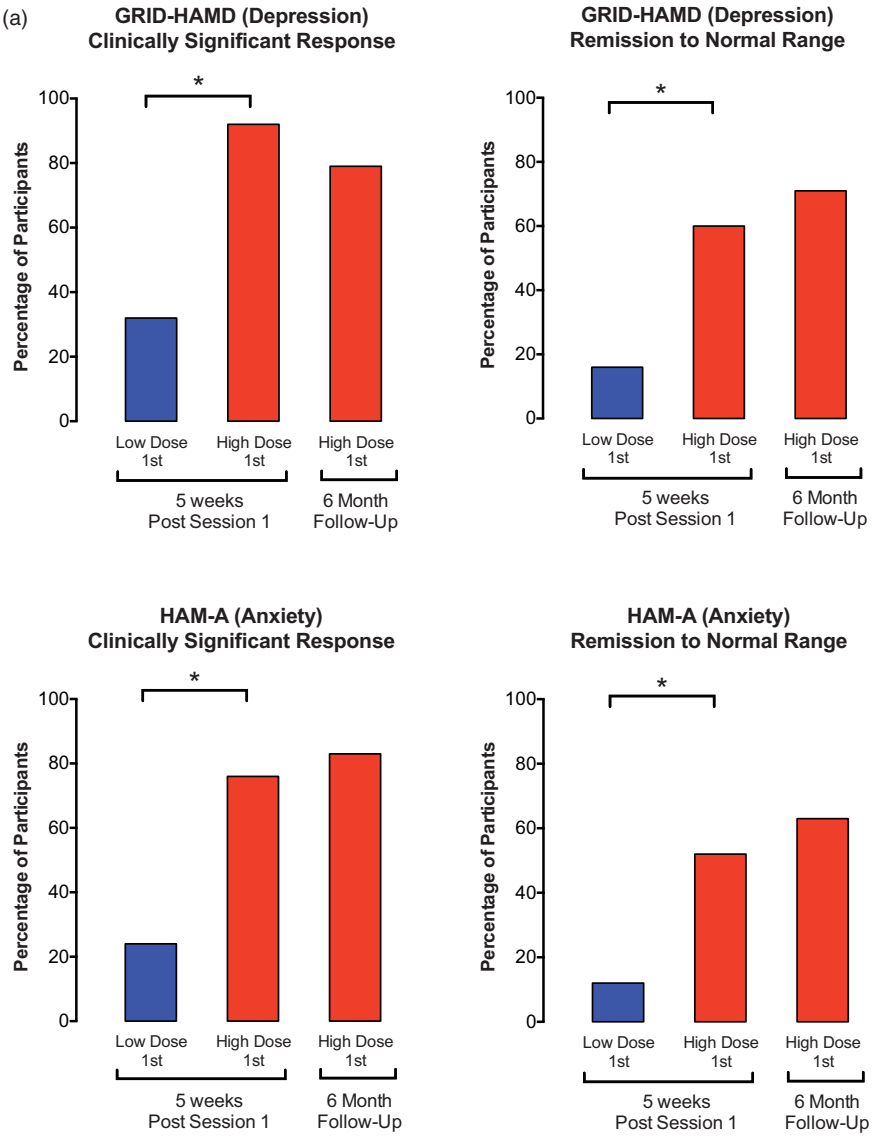

Figure 2. (a) Effects of psilocybin on clinically-signficant anti-depressant and anxiolytic response and remission rates. Effects of psilocybin on clinically significant response rate and symptoms remission rate as assessed with clinician-rated measures of depression and anxiety. Data are the percentage 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 ($p > .001$); data at 6 months show these effects were sustained at follow-up. Figure 2a was originally published under a CC-BY 3.0 Creative Commons License (http://www.creativecommons.org/licenses/by/3.0/) in Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P. & Klinedinst, M.A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *J Psychopharmacol*, 30(12), 1181-1197. Available at: http://journals.sagepub.com/doi/10.1177/0269881116675513 (b) Percentage of participants with anti-depressant and anxiolytic response rates and anti-depressant symptom remission. Percentages of participants in each treatment group who met criteria for anti-depressant or anxiolytic response or anti-depressant symptom remission (BDI, HAD D) at 1 day post-dose 1 (psilocybin first $n = 14$, niacin first $n = 15$), 7 weeks post-dose 1 (psilocybin first $n = 12$, niacin first $n = 14$), and at 26 weeks post-dose 2 (psilocybin first $n = 11$, niacin first $n = 12$). Asterisks indicate significance level of between-group comparisons at each time point. Figure 2b was originally published under a CC-BY 3.0 Creative Commons License (http://www.creativecommons.org/licenses/by/3.0/) in Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzi, Kl, Babb, J., Su, Z., Corby, P. & Schmidt, B.L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*, 30(12), 1165-1180. Available at: http://journals.sagepub.com/doi/pdf/10.1177/0269881116675512

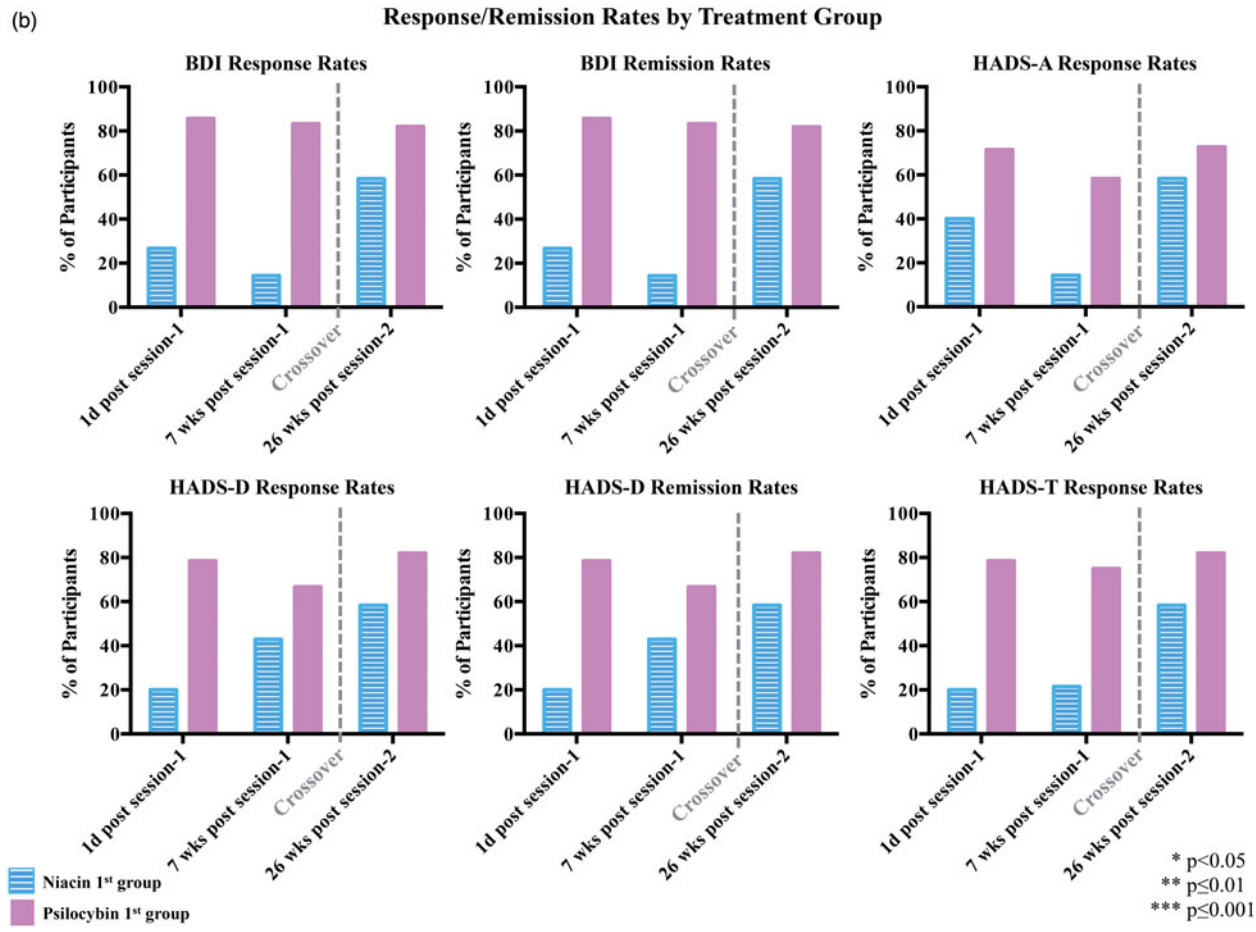

Figure 2. Continued.

demonstrated prior to the cross-over in comparing the psilocybin-1st to niacin-1st groups, where psilocybin produced rapid (e.g. measured from 1 day prior to 1 day post-dosing), substantial (i.e. large effect sizes), and sustained (up to 7-weeks post-single dosing) improvements in anxiety and depressive symptoms associated with cancer (see Figure 1b). These improvements were clinically significant. For instance, at 7-weeks post dose-1: 58% of participants in the psilocybin-1st group met criteria for an anxiolytic response (i.e. ≥50% decrease relative to baseline) using the HADS Anxiety sub-scale (compared to 14% in the niacin first group), and 83% of subjects in the psilocybin-1st group (compared to 14% in the niacin-1st group) met criteria for anti-depressant response (i.e. ≥50% decrease relative to baseline with the BDI) (see Figure 2b). Although it is not possible to attribute enduring clinical improvements in anxiety or depression to psilocybin after the cross-over, this trial reported anxiolytic or anti-depressant response rates of 60–80% at the 6.5 month final follow-up assessment. Complementing the primary outcomes, prior to the cross-over (at 2-weeks post dose-1), psilocybin produced statistically significant improvements in: cancer-related hopelessness and demoralization, quality-of-life, and spiritual well-being. At the final 6.5 month follow-up, in addition to sustained improvements in quality-of-life, spiritual well-being, and existential distress (hopelessness, demoralization), there was an improvement in a measure of attitudes towards death and dying (although there were no acute or longer-term improvements in a death anxiety measure). Participants rated the psilocybin experience as being one of the most significant events of their lives: 70% and 52% rated the experience as the singular or top 5 most personally meaningful or spiritually significant experience of their entire lives, respectively. Similar to the JHU trial, the psilocybin induced mystical experience was found to both correlate with and to partially mediate the anti-depressant and anxiolytic effects of psilocybin. The findings (in these two RCTs) that the mystical experience in part mediates the therapeutic effects of psilocybin extends the earlier findings of the Spring Grove group (in their open

label trials) that reported on positive correlations between the mystical experience and therapeutic outcomes (Pahnke et al., 1969; Richards et al., 1977).

Discussion and conclusion

Historical early-phase research

This review identified 10 published clinical trials (in a systematic search between 1960 and 2018), where serotoninergic psychedelics were studied in the treatment of cancer-related psychiatric illness. Six trials were published between 1964 and 1980 and included 341 participants (almost exclusively with cancer diagnoses and related psychological and existential distress) treated with psychedelic-assisted therapy. All of these trials were open-label in design and predominantly studied LSD. The first trial by Eric Kast focused on potential analgesic and pharmacologic-only effects of LSD in terminally ill patients; however, in addition to finding anti-nociceptive properties of LSD, Kast and Collins (1964) reported on improvements in psychological and existential domains. This set the stage for Kast to treat several hundred more patients with terminal cancer (paying more attention to the unique psychological effects of LSD) and reported on improvements in depression and fear of death, and the induction of mystical states of consciousness (Kast, 1966; 1967). The clinical trials conducted at Spring Grove in the 1960s and early 1970s treated 83 participants with terminal cancer-related psychiatric distress and developed an optimized treatment model that accounted for the now well-known variables of set, setting, dose, as well as preparatory and post-dosing integrative psychotherapy (Grof & Halifax, 1977). These trials extended Kast's findings by reporting on improvements in cancer-related depression, anxiety, and fear of death (Grof et al., 1973; Pahnke et al., 1969; Richards, 1980).

Recent middle-phase RCT research

The promising findings from these early open-label trials set the stage for the next phase of research using psychedelic therapy to treat cancer-related psychiatric disorders. Four trials were published between 2011 and 2016 and included a total of 104 participants. These trials all represented an improvement in research methodology, compared to the earlier historical trials, in a number of ways including: randomization of participants, use of active placebo control, double-blinding, use of current psychiatric structured diagnostic instruments and validated outcome measures, and prospective long-term follow-up (Reiche et al., 2018). The three FDA phase II trials in the US all used single dose psilocybin and included a combined cohort of 92 participants with life-threatening or terminal cancer diagnoses. Combined, these trials strongly suggest that psilocybin-assisted therapy for patients with cancer-related psychiatric illness produces rapid, robust (e.g. large effect sizes, large antidepressant and anxiolytic response and remission rates), and sustained improvements (e.g. up to several months) in cancer-related anxiety and depression, as well as improvements in existential distress (e.g. demoralization, hopelessness, death and anxiety) and quality-of-life (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Two of the trials demonstrated correlation and partial mediation between the psilocybin occasioned mystical experience and therapeutic outcomes (e.g. improvements in depression and anxiety) (Griffiths et al., 2016; Ross et al., 2016).

Advanced phase research (the future): phase III clinical trials, re-scheduling, and licensed psychedelic treatment clinics

The data from these three trials has set the stage in the US for proposed FDA phase III trials (sponsored by the Usona Research Institute), utilizing single dose psilocybin-assisted therapy for MDD, one proposed trial would focus exclusively on cancer patients with MDD, and the other would focus on MDD more broadly in the general population. It is possible that the FDA would allow contemporaneous 'compassionate use' (also known as expanded access) to be conducted alongside the phase III trials, which would allow a greater cohort of the population with cancer-related psychiatric distress to potentially benefit from psilocybin treatment in a more expedited manner. Similar advanced-phase trials are being considered in Europe through the EMA. If the trials were to demonstrate a statistically and clinically meaningful therapeutic effect of psilocybin-assisted treatment (vs placebo) in patients with MDD, it could potentially lead to the re-scheduling of psilocybin out of the most restrictive category (where it is currently not available for clinical use in humans) to another category where it becomes available for therapeutic use in clinical populations (e.g. in the US, re-scheduling from I to II or III). This would make psilocybin available as a prescription medication, to be used in conjunction with preparatory and integrative psychotherapy. It could be used to treat psychological (e.g. depression) distress associated with cancer, whether it occurs early in the illness or as part of the

death and dying process. Off-label use could be allowed by regulatory agencies and extended to include other types of psychiatric distress in cancer patients (i.e. anxiety, existential distress), and could more broadly be extended to include psychological and existential distress occurring in other serious general medical conditions (e.g. AIDS). Psilocybin would likely be dispensed and administered only in specially designated and certified psychedelic-assisted treatment clinics. Training of therapists and fidelity to treatment models would have to be considered, and it would be important to establish specific psychedelic-assisted therapy training programmes. Regulatory oversight, quality control, and strict protocols to ensure drug accountability (e.g. protecting against drug diversion), patient safety, and treatment efficacy would have to be key components of managing hallucinogen-assisted treatments.

The availability of psilocybin-assisted therapy could provide a novel and revolutionary treatment model for patients with cancer-related psychological and existential distress in a number of ways, including: (1) Rapidity of therapeutic onset (the Ross et al. (2016) trial demonstrated onset of anxiolytic and anti-depressant action as measured from 1 day prior to 1 day post-dosing). Having a psychotropic intervention that can work immediately for cancer-related depression would have obvious benefits for patients given the delay (e.g. weeks) for typical anti-depressants to work and given the increased risk of suicide for patients who experience cancer-related psychological and existential distress; (2) Sustained anxiolytic and anti-depressant effects from single dosing (e.g. up to 5 weeks in the Griffiths et al. (2016) trial and up to 7 weeks in the Ross et al. (2016) trial). The implications here would include minimization of side-effects related to having to take an anti-depressant or anxiolytic chronically. Further research is needed to validate the length of therapeutic benefit of single dose psilocybin and test the potential need for booster or multiple dosing intervention models; (3) The use of psilocybin early in a cancer diagnosis when psychological symptoms start to manifest. This could have the potential benefit of preventing progression to more severe psychological symptoms, and could protect against suicide, and even protect against cancer disease progression. This later statement is speculative, and would need more extensive research to validate, but there is a known link between psychiatric distress in cancer patients and decreased survival rates from the cancer (Brown et al., 2003); (4) Providing a pharmacologic (or pharmacologic-psychosocial) intervention for existential distress in cancer patients. Existential distress is under-recognized and under-treated in cancer patients within western medicine, there are no established medications with efficacy for this typology of distress, and having an intervention that can diminish the psychic agony and fear associated with the dying process could have enormous benefit for patients as they approach death. Use of psilocybin-assisted treatment in the terminally ill could be especially useful for patients in inpatient or outpatient hospice settings, and could aid the process of dying with dignity to help occasion a 'good' death process, in contrast to the current poor state of existential care of the dying in the US and internationally (Meier et al., 2016).

Disclosure statement

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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