

Use of the Classic Hallucinogen Psilocybin for Treatment of Existential Distress Associated with Cancer

Charles S. Grob, Anthony P. Bossis,
and Roland R. Griffiths

This chapter will review the potential of a treatment approach that uses psilocybin, a novel psychoactive drug, to ameliorate the psychospiritual distress and demoralization that often accompanies a life-threatening cancer diagnosis. Early research with classic hallucinogens in the 1950s had a major impact on the evolving field of psychiatry, contributing to early discoveries of basic neurotransmitter systems and to significant developments in clinical psychopharmacology. While published reports of therapeutic breakthroughs with difficult to treat and refractory patient populations were initially met with mainstream professional enthusiasm, by the late 1960s and early 1970s the growing association of hallucinogens with widespread indiscriminate use led to the temporary abandonment of this promising psychiatric treatment model. After a hiatus lasting several decades, however, regulatory and scientific support has grown for the resumption of clinical research investigations exploring the safety and

efficacy of a treatment model utilizing the classic hallucinogen, psilocybin, in a subject population that had previously demonstrated positive therapeutic response, patients with existential anxiety due to a life-threatening cancer diagnosis.

Psilocybin

Psilocybin is a naturally occurring compound that is an active constituent of many species of mushrooms, including the genera *Psilocybe*, *Conocybe*, *Gymnopilus*, *Panaeolus*, and *Stropharia*. Psilocybin containing mushrooms grow in various parts of the world, including the United States and Europe, but until recently they have been consumed primarily in Mexico and Central America, where they were called by the ancient Aztec name of *teonanacatl* (flesh of the gods). In addition to psilocybin, other naturally occurring classic hallucinogens include mescaline from peyote and dimethyltryptamine (DMT) from various plants. All three of these substances have a long history of ceremonial use by indigenous people for religious and healing purposes. Following the arrival of Europeans in the New World in the sixteenth and seventeenth centuries, however, the use of plant hallucinogens by native people was harshly condemned and punished under the strict laws of the Spanish Inquisition, and forced to go underground. This suppression was so effective that hallucinogenic mushroom use was eventually assumed to be nonexistent, until the discovery by amateur mycologist,

C.S. Grob, M.D. (✉)
Department of Psychiatry,
Harbor-UCLA Medical Center, Box 498
1000W, Carson St., Torrance, CA 90509, USA
e-mail: cgrob@labiomed.org

A.P. Bossis, Ph.D.
Department of Psychiatry, New York University School
of Medicine, New York, NY, USA

R.R. Griffiths, Ph.D.
Departments of Psychiatry and Neuroscience,
Johns Hopkins University School of Medicine,
Baltimore, MD, USA

R. Gordon Wasson, of their extant ceremonial use by indigenous Mazatec people of Oaxaca, in the central Mexican highlands. Invited to participate in a healing ritual using mushrooms as a psychoactive sacrament, Wasson published his observations in the popular American press in 1957, catalyzing both popular and professional interest [65, 85]. Subsequently, the eminent Swiss natural products chemist, Albert Hofmann, succeeded in isolating the active tryptamine alkaloid, psilocybin, from samples of the hallucinogenic mushrooms from Mexico sent to him by Wasson.

Psilocybin is 4-phosphoryloxy-*N,N*-dimethyltryptamine and possesses a chemical structure similar to the neurotransmitter serotonin (5-hydroxytryptamine). Psilocybin is rapidly metabolized to psilocin, which is a highly potent agonist at serotonin 5-HT-2A and 5-HT-2C receptors [79, 80]. Research suggests that the primary site of action for the psychoactive effects of psilocybin is the 5-HT-2A receptor [73, 98]. During the 1960s psilocybin was subjected to psychopharmacological investigation, and found to be active orally at around 10 mg, with stronger effects at higher doses, and to have a 4–6-h duration of experience. Psilocybin was also determined to be thirty times stronger than mescaline and approximately 1/100–150 as potent as lysergic acid diethylamide (LSD) [44]. Compared to LSD, psilocybin was considered to be more strongly visual, less emotionally intense, more euphoric, and with fewer panic reactions and less likelihood of inducing paranoia [78]. Similar to other classic hallucinogens, psilocybin was observed to produce an altered state of consciousness that was characterized by changes in perception, cognition, and mood in the presence of an otherwise clear sensorium, along with visual illusions and internal visionary experience (though rarely frank hallucinations), states of ecstasy, dissolution of ego boundaries, and the experience of union with others and with the natural world.

In the late 1990s, psilocybin was subjected to renewed examination by contemporary investigators, including Franz Vollenweider and colleagues at the Heffter Research Center and the University of Zurich, in Switzerland. Careful medical and laboratory evaluations conducted there identified a relatively safe physiological range of action in

normal volunteer subjects [36, 94]. Positron emission tomographic (PET) studies also demonstrated that psilocybin induces a global increase in cerebral metabolic rate of glucose, most markedly in the frontomedial and frontolateral cortex, anterior cingulate and temporomedial cortex [97]. In another recent study, at the University of Arizona, Francisco Moreno examined the use of psilocybin in the treatment of severe, refractory obsessive-compulsive disorder, observing that psilocybin appeared to be safe, well tolerated, and capable of inducing “robust acute reductions” in OCD symptoms [67]. Further investigations of psilocybin in normal volunteers were conducted at the Johns Hopkins University exploring the emergence of psychospiritual states of consciousness following psilocybin administration [30] (see section below). The Johns Hopkins group also published a set of recommended guidelines for safe conduct of high-dose research with classic hallucinogens [47].

Psychiatric Research with Classic Hallucinogens: Historical Perspective

Hallucinogens consist of a diverse group of biologically active compounds. Hallucinogens in plant form are thought to have been utilized by prehistoric and early civilizations as essential features of their religious, initiation, and healing rituals. Ethnobotanists have catalogued more than one hundred species of plant hallucinogens, the majority in the Western hemisphere, where they played a vital role within indigenous ceremonial practices [91]. In the late nineteenth Century, interest in psychoactive plants was catalyzed by discoveries of anthropologists studying native people around the world, who shipped specimens to leading European pharmacologists of that era, including Arthur Heffter and Louis Lewin, who succeeded, respectively, in isolating mescaline from the southwest American cactus peyote, *Lophophora williamsii*, and harmine from *banisteriopsis caapi*, one of the plants brewed to create the Amazonian plant hallucinogen decoction, ayahuasca.

The classic hallucinogens can be divided structurally into two classes of alkaloids: the

tryptamines, including psilocin and psilocybin (constituents of *Psilocybe* and several other mushroom genera), DMT (constituent of the plant admixture ayahuasca and other hallucinogenic preparations), and D-LSD, and the phenethylamines, including mescaline (constituent of peyote) and various synthetic compounds. The primary pharmacological effects of these substances are mediated at 5-HT_{2A} receptors where they function as agonists. The first classic hallucinogen to be characterized pharmacologically was mescaline, which was discovered in 1896 and synthesized de novo in the laboratory in 1919 [45]. While some attention was given in the early twentieth Century to potential medicinal applications of hallucinogens and there were preliminary efforts to formally classify and analyze visions induced by alkaloids discovered in particular plants [1, 55], widespread medical and psychiatric interest did not emerge until the mid-twentieth Century, following Albert Hofmann's serendipitous discovery of LSD at the Sandoz Laboratories in Basel, Switzerland, in 1943 [40].

From the 1950s, when formal study of the range of effect of hallucinogens and their potential in treatment models was initiated, until the early 1970s, when cultural and political turmoil led to the termination of studies, over 1,000 clinical and research reports were published in the medical and psychiatric literature describing the response to hallucinogen administration of approximately 40,000 research subjects and patients [33]. While initial research focused on the presumed capacity of hallucinogens to induce psychotic-like experience, interest in this psychotomimetic model waned [2, 32]. By the late 1950s and into the 1960s, however, significant new research activity was catalyzed by studying potential treatment applications of hallucinogens, most notably for several notoriously difficult-to-treat clinical conditions, including alcoholism, drug addiction, obsessive-compulsive disorder, chronic post-traumatic stress disorder, antisocial disorder, infantile autism, and the overwhelming existential anxiety often experienced in the presence of terminal cancer. Two discrete treatment models were proposed, involving the administration of lower versus higher dosages of hallucinogens and the application of different theoretical

mechanisms of action for their observed therapeutic effect. The initial treatment structure investigated, the psycholytic model, called for the administration of relatively low dosages of hallucinogens, with the postulated goal of facilitating the release of repressed psychic material, particularly in anxiety states and obsessional neuroses. Using this approach, some clinicians claimed to have achieved breakthroughs in reducing the duration and improving the outcome of psychotherapeutic treatment, presumably by facilitating ego regression, uncovering early childhood memories, and inducing an affective release [10].

As investigators began to explore the effects of higher dosages of hallucinogens on clinical subjects and patients, however, they began to appreciate that hallucinogens were capable of occasioning entirely new and novel dimensions of consciousness. Humphrey Osmond, a Canadian alcoholism researcher, noted that this high-dose hallucinogen, or *psyche-delic* (translated from the ancient Greek as "mind revealing") treatment model, appeared to free up the mind from its habitual moorings and allow it to access states of consciousness resembling spontaneous psychospiritual epiphanies. Osmond observed that even after the effects of the administered drug had worn off, individuals were still left with a deeply positive and therapeutic impact from having had a mystical level transcendent experience [74]. With certain conditions in particular, including alcoholism and other addictive disorders, the mysticomimetic capacity of the hallucinogen experience often appeared to have induced remissions from intractable psychological conditions to a greater degree unique than conventional treatment modalities. While the low-dose psycholytic model usually involved active discourse between patient and psychotherapist in the service of analyzing underlying neurotic complexes, the high-dose psychedelic model involved the development of an alternative treatment structure, with the subject lying down, wearing eyeshades and listening to preselected music throughout much of the session. During the session, the patient was encouraged to go deeply into the experience, with the facilitator maintaining an active presence but generally not engaging in

verbal dialogue until the concluding phase of the treatment session.

One patient population that demonstrated positive response to the hallucinogen treatment model were individuals with advanced cancer with overwhelming anxiety in reaction to their terminal illness. Beginning with the observations of internal medicine investigators in the late 1950s at the Chicago Medical School [51, 52] and UCLA [15], and extending by the mid 1960s to psychiatrists and psychologists at the University of Maryland [35, 77, 84] and UCLA [23], a growing consensus within the field of hallucinogen investigations was achieved that patients with advanced-stage cancer treated with this novel approach frequently sustained significant improvements of their psychospiritual status. Moving accounts were reported of patient experiences, including reduced physical pain and lessened need for narcotic medication, improved quality of life, and greater acceptance of the inevitable and in some cases imminent end of their lives. Of particular interest, the most positive therapeutic outcomes, reflected in lowered anxiety, demoralization, and fear of death, and in improved mood and quality of meaningful interpersonal relations, were in patients who during the course of what was often their only hallucinogen treatment session experienced a deeply felt mystical state of consciousness. Unfortunately, these promising observations were terminated prematurely, largely in response to public and political concern about the misuse of these compounds in the 1960s.

Contemporary Psilocybin Research in Patients with Life-Threatening Cancer

Following decades of inactivity, it has been possible in recent years to obtain the regulatory approval and funding necessary to resurrect this long neglected treatment model. While improvements in caring for patients at the end of life have occurred in the intervening years, including the development of the hospice movement and the field of palliative medicine, it is still clear that even with these innovative approaches many individuals still go through the final phase of their life with

high levels of anxiety, depression, and demoralization. Given the pressing need for more effective therapeutic interventions in individuals struggling with cancer and reactive existential crisis, along with the promising preliminary findings of the hallucinogen treatment model from the previous generation of research in patients with terminal medical illness, it is not surprising that this has become a prominent focus for current research efforts as well. Indeed, in recent years three investigations have been approved in the United States that have examined the use of psilocybin treatment for anxiety and demoralization in patients with a life-threatening cancer diagnosis—at Harbor-UCLA Medical Center, Johns Hopkins University, and New York University.

In 2004 the Harbor-UCLA psilocybin treatment protocol for anxiety in patients with advanced cancer was initiated. A total of 12 patients were recruited for a double-blind, placebo-controlled investigation, using a moderate dose (0.2 mg/kg) of psilocybin. All patients were screened to meet inclusion and exclusion criteria, which included a diagnosis of advanced-stage cancer but still functional enough to undergo full screening, preparation for the psilocybin sessions, and participation in two all-day sessions spaced several weeks apart, one active drug and the other placebo. Support with integration of the experience and collection of follow-up reports and quantitative data analyses continued with each patient for at least 6 months. Recruitment for all patients into the study, their participation in both psilocybin and placebo treatment sessions, and collection of data concluded in early 2008. At the time of the writing of this chapter, in 2011, 11 of the 12 participants have died.

The report describing the rationale for the investigation, methodology employed, and findings up to 6 months after treatment was published in the *Archives of General Psychiatry* [34]. All patients tolerated the psilocybin experience well, and there were no medical or psychological crises. Repeated administration of quantitative rating scales revealed improved mood and lessened anxiety, reaching significance at some monthly data collection points. Overall, patients reported their participation in the psilocybin treatment as having been a very valuable

experience, allowing them to improve their quality of life and augmenting their capacity to withstand the psychological stressors of their medical condition. While the Harbor-UCLA research investi-



gation has been completed, both the Johns Hopkins and NYU projects are currently ongoing. The Johns Hopkins and NYU studies, initiated in 2006 and 2009, respectively, both approved to use a significantly higher dose than the Harbor-UCLA protocol, which will likely allow for more exploration of the psychospiritual dimension of the experience. These studies also offer more flexibility for subject inclusion, and allow for the entry of early-stage cancers that are nonetheless considered potentially life threatening. It is strongly hoped that additional research groups will also initiate treatment protocols exploring the utility of the psilocybin treatment model with medical patients encountering existential crisis and demoralization at the end of life.

Comments from Annie L, a 53-year-old woman with a diagnosis of metastatic ovarian cancer, 6 months after her participation in a Harbor-UCLA psilocybin cancer-anxiety study:

“I had lost my faith because of anxiety, and I was just terrified. I was so anxious that it was hard to think about anything else. I didn’t think I was so worried about death as I was about the process of dying. About suffering and being in pain and having all kinds of medical procedures. I was becoming so irritable with my husband. I was just so anxious... My intention (for participation in the study) was to be able to control my anxiety so

I could enjoy the rest of my life. I was not enjoying my life at all.

As soon as it (the psilocybin) started working I knew I had nothing to be afraid of... It connected me with the universe... It was very gentle... And there were people (the treatment team) right there if I got upset... Everything looked absolutely beautiful. I didn’t see things that weren’t there. With my eyes closed I saw patterns, and visions and faces. I thought about being involved with people I loved, things I would do with people I knew, things I would tell them... I had an amazing spiritual experience. It re-connected me to the universe.

Comments from her husband 4 months after her death:

“Annie’s mood remained greatly improved for some time after the treatment. She also had much less anxiety, and her fear of getting sicker and her fear of the dying process also diminished a great deal. Beyond that, she and I got along much better after her psilocybin treatment ... I have no doubt that the treatment Annie went through was of great value to her ...”

Overview and Prevalence of Emotional Distress in Advanced Cancer

For many cancer patients, the advanced stage of illness is fraught with a significant degree of emotional suffering. As the illness trajectory progresses from diagnosis through medical treatment and eventually to the prospect of dying, the patient may be faced with considerable psychological distress and despair. In recent years, there has been a growing focus on the prevalence and clinical treatment of psychological distress in patients with advanced cancer that are facing the end of life [20, 48, 50, 57, 86]. Emotional suffering in advanced illness has been characterized as “severe distress associated with events that threaten the intactness of the person” ([9], p. 640).

The occurrence of psychological distress in cancer patients has been well documented with the highest prevalence rates among advanced cancer and end-of-life patients. While some cancer patients may cope effectively with the challenges of the disease, others experience a broad range of psychological stressors and symptoms. The prevalence of psychiatric disorders in cancer patients has been reported at approximately 50 %

[17, 61, 71] with the presence of any depressive or anxiety disorder at 24 % [102]. The prevalence of major depression has been reported at 15 % [41, 42, 101] with a range of all depressive disorders in cancer patients at 20 [102] to 26 % [19, 27]. Anxiety spectrum disorders have been documented at 14 % [102] with the prevalence of any anxiety symptoms at 21 % [17]. The prevalence of suicide in advanced and end-stage cancer is twice as high as that found in the general population [11] and an increased desire for hastened death in terminal patients has been established [5]. Kelly and colleagues [53] found that 22 % of advanced cancer patients had a desire for hastened death.

Focus on Spiritual and Existential Distress in Palliative Care

With a growing awareness of emotional suffering at the end of life, palliative care has increasingly focused on the specific domain of spiritual and existential distress as a significant component of quality of life in cancer and end-of-life cancer patients [16, 20, 66, 70, 88]. In palliative care, outcomes are no longer focused solely on biomedical or physical measures such as tumor or disease progression, but have expanded to include quality of life, now considered a central focus. Spiritual and existential factors are currently regarded as determinants of quality of life in advanced cancer and end-of-life patients. Distress in cancer and palliative care patients is viewed as a “multifactorial unpleasant emotional experience of a psychological, social, and/or spiritual nature” that impacts patients’ capacity to effectively cope with the myriad challenges of cancer [71].

Existential or spiritual pain of terminal cancer patients has been defined as “the extinction of the being and meaning of the self due to the approach of death. It can be explained as meaninglessness of life, loss of identity, and worthlessness of living that are derived from deprivation of the future, others, and autonomy of people as beings founded on temporality, beings in relationship, and beings with autonomy” [69]. An individual’s search for spiritual and existential meaning is frequently triggered by a diagnosis of cancer.

The alleviation of spiritual and existential distress is a primary objective of palliative and end-of-life care. A report by the Institute of Medicine listed spiritual well-being as an essential influence on quality of life and one of the six domains of quality supportive care of the dying [22]. Similarly, a report by the Consensus Conference in association with the National Consensus Project for Quality Palliative Care identified spiritual and existential issues as two of the eight core essential domains of quality palliative care [81]. The World Health Organization describes palliative care as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” [103].

Religion vs. Spirituality

Despite the overlap and ambiguity that have existed between the concepts of religion and spirituality, a consensus in the research literature has begun to emerge regarding the distinction between these two research constructs. Religion has been defined as structured belief systems that address universal questions and may provide a framework for making sense of ultimate questions of meaning and for expressing spirituality [93]. Spirituality tends to be a broader, more inclusive category than religion. It can be defined as “that which allows a person to experience transcendent meaning in life” [82] and “a personal search for meaning and purpose in life, which may or may not be related to religion” [95].

Whereas religion may be commonly viewed as a structured framework of beliefs and rituals that may include an expression of spirituality, spirituality may be experienced without the context of an organized religious system as a search for transcendence, meaning, and connection to ultimate meaning, nature, or to how an individual defines or experiences the concept of God. The Report of the Consensus Conference on spirituality in palliative care suggested the following definition (National Consensus Panel Report):

Spirituality is the aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred [81].

Spiritual Well-Being and Psychological Distress

The domain of spiritual and existential well-being is now widely accepted as an important determinant in the quality of life in palliative care and end-stage cancer [16, 21, 39, 60, 66, 92]. Coping with terminal cancer is a multifactorial and variable process. Enhanced spiritual well-being and the ability to attain meaning when facing end-stage cancer appears to be a key factor in effectively coping with advanced disease. Psychosocial factors in advanced cancer associated with heightened existential and spiritual distress include anxiety and depression [26, 72], anger, alienation, hopelessness, loss of meaning, loss of dignity, vulnerability, isolation, fear, and shock [39, 99, 100]. Chochinov and colleagues [12] identified specific psychosocial correlates of spiritual and existential suffering in advanced cancer patients that include loss of will to live, loss of a sense of dignity, hopelessness, and feeling as a burden to others. Impaired spiritual well-being has also been associated with a poorer tolerance of physical symptoms whereas an enhanced sense of meaning and spirituality has been shown to increase an individual's tolerance levels for physical symptoms [3]. Myriad health care domains and outcomes have been associated with existential distress including quality of life, symptom and disease progression, psychological distress, depression [86], interpersonal functioning [16, 102], suicidal ideation [63], and demoralization syndrome, defined as "a psychiatric state in which hopelessness, helplessness, meaningless, and existential distress are the core phenomena" (p. 13. [54]).

Demoralization is defined by Kissane et al. [54] as a syndrome characterized by hopelessness, loss of meaning, and existential distress. This syndrome, which is delineated as a separate construct, has been identified as a primary risk

factor for depression in advanced cancer patients. A desire for hastened death in advanced cancer patients has also been identified with this syndrome. Observed in palliative care and advanced cancer populations, this syndrome is associated with chronic medical illness, fear of loss of dignity, social isolation, and the sense of being a burden on others [54]. Kissane and colleagues propose that for targeted psychotherapies or interventions to be effective, they must aim to explore and restore meaning and hope within the context of advancing disease and impending death.

A desire for hastened death has been associated with lower levels of spiritual well-being [4, 86, 87]. A growing number of studies have presented evidence supporting a model that depression and hopelessness are chief determinants and predictors of a desire for hastened death (Rodin et al., 2008; [5, 48]). For example, in a study exploring the relationships among depression, hopelessness, and desire for hastened death, Breitbart and colleagues [5] identified depression as a robust predictor of desire for hastened death. In this study, patients with major depression were four times more likely to have a desire for hastened death.

Enhanced Spiritual Well-Being as a Buffer Against Emotional Distress

While there has been a documented relationship between lack of spiritual well-being and elevated psychosocial distress, there is increasing evidence to support the hypothesis that *enhanced* spiritual or existential well-being is associated with *improved* psychological functioning and might even prove to be a buffer against psychological syndromes associated with the end of life. Exploring the relationship between spiritual well-being, depression, and psychological distress in end-of-life cancer patients, a growing body of research has shown that higher levels of spiritual well-being are correlated with lower levels of emotional distress and serve as a buffer against depression, desire for hastened death, loss of will to live, and hopelessness as well as provide an

increase in quality of life [5, 21, 50, 63, 72]. Individuals with an enhanced sense of spiritual well-being are also emotionally equipped to cope more effectively with the physical challenges of advanced and end-stage cancer [3].

The concept of meaning has received considerable attention in palliative care and psychoncology research as an important construct related to improved quality of life. Cultivating a sense of meaning in advanced cancer has been shown to improve spiritual well-being and overall quality of life while reducing levels of psychological distress [60, 64, 68]. For some patients, the search for meaning in end-of-life cancer, while a psychologically and spiritually complex, arduous, and courageous process, may provide them with a sense of peace and acceptance. Viktor Frankl, in *Man's Search for Meaning*, wrote that "man is not destroyed by suffering; he is destroyed by suffering without meaning" ([24], p. 135). Although not written about the end-of-life struggle with cancer or life-threatening disease, Frankl's landmark book was written from his personal experience of survival during his 3 years in Auschwitz and other concentration camps. His struggle to derive personal meaning in the face of horror and death has resulted in universal life lessons for those facing severe suffering or existential distress. In *The Will to Meaning: Foundations and Applications of Logotherapy* [25], Frankl wrote, "Meaning can be found in life literally up to the last moment, up to the last breath, in the face of death" (p. 76).

Meaning-enhancing interventions have been demonstrated to improve quality of life in palliative care and decrease wishes for euthanasia and for hastened death [6, 102]. Dame Cicely Saunders, who gave rise to the hospice movement and emphasized spiritual and psychological factors in palliative and hospice care, introduced the concept of "total pain" of the terminal patient that emphasizes psychospiritual as well as physical aspects of care and distress. Influenced by Frankl, she believed that the "total pain" of the terminal patient was related to a "lack of meaning" [89, 90]. In a quantitative thematic analysis [96] of all published literature on spirituality in palliative care, the most cited themes were meaning

and purpose followed by self-transcendence and transcendence.

With an increasing body of evidence [5, 50, 63, 72] supporting the premise that enhanced spiritual well-being provides protection against depression, hopelessness, and desire for hastened death among other psychosocial forms of suffering, there is growing interest in interventions that enhance or improve psychological well-being and provide meaning in terminal patients. In recent years, there have been published reviews of interventions targeted at improving end-of-life psychological well-being and reducing various aspects of psychiatric distress [13, 38, 58, 92]. Interventions aimed at enhanced spiritual well-being, meaning, and dignity in advanced cancer patients are now being developed and studied for effectiveness [6, 14, 38].

Despite the growing awareness of spiritual and existential distress among end-of-life cancer patients and the impact on quality of life, there remains a paucity of psychotherapeutic approaches and interventions to directly address this suffering. In a study evaluating spiritual and existential needs among cancer patients, Moadel and colleagues [66] found that from 21 to 51 % of patients reported unmet spiritual or existential needs. The unmet spiritual or existential needs cited by patients were overcoming fears (51 %), finding hope (42 %), finding meaning in life (40 %), and finding spiritual resources (39 %).

Breitbart (2010) [6] notes that while some interventions are aimed at improved mood, none examine the effect of spiritual well-being and few interventional studies are directed at advanced or end-stage cancer patients. Furthermore, aside from hallucinogen-induced mystical experience (discussed below), none provide the means for a direct intensive alteration in consciousness with the potential for a transformative experience directly related to the sacred or to broad spiritual and existential phenomena. Blinderman and Cherny [7] note, "It has been observed that existential distress is the least studied domain of patient distress. Given the paucity of research in this area, additional qualitative and quantitative studies are needed to help further understand this

domain of suffering and the possible areas of intervention by health care professionals” (p. 380). Lethborg et al. [59] suggest that “the specific techniques most effective in enhancing meaning and connection (in advanced cancer) are yet to be defined, and such clarification would require intervention-focused research that, in order to appropriately demonstrate change, would need to be longitudinal” (p. 387).

Uniqueness of Psilocybin Mystical Experience Treatment Model

The hallucinogen treatment model, which has been shown to generate a mystical or spiritual experience [30], offers a highly unique and novel therapeutic approach to promote transcendence, meaning, and reduction in anxiety for terminal cancer patients [34]. It is the only approach with the dying of its kind in medicine, psychiatry, and the behavioral sciences. Reviews of the literature on the importance of spirituality in end-of-life suffering [83, 96] identify transcendence and meaning as the most common factors. Of the few spiritual well-being-enhancing interventions for end-of-life patients currently available, the hallucinogen treatment model is the only approach that potentially facilitates a radical shift in consciousness yielding a transpersonal, transcendent, spiritual, and mystical experience.

Access to the transpersonal and transcendent non-ordinary dimensions of consciousness is an integral aspect of the enhanced spiritual well-being generated by the hallucinogen-induced mystical experience. Eric Cassell, the distinguished internist who has contributed considerably to the conversation on dying in America and who has written extensively about the nature of suffering, medicine, and the compassionate and ethical treatment of the terminally ill, writes in his classic article *The Nature of Suffering and The Goals of Medicine*, “Transcendence is probably the most powerful way in which one is restored to wholeness after an injury to personhood. When experienced, transcendence locates the person in a far larger landscape. The suffering is not isolated by pain but is brought closer to a transpersonal

source of meaning and to the human community that shares those meanings. Such an experience need not involve religion in any formal sense; however, in its transpersonal dimension, it is deeply spiritual” [9]. Meaning and transcendence, Cassell suggests, provide unique avenues for the amelioration of suffering at the end of life.

Access to the transpersonal realm has the potential to alter a terminal cancer patient’s perspective to his or her existential suffering. Transpersonal psychology “is concerned with the study of humanity’s highest potential, and with the recognition, understanding, and realization of unitive, spiritual, and transcendent states of consciousness” (p. 91, [56]). For Aldous Huxley [43], the British writer who dedicated attention to comparative spirituality and to the application of hallucinogens in the dying, the hallucinogen-induced mystical experience may reveal the individual to the “perennial philosophy.” This *philosophia perennis* is the philosophical concept which states that all the world’s religions and philosophical traditions share a single truth. Mystical, numinous, and peak states of consciousness have been written about extensively throughout history by observers and investigators of philosophy, religion, and consciousness including Carl Jung [49], Abraham Maslow [62], Rudolph Otto [75], William James [46], and Richard Bucke [8], and appear within the canon of the major religious and wisdom traditions.

For many cancer patients, the mystical experience of consciousness provides a profound ontological shift. This ontological or paradigm shift in awareness has the capability to alter and transform a cancer patient’s assumptions and beliefs regarding the nature of being, the self, the body, disease, and death itself. Often, for the patient who has had this awareness, the body and cancer are experienced as separate (i.e., “I am not my cancer”). The self-experience or self-image of the patient may be recalibrated into a broader existential view where the meaning of cancer and even death itself may be transformed and may no longer be a profoundly anxiety-provoking experience as it was before. The terror of death may be altered as an individual experiences connection to the transpersonal realm, to others, to nature

Table 17.1 Phenomenological features of a mystical type experience—either naturally occurring or occasioned by a classical hallucinogen

- *Unity*: A core feature—a strong sense of the interconnectedness of all people and things—All is one—sometimes a sense of pure consciousness or a sense all things are alive
- *Sacredness*: Reverence, awe, or holiness
- *Noetic quality*: A sense of encountering ultimate reality
- *Transcendence of time and space*: A sense of timelessness, when past and future collapse into the present moment—an infinite realm with no space boundaries
- *Deeply felt positive mood*: Universal love, joy, peace, tranquility
- *Ineffability and paradoxicality*: A sense that the experience cannot be adequately described in words—a sense of the reconciliation of paradoxes

itself, or to the sacred. Often, the patient may experience consciousness as continuing indefinitely, thereby dramatically modifying or transforming the concept of death of the self.

The primary characteristics of a mystical experience, which are summarized in Table 17.1, appear directly related to the potential for a reduction in existential and psychospiritual distress. The potential primary effects or benefits of mystical or peak consciousness states in cancer patients are (1) improved psychological, spiritual, and existential well-being; (2) ability to cognitively or emotionally reframe the impact of cancer, dying, and death; (3) increased capacity for appreciation of time living; (4) increased appreciation and experience of connectedness to sacredness, nature, relationships, and family; (5) ability to attend to unfinished business; (6) the possibility to conceptualize death as “not the end” but a transition of some manner in continuing consciousness; (7) increased sense of meaning and purpose; and (8) increased acceptance and peace with death.

Johns Hopkins Studies of Psilocybin-Occasioned Mystical Type Experience

Building on observations made in a study conducted in early 1960s in seminary students at Harvard [18, 76], two recent double-blind studies

conducted at Johns Hopkins [29–31] have demonstrated that under carefully controlled conditions, high doses of psilocybin occasion profound personally and spiritually meaningful experiences in the majority of healthy, normal healthy participants. One study [30, 31] involved 36 volunteers who participated in 2 or 3 day-long sessions during which they received, on separate sessions, a high dose of psilocybin (30 mg/70 kg) or a dose of methylphenidate hydrochloride. The design of the study effectively obscured to volunteers and study staff who monitored the sessions exactly what drug conditions were being tested. A subsequent study [29] involved 18 participants who received, in mixed order, a range of psilocybin doses (placebo, 5, 10, 20, and 30 mg/70 kg) over five sessions. The participants in both studies had a mean age of 46 years and were well educated and high functioning. All but one was hallucinogen naïve. Study monitors met individually with each participant for a total of 8 h before the first session and for 2 h between sessions to help develop rapport and trust, which are believed to minimize the risk of adverse reactions to classic hallucinogens. The 8-h drug sessions were conducted in an aesthetic living room-like environment designed specifically for the study (Fig. 17.1). Two monitors were present throughout the session. For most of the time during the session, participants were encouraged to lie on the couch and use an eye mask and headphones. Participants were encouraged to focus their attention on their inner experiences throughout the session. Details and rationale for screening, preparing volunteers, and managing sessions and aftercare were similar to those described by Johnson et al. [47].

As expected, psilocybin produced increases in measures previously shown to be sensitive to hallucinogenic drugs, including perceptual changes (e.g., visual illusions), greater emotionality (e.g., increased joy and peacefulness and, less frequently, fear and anxiety), and cognitive changes (e.g., changes in a sense of meaning, sometimes suspiciousness). But perhaps the most interesting effect was that psilocybin produced large increases on extensively studied, well-validated questionnaires that were designed to measure naturally occurring mystical type experiences as described



Fig. 17.1 The living room-like session room used in the Johns Hopkins psilocybin research studies. Comfortable, aesthetic environments free of unnecessary medical or research equipment, in combination with careful volunteer screening, volunteer preparation, and interpersonal support from two or more trained monitors, help to mini-

mize the probability of acute psychological distress during sessions. The use of eyeshades and headphones (through which supportive music is played) may contribute to safety by reducing distractions as well as social pressure to verbally interact with research personnel (reprinted from [47])

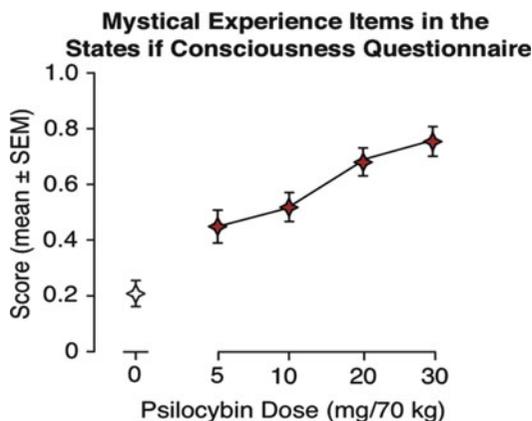


Fig. 17.2 Post-session ratings on a questionnaire designed to assess mystical experience. Psilocybin produced orderly dose-related increases, with most participants fulfilling the criteria for having had a “complete” mystical experience (data from [29])

by mystics and religious figures worldwide and throughout the ages, including measures not previously used to assess changes after a drug experience. Figure 17.2 shows that psilocybin produced orderly dose-related increases in a mea-

sure of mystical experience obtained at the end of the session day [29]. “Complete” mystical experiences were those in which volunteers met a priori criteria on all six phenomenological dimensions of the mystical experience (Table 17.1). The percentage of volunteers who fulfilled criteria for having had a “complete” mystical experience was an increasing function of dose: 0 %, 5.6 %, 11.1 %, 44.4 %, and 55.6 % at 0 mg/70 kg, 5 mg/70 kg, 10 mg/70 kg, 20 mg/70 kg, and 30 mg/70 kg, respectively. Seventy-two percent of volunteers had “complete” mystical experiences at either or both the 20 and 30 mg/70 kg session. On retrospective questionnaires completed 1 or 2 months after the psilocybin session and 14 months after the last session, volunteers reported sustained positive changes in attitudes, mood, altruism, behavior, and life satisfaction. Figure 17.3 shows that most participants considered the experience to be among the five most spiritually significant experiences of their lives, including single most. Participants also endorsed various domains of change that suggest increased self-efficacy (e.g., increased self-confidence and sense of inner

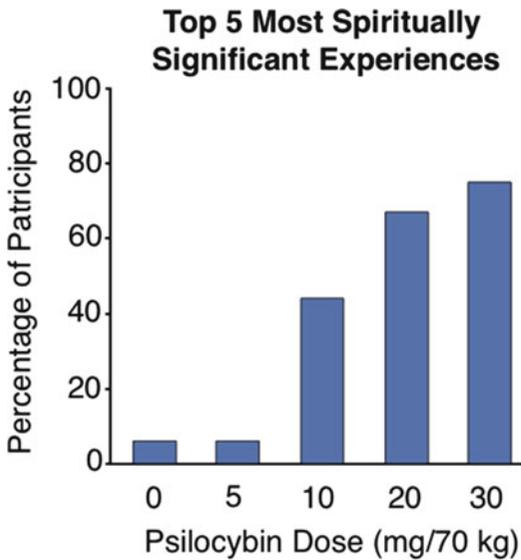


Fig. 17.3 Retrospective ratings of the spiritual significance of the psilocybin experience 1 month after sessions. Not shown, at 14 months after the last session, 94 % of participants rated the experience during the 20 and/or 30 mg/70 kg sessions to be among the top five most spiritually significant experiences of their lives, including single most (data from [29])

authority) and decreased perceived stress (e.g., decreased nervousness, increased inner peace, and ability to tolerate frustration). Ratings of the volunteers' behavior by community observers (friends, family members, colleagues at work) who were blind to drug condition were consistent with the volunteer self-ratings, indicating that the changes were real rather than imagined.

Of further relevance to the use of psilocybin in palliative treatment of existential anxiety associated with terminal illness, Griffiths et al. [29] also showed that the religious subscale of the Death Transcendence Scale was significantly increased over screening levels at both 1- and 14-month follow-up. This is notable, because questions on this scale assess a sense of continuity after death (i.e., Death is never just an ending but part of a process; Death is a transition to something even greater in this life; My death does not end my personal existence; I believe in life after death; There is a Force or Power that controls and gives meaning to both life and death).

Clinical Case Vignette of a Patient in an Ongoing Psilocybin Cancer-Anxiety Study

Roy is a 53-year-old white, American-born male. He is married, has no children, and is a college graduate. Roy is a warm, well-related, highly intelligent man with no psychiatric history or mental status alterations aside from existential distress, anxiety, and depressive affects associated with living with cancer. Both his parents are deceased, his father of cancer. Roy's sister-in-law died of cancer. He reports a fulfilling and very happy relationship with his wife that was evident when they were together in the preliminary research meetings. He cited that one of the primary sources of emotional distress in contemplating the progression and possibility of eventually dying of cancer is losing time and a future with his wife. In August 2007, Roy was diagnosed with cholangiocarcinoma, a cancer of the bile ducts involving malignant growths in the ducts that carries bile from the liver to the small intestine. In September of that same year, he underwent a partial Whipple and liver resection. His gallbladder, major bile ducts, parts of the duodenum and pancreas, and the right lobe of his liver were removed. Surgery was followed by 6 months of chemotherapy. In November 2008, a CT scan showed metastasis to the lungs.

Since February 2009, chemotherapy was implemented biweekly. He reported that this biweekly intensive chemotherapy had been extraordinarily difficult causing extreme fatigue, cognitive "cloudiness," pain, overall body aches, discomfort, and psychological distress. He required assistance during weeks when chemotherapy was administered. He has chemotherapy-induced neuropathy in the hands and feet. After 3 years of contending with the physical and psychological effects of cancer along with the debilitating effects of chemotherapy, Roy had grown increasingly anxious and depressed at which point he inquired about the psilocybin research study at New York University School of Medicine and Bluestone Center for Clinical Research.

The patient had two research study sessions, one with psilocybin and the other with placebo. Both the patient and the study monitors were blinded to the study drug administration. During one of the experimental study sessions, presumably the psilocybin session, Roy swallowed the capsule and sat on the couch listening to soft classical music and viewing picture books with images of nature. Two clinical researchers, male and female, were present throughout the session. Thirty minutes after taking the capsule, the patient was encouraged to lie down on a couch prepared like a bed with sheets, pillows, and blankets. Throughout the session, it was recommended that the patient wear eyeshades and headphones. The music played was mostly classical and instrumental. The room replicates a warm and nicely furnished living area with paintings, Asian area rug, soft lighting, flowers, books, and personal items from the patient.

At 2 h post ingestion and following a period of silence, the patient stated, “Birth and death is a lot or work” repeating it twice and began to cry softly. Over the course of the session, which lasted approximately 6 h, Roy alternated between crying softly, smiling, and laughing. For long periods of time, he lay completely still and silent sometimes uttering short sentences, sometimes with a look of awe on his face. During a 2-h period while lying completely still he stated, “it’s really so simple, it’s really so simple.” All this occurred with eyeshades and headphones on and only with minimal interaction from the monitors. Statements that Roy made during those 2 h which when compared to his written journal and post-session interviews suggest that he had a “complete” mystical experience by fulfilling all of the major criteria for such an experience (see Table 17.1). He later said to the monitors that, during this period, he experienced himself as completely safe—the safest he had ever felt—and he had an intense experience of maximal love. He indicated that he experienced existence or consciousness as continuing infinitely and it was all filled with love, it *was* love, there was neither death nor a beginning. He reported that these insights and experience gave him enormous comfort and meaning. He appeared at complete peace, but as if engaged in an active internal scene.

Approximately 5 h after he took the capsule, he sat up as the experience began to wane in its intensity. He reported that the experience was “life changing” and he was motivated to live more fully in the present moment. He repeated that the message was “so simple, it is love, it’s all about the purity of love, energy of love.” He felt as if his cancer and the prospect of dying lost significance with this new “knowledge” or awareness. He stated that he experienced love that was of indescribable intensity—“like nothing I’ve experienced here.” At one point during the experience, he reported, “I went into my lungs and saw two spots” (referring to the nodules identified by medical imaging), and said he felt “they were no big deal,” that the “cancer is not important, the important stuff is love.” He continued to discuss his newfound perspective on cancer that grew from the experience stating, “cancer is nothing to fear,” and “cancer wasn’t very important.” He stated the most important “ingredient” in life is “the purity and simplicity of love.” His wife rejoined him in the session room. They hugged, cried, and the patient stated to her, “It was amazing, amazing, I saw, I touched ... the face of God.”

Roy has continued to report and present with sustained and marked positive changes in attitude, coping, and mood 18 weeks after the session. He has characterized this experience as the most important life experience he has had second only to his marriage. Despite his cancer and uncertain future, he remarked, “I am the luckiest man on earth” and that “my quality of life is dramatically improved.” He has begun a meditation practice since this experience. He stated that “I experienced infinity that lasts forever and that is love” and that this insight and awareness have stayed with him and shaped his attitude towards others, his wife, his disease, and the world. Despite the continuing difficult chemotherapy schedule and struggling with sickness for days at a time and additional surgical procedures, he is coping in a highly effective manner. He still feels that “the cancer is irrelevant” within the context of his new awareness, although he remains highly committed and involved in his medical treatments and decisions. Weeks after the session he stated that “this is the best I’ve felt in years” and that he

felt “the happiest in his life.” While realistic about his diagnosis and prognosis, he remains committed to cultivating a positive attitude and has been able to remain emotionally connected to the imagery and existential insights of the psilocybin research session. In the end, he states that the overwhelming message was that of “love, warmth, acceptance” and connection to something greater, eternal, and sacred. The experience of transcendence and the cultivation of meaning appear to be the primary factors contributing to his insight, to the awareness drawn from the session, and to his coping with the existential and spiritual challenges of cancer.

The following are excerpts from a journal entry the patient wrote on the evening and in the days following his experience:

From here on love was the only consideration. Everything that happened, anything and everything that was seen or heard centered on love. It was and is the only purpose. Love seemed to emanate from a single point of light ... It was so pure. The sheer joy ... the bliss was indescribable. And in fact there are no words to accurately capture my experience ... my state ... this place. I know I've had no earthly pleasure that's ever come close to this feeling ... no sensation, no image of beauty, nothing during my time on earth has felt as pure and joyful and glorious as the height of this journey ... I felt very warm but pleasantly so ...

I was beginning to wonder if man spent too much time and effort at things unimportant ... trying to accomplish so much ... when really, it was all so simple. No matter the subject, it all came down to the same thing. Love. Earthly matters such as food, music, architecture, anything, everything ... aside from love, seemed silly and trivial. I was convinced in that moment that I had figured it all out (or it was figured out for me) ... it was right there in front of me ... love ... the only thing that mattered. This was now to be my life's cause. I announced, “OK, I get it! You can all punch out now ... our work is done!” But quickly I realized that no ... our work ... our existence ... our energy ... is never done ... it goes on and on without end.

I thought about my cancer ... I took a tour of my lungs. I could see some things but it was more a matter of feeling the inside of my lungs. I remember breathing deeply to help facilitate the “seeing.” There were nodules but they seemed rather unimportant ... I was being told (without words) to not worry about the cancer ... it's minor in the scheme of things ... simply an imperfection of your humanity and that the more important matter ... the real work to be done is before you. Again love.

[On the day after the experience] ... I felt spectacular ... both physically and mentally! It had been a very long time since I'd felt that good ... a serene sense of balance ... a level of contentedness, peace and happiness that lasted all day and into the evening. Undoubtedly, my life has changed in ways I may never fully comprehend. But I now have an understanding ... an awareness that goes beyond intellect ... that my life, that every life, and all that is the universe, equals one thing ... love.

Conclusion: Psilocybin Treatment Implications for Palliative Care and Psycho-Oncology

While living with advanced cancer may for some patients be a process of depression, despair, and increased distress, for others it can provide an opportunity for personal meaning, enhanced interpersonal relationships, spiritual growth, clarity, and acceptance. Frequently, a life-threatening cancer triggers a search for meaning and transcendence and an awakening of spirituality. A growing body of literature now substantiates the importance and relevance of spiritual well-being and spirituality in palliative and hospice care. For many patients, the search for meaning that is frequently triggered by end-of-life-stage cancer is a courageous and difficult journey. Ideally, dying should be viewed, not as a medical problem, but as an important and vital part of life experience with potential for discovery and meaning.

Researchers from several decades ago reported encouraging results from their early efforts developing a hallucinogen treatment model with patients suffering from the psychospiritual distress and demoralization often associated with advanced-stage cancer. More recent efforts to reexplore the judicious application of hallucinogen treatment with patients struggling with existential anxiety in the face of a life-threatening cancer diagnosis have similarly observed significant amelioration of psychological suffering. While valuable knowledge can be gleaned from clinical studies conducted from the 1950s to the early 1970s, it is necessary to conduct modern investigations utilizing state-of-the-art research methodologies in order to definitively establish

the safety and efficacy of this novel treatment. To date, contemporary studies conducted at three academic medical centers are producing positive results. While still preliminary, these encouraging reports will hopefully facilitate the development of additional investigations with the hallucinogen treatment model, particularly in patient populations refractory to conventional therapeutic approaches [28].

A unique aspect of utilizing a classic hallucinogen (e.g., psilocybin) to treat the severe psychological demoralization and existential anxiety seen in life-threatening medical illness is its seeming capacity to facilitate powerful states of spiritual transcendence that exert in the patient a profound therapeutic impact with often dramatic improvements in psychological well-being. Recently conducted research at Johns Hopkins University has demonstrated that, under carefully structured conditions in normal volunteer subjects, induction of such transcendent and mystical states of consciousness occurs in most subjects studied. This is a critical advancement in the field because, for the first time, a specific treatment has been developed that is able to reliably facilitate the emergence of a transpersonal level of consciousness that appears to have significant therapeutic value. For a patient population struggling with often overwhelming levels of existential anxiety and demoralization, such a therapeutic intervention may have the capacity to reinfuse a sense of meaning and purpose into their lives. The hallucinogen treatment model therefore offers a novel and potentially valuable approach for addressing the existential crisis often observed in cancer patients, with the potential of significantly improving overall quality of life and psychospiritual well-being for the time that remains in their lives.

References

1. Berringer K. *Der mescalinausgang*. Berlin: Springer; 1927.
2. Bleuler M. Comparison of drug-induced and endogenous psychoses in man. In: Breatly PB, Deniker R, Raduco-Thomas D, editors. *Proceedings of the first international congress of neuropsychopharmacology*. Amsterdam: Elsevier; 1958.

3. Brady MJ, Peterman AH, Fitchett G, Mo M, Cella D. A case for including spirituality in quality of life measurement in oncology. *Psychooncology*. 1999;8:417–28.
4. Breitbart W, Gibson C, Chochinov HM. Palliative care. In: Levenson JL, editor. *The American psychiatric publishing textbook of psychosomatic medicine*. Washington, DC: American Psychiatric Publisher; 2005.
5. Breitbart W, Rosenfeld B, Pessin H, Kaim M, Funesti-Esch J, Galiotta M, Nelson CJ, Brescia R. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. *J Am Med Assoc*. 2000;284:2907–11.
6. Breitbart W, Rosenfeld B, Gibson C, Pessin H, Poppito S, Nelson C, Tomarken A, Kosinski A, Berg A, Jacobson C, Sorger B, Abbey J, Olden M. Meaning-centered group psychotherapy for patients with advanced cancer: a pilot randomized controlled trial. *Psychooncology*. 2010;19:21–8.
7. Blinderman C, Cherny N. Existential issues do not necessarily result in existential suffering: lessons from cancer patients in Israel. *Palliat Med*. 2005;19:371–80.
8. Bucke RM. *Cosmic consciousness*. Philadelphia, PA: Innes & Sons; 1901.
9. Cassel EJ. The nature of suffering and the goals of medicine. *N Engl J Med*. 1982;306:639–45.
10. Chandler AL, Hartman MA. Lysergic acid diethylamide (LSD-25) as a facilitating agent in psychotherapy. *Arch Gen Psychiatry*. 1960;2:286–9.
11. Chochinov HM, Wilson KG, Lander S. Depression, hopelessness, and suicidal ideation in the terminally ill. *Psychosomatics*. 1998;39:336–70.
12. Chochinov HM, Hack T, Hassard T, Krisjanson L, McClellent S, Harlos M. Understanding the will to live in patients nearing death. *Psychosomatics*. 2005;46:7–10.
13. Chochinov HM, Cann BJ. Interventions to enhance the spiritual aspects of dying. *J Palliat Med*. 2005;8(Supplement 1):S103–15.
14. Chochinov HM, Hack T, Hassard T, Kristjanson LJ, McClellent S, Harlos M. Dignity therapy: a novel psychotherapeutic intervention for patients near the end of life. *J Clin Oncol*. 2005;23:5520–5.
15. Cohen S. LSD and the anguish of dying. *Harper's*. 1965 Sept: 69–78
16. Cohen SR, Mount BM, Tomas JN, Mount LF. Existential well-being is an important determinant of quality of life. *Cancer*. 1996;77:576–86.
17. Derogatis LR, Morrow GR, Fetting J, Penman D, Piasetsky C, Schmale AM, Henrichs M, Carnicce CL. *J Am Med Assoc*. 1983;249:751–7.
18. Doblin R. Pahnke's Good Friday experiment: a long-term follow-up and methodological critique. *J Transpersonal Psychol*. 1991;23:1–28.
19. Durkin I, Kearney M, O'Siorain L. Psychiatric disorder in a palliative care unit. *Palliat Med*. 2003;17: 212–8.
20. Edwards A, Pang N, Shiu V, Chan C. The understanding of spirituality and the potential role of spiritual care in end-of-life and palliative care: a

- meta-study of qualitative research. *Palliat Med.* 2010;24(8):753–70.
21. Fernsler J, Klemm P, Miller M. Spiritual well-being and demands of illness in people with colorectal cancer. *Cancer Nurs.* 1999;22:134–40.
 22. Field M, Cassel C, editors. *Approaching death: improving care at the end-of-life.* Washington, DC: National Academy Press; 1997.
 23. Fisher G. *Psychotherapy for the dying: principles and illustrative cases with special reference to the use of LSD.* Omega. 1970;1:3–15.
 24. Frankl VE. *Man's search for meaning.* Boston, MA: Beacon; 1984.
 25. Frankl VF. *The will to meaning: foundations and applications of logotherapy.* New York: Penguin; 1988.
 26. Galfin JM, Walkins ER, Harlow T. Psychological distress and rumination in palliative care patients and their caregivers. *J Palliat Med.* 2010;13:1345–8.
 27. Greenberg L, Lantz MS, Likourezos A, Burack OR, Chichin E, Carter J. Screening for depression in nursing home palliative care patients. *J Geriatr Psychiatry Neurol.* 2004;17:212–8.
 28. Griffiths RR, Grob CS. Hallucinogens as medicine. *Sci Am.* 2010;303(December):77–9.
 29. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berl).* 2011;218:649–65.
 30. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl).* 2006;187:268–83.
 31. Griffiths RR, Richards WA, Johnson MW, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol.* 2008;22(6):621–32.
 32. Grinspoon L, Bakalar JB. *Psychedelic drugs reconsidered.* New York: Basic Books; 1979.
 33. Grinspoon L, Bakalar JB. Can drugs be used to enhance the psychotherapeutic process? *Am J Psychother.* 1986;40:393–404.
 34. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer G. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry.* 2011;68:71–8.
 35. Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. *Int Pharmacopsychiatry.* 1973;8:129–44.
 36. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose effects study. *Psychopharmacology (Berl).* 2004;172:145–56.
 37. Henschel I, Danielson E. Existential concerns among patients with cancer and interventions to meet them: an integrative literature review. *Psychooncology.* 2009;18:225–36.
 38. Henry M, Cohen R, Lee V, Sauthier P, Provencher D, Drouin P, Gauthier P, Gotlieb W, Lau S, Drummond N, Gilbert L, Stanimir G, Sturgeon J, Chasen M, Mitchell J, Nixon Huang L, Ferland M, Mayo N. The meaning making intervention (MMi) appears to increase meaning in life in advanced ovarian cancer: a randomized controlled pilot study. *Psychooncology.* 2010;19:1340–7.
 39. Hills J, Paice JA, Cameron JR, Shott S. Spirituality and distress in palliative care consultation. *J Palliat Med.* 2005;8:782–8.
 40. Hofmann A. *LSD—my problem child: reflections on sacred drugs, mysticism and science.* Los Angeles, CA: J.P. Tarcher; 1985.
 41. Hotopf M, Chidgey J, Addington-Hall J, Ly KL. Depression in advanced disease: a systematic review. Part 1. Prevalence and case finding. *Palliat Med.* 2002;16:81–97.
 42. Hotopf M, Price A. Palliative care psychiatry. *Psychiatry.* 2009;8:212–5.
 43. Huxley A. *The perennial philosophy.* New York: Harper & Brothers; 1945.
 44. Isbell H. Comparison of the reactions induced by psilocybin and LSD-25 in man. *Psychopharmacologia.* 1959;1:29–38.
 45. Jacob P, Shulgin AT. Structure-activity relationships of the classic hallucinogens and their analogs. *NIDA Res Monogr.* 1994;146:74–91.
 46. James W. *The varieties of religious experience.* New York: Longman's Green, and Co.; 1919.
 47. Johnson MW, Richards WA, Griffiths RR. Human hallucinogen research: guidelines for safety. *J Psychopharmacol.* 2008;22:603–20.
 48. Jones JM, Huggins MA, Rydall AC, Rodin GM. Symptomatic distress, hopelessness, and the desire for hastened death in hospitalized cancer patients. *J Psychosom Res.* 2003;55:411–8.
 49. Jung C. *Psychology and religion.* New Haven, CT: Yale University Press; 1938.
 50. Kandasamy A, Chaturvedi S, Desai G. Spirituality, distress, depression, anxiety, and quality of life in patients with advanced cancer. *Indian J Cancer.* 2011;48:55–8.
 51. Kast EC. The measurement of pain, a new approach to an old problem. *J New Drugs.* 1962;2:344–51.
 52. Kast EC, Collins VJ. Lysergic acid diethylamide as an analgesic agent. *Anesth Analg.* 1964;43:285–91.
 53. Kelly B, Burnett P, Pelusi D, Badger S, Varghese F, Robertson M. Terminally ill cancer patients' wish to hasten death. *Palliat Med.* 2002;16:339–45.
 54. Kissane D, Clarke DM, Street AF. Demoralization syndrome-A relevant psychiatric diagnosis for palliative care. *J Palliat Care.* 2001;17:12–21.
 55. Kluver H. *Mescal: the 'Divine' plant and its psychological effects.* London: Keegan Paul; 1928.

56. Lajoie DH, Shapiro SI. Definitions of transpersonal psychology: the first twenty-three years. *J Transpersonal Psychol.* 1992;24:79–98.
57. Lee V. The existential plight of cancer: meaning making as a concrete approach to the intangible search for meaning. *Support Care Cancer.* 2008;16:779–85.
58. LeMay K, Wilson KG. Treatment of existential distress in life threatening illness: a review of manualized interventions. *Clin Psychol Rev.* 2008;28: 472–93.
59. Lethborg C, Aranda S, Cox S, Kissane D. To what extent does meaning mediate adaptation to cancer? The relationship between physical suffering, meaning in life, and connection to others in adjustment to cancer. *Palliat Support Care.* 2007;5:377–88.
60. Lin HR, Bauer-Wu SM. Psycho-spiritual well-being in patients with advanced cancer: an integrative review of the literature. *J Adv Nurs.* 2003;44:69–80.
61. Massie MJ. Prevalence of depression in patients with cancer. *J Natl Cancer Inst Monogr.* 2004;32:57–71.
62. Maslow AH. *Religions, values, and peak experience.* Columbus, OH: Ohio State University Press; 1964.
63. McClain CS, Rosenfeld B, Breitbart W. Effect of spiritual well-being on end-of-life despair in terminally-ill cancer patients. *Lancet.* 2003;361:1603–7.
64. McMillan SC, Weitzner M. How problematic are various aspects of quality of life in patients with cancer at the end of life? *Oncol Nurs Forum.* 2000;27:817–23.
65. Metzner R. *Teonanacatl: sacred mushroom of visions.* Verona, CA: Four Trees Press; 2004.
66. Moadel A, Morgan C, Fatone A, Grennan J, Carter J, Laruffa G, Skummy A, Dutcher J. Seeking meaning and hope: self-reported spiritual and existential needs among an ethnically-diverse cancer population. *Psychooncology.* 1999;8:378–85.
67. Moreno FA, Wiegand CB, Taitano K, Delgado PL. Safety, tolerability and efficacy of psilocybin in patients with obsessive-compulsive disorder. *J Clin Psychiatry.* 2006;67:1735–40.
68. Morita T, Tsunoda J, Inoue S, Chihara S. An exploratory factor analysis of existential suffering in Japanese terminally ill cancer patients. *Psychooncology.* 2000;9:164–8.
69. Murata H. Spiritual pain and its care in patients with terminal cancer: construction of a conceptual framework by philosophical approach. *Palliat Support Care.* 2003;1:15–21.
70. National Institute for Clinical Excellence. *Improving supportive and palliative care for adults with cancer.* London: National Institute for Clinical Excellence; 2004.
71. The National Comprehensive Cancer Network: *Distress Management Clinical Practice Guidelines in Oncology.* www.NCCN.org (2009; 2010)
72. Nelson CJ, Rosenfeld B, Breitbart W, Galietta M. Spirituality, religion, and depression in the terminally ill. *Psychosomatics.* 2002;43:213–20.
73. Nichols DE. Hallucinogens. *Pharmacol Ther.* 2004;101:131–81.
74. Osmond H. A review of the clinical effects of psychotomimetic agents. *Ann N Y Acad Sci.* 1957;66:418–34.
75. Otto R. *The idea of the holy.* London: Oxford University Press; 1923.
76. Pahnke W. *Drugs and mysticism: an analysis of the relationship between psychedelic drugs and the mystical consciousness.* Thesis presented to the President and Fellows of Harvard University for the Ph.D. in Religion and Society; 1963
77. Pahnke WN. The psychedelic mystical experience in the human encounter with death. *Harvard Theol Rev.* 1969;62:1–21.
78. Passie T. A history of the use of psilocybin in psychotherapy. In: Metzner R, editor. *Teonanacatl: sacred mushroom of vision.* El Verano, CA: Four Trees Press; 2004.
79. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. *Addict Biol.* 2002;7:357–64.
80. Presti DE, Nichols DE. Biochemistry and neuropharmacology of psilocybin mushrooms. In: Metzner R, editor. *Teonanacatl: sacred mushroom of vision.* El Verano, CA: Four Trees Press; 2004.
81. Puchalski C, Ferrell B, Virani R, Otis-Green S, Baird P, Bull J, Chochinov M, Handzo G, Nelson-Becker H, Prince-Paul M, Pugliese K, Sulmasy D. Improving the quality of spiritual care as a dimension of palliative care: the report of the consensus conference. *J Palliat Med.* 2009;12:885–904.
82. Puchalski CM, Romer AL. Taking a spiritual history allows clinicians to understand patients more fully. *J Palliat Med.* 2000;3:129–37.
83. Puchalski CM, Kilpatrick SD, McCullough ME, Larson DB. A systematic review of spiritual and religious variables in Palliative Medicine, *American Journal of Hospice and Palliative Care, Hospice Journal, Journal of Palliative Care, and Journal of Pain and Symptom Management.* *Palliat Support Care.* 2003;1:7–13.
84. Richards WA, Rhead JC, DiLeo FB, Yensen R, Kurland AA. The peak experience variable in DPT-assisted psychotherapy with cancer patients. *J Psychedelic Drugs.* 1977;9:1–10.
85. Riedlinger TJ. *The sacred mushroom seeker: essays for R. Gordon Wasson.* Portland, OR: Dioscorides Press; 1990.
86. Rodin G, Lo C, Mikulincer M, Donner A, Gagliese L, Zimmermann C. Pathways to distress: the multiple determinants of depression, hopelessness, and the desire for hastened death in metastatic cancer patients. *Soc Sci Med.* 2009;68:562–9.
87. Rodin G, Zimmermann C, Rydall A, Jones J, Shepherd FA, Moore M, Fruh M, Donner A, Gagliese L. The desire for hastened death in patients with metastatic cancer. *J Pain Symptom Manage.* 2007;6: 661–75.
88. Rousseau P. Spirituality and the dying patient. *J Clin Oncol.* 2000;18:2000–2.

89. Saunders CM. The management of terminal malignant disease. London: Edward Arnold; 1978.
90. Saunders C. Spiritual pain. *J Palliat Care*. 1988;4: 29–32.
91. Schultes RE, Hofmann A. Plants of the gods: their sacred, healing and hallucinogenic powers. Rochester, VT: Healing Arts Press; 1992.
92. Sinclair S, Pereira J, Raffin S. A thematic review of the spirituality literature within palliative care. *J Palliat Med*. 2006;9:464–79.
93. Storey P, Knight CF. UNIPAC Two: alleviating psychological and spiritual pain in the terminally ill. Gainesville, FL: American Academy of Hospice and Palliative Medicine; 1997.
94. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PLoS One*. 2010;5: 1–19.
95. Tanyi RA. Towards clarification of the meaning of spirituality. *J Adv Nurs*. 2002;39:500–9.
96. Vachon M, Fillion L, Achille M. A conceptual analysis of spirituality at the end of life. *J Palliat Med*. 2009;12:53–7.
97. Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology*. 1997;16:357–72.
98. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport*. 1998;9: 3897–902.
99. Weisman AD. Early diagnosis of vulnerability in cancer patients. *Am J Med Sci*. 1976;271:187–96.
100. Weisman AD, Worden JW. The existential plight in cancer: significance of the first 100 days. *Int J Psychiatry Med*. 1976;7:1–15.
101. Wilson KG, Chochinov HM, de Faye BJ, Breitbart W. Diagnosis and management of depression in palliative care. In: Chochinov HM, Breitbart W, editors. *Handbook of psychiatry in palliative medicine*. New York: Oxford University Press; 2000. p. 25–49.
102. Wilson KG, Chochinov HM, Skirko MG, Allard P, Chary S, Gagnon PR, Macmillan K, De Luca M, O'Shea F, Kuhl D, Fainsinger RL, Clinch JJ. Depression and anxiety disorders in palliative cancer care. *J Pain Symptom Manage*. 2007;33:118–29.
103. World Health Organization: WHO definition of palliative care. www.who.int/cancer/palliative/definition/en/ (2011). Accessed Feb 2011