

# Therapeutic Applications of Classic Hallucinogens

Michael P. Bogenschutz and Stephen Ross

**Abstract** This chapter reviews what is known about the therapeutic uses of the serotonergic or classic hallucinogens, i.e., psychoactive drugs such as LSD and psilocybin that exert their effects primarily through agonist activity at serotonin 2A (5HT<sub>2A</sub>) receptors. Following a review of the history of human use and scientific study of these drugs, the data from clinical research are summarized, including extensive work on the use of classic hallucinogens in the treatment of alcoholism and other addictions, studies of the use of LSD and psilocybin to relieve distress concerning death, particularly in patients with advanced or terminal cancer, and more limited data concerning the use of classic hallucinogens to treat mood and anxiety disorders. A survey of possible mechanisms of clinically relevant effects is provided. The well-established safety of classic hallucinogens is reviewed. To provide a clinical perspective, case summaries are provided of two individuals who received treatment in recent controlled trials of psilocybin: one being treated for alcoholism, the other suffering from anxiety and depression related to fear of death due to a cancer diagnosis. Although promising early phase research conducted from the 1950s through the early 1970s was discontinued before firm conclusions could be reached concerning the efficacy of any of the classic hallucinogens for any clinical condition, the research that was conducted in that era strongly suggests that classic hallucinogens have clinically relevant effects, particularly in the case of LSD treatment of alcoholism. In the past decade, clinical trials have resumed investigating the effects of classic hallucinogens in the treatment of existential distress in the face of cancer, and in the treatment of addictions including alcoholism and nicotine addiction. The studies that have been completed to date are not sufficient to establish efficacy, but the outcomes have been very encouraging, and larger trials,

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up to and including phase 3, are now underway or being planned. Although research has elucidated many of the acute neurobiological and psychological effects of classic hallucinogens on humans, animals, and in vitro systems, the mechanisms of clinically relevant persisting effects remain poorly understood.

**Keywords** Hallucinogens • Psychedelics • Review • Psychopharmacology • Psilocybin • LSD • Cancer • Addiction

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## 1 Introduction

In this chapter, we review historical and recent literature on the clinical use of the classic serotonergic hallucinogens, i.e., those hallucinogens that are thought to exert their effects primarily through agonist activity at serotonin 2A (5HT2A) receptors. In order to maintain this focus, we will not attempt to cover several related topics. Clinical research on non-serotonergic hallucinogens such as ketamine will not be

discussed. We also will not include discussion of MDMA and related compounds or iboga alkaloids. Although these drugs have clinically relevant effects and are subject to current clinical research, their effects and mechanisms of action are sufficiently distinct from those of the classic hallucinogens that they are best considered separately. Finally, we focus primarily on those indications for which meaningful data are available.

Although classic hallucinogens have been used by humans for at least 5 millennia (El-Seedi et al. 2005), western scientific study of hallucinogens dates to the late 1800s, when mescaline was isolated and its effects described by Arthur Heffter (Heffter 1898, 1896). In 1943, Albert Hofmann discovered the psychoactive effects of lysergic acid diethylamide (LSD) when he accidentally ingested traces of an ergot derivative he had synthesized, and confirmed the effects through self-experimentation (Hofmann 1979). He quickly recognized the therapeutic potential of LSD, as did other investigators (Busch and Johnson 1950). Following Gordon Wasson's report of hallucinogenic mushroom use by the Mazatec tribe in Mexico (Wasson 1957), Hofmann isolated psilocybin from samples of the mushrooms and synthesized it in the laboratory (Hofmann et al. 1958a, b).

Following the discovery of LSD, research on LSD and other classic hallucinogens expanded rapidly. Initially, the main focus of research was on the use of LSD as a model of psychosis (Rinkel et al. 1952). However, clinicians and clinical scientists soon began to explore the use of these unregulated chemicals in the treatment of alcohol and drug addiction, existential crisis related to death in the terminally ill, and various neurotic conditions being addressed in the context of psychodynamic psychotherapy. From the early 1950s to the mid-1960s, over 1000 scientific articles were published reporting on the treatment of over 40,000 patients with classic hallucinogens (Grinspoon and Balakar 1997).

Although classic hallucinogens were sometimes used in a strictly biological model of treatment, most clinicians and researchers combined the administration of hallucinogens with psychotherapy before, during, and/or after the drug experience, believing that the subjective experience during the drug's acute effects, and the successful integration of these experiences, was crucial to the therapeutic benefit of the treatment. The two prominent therapeutic models used in the 1950s through early 1970s were psycholytic and psychedelic therapy. Although both combined administration of hallucinogens with psychotherapy to achieve therapeutic change, they emphasized different processes in bringing about these changes (Grinspoon and Balakar 1997; Grof 2008). In the psycholytic method, low to moderate doses of hallucinogens were administered on multiple occasions to facilitate therapy that was based on traditional psychoanalytic principles, i.e., helping the patient to become aware of unconscious desires, emotions, attachments, and self-representations, and resolving intrapsychic conflicts (Leuner 1967; Buckman 1967). Therapy was conducted while the patient was under the influence of the drug. The psychedelic method used higher doses of LSD administered on no more than a few occasions, with the goal of occasioning a "peak-psychedelic" or mystical experience. These experiences are characterized by the phenomenology of unity (sense of oneness), transcendence of the ordinary experience of sense and time, sense of sacredness,

sense of deep truth or ultimate meaning (noetic quality), deeply felt positive mood, and ineffability (Pahnke 1969). It was held that such experiences often facilitated lasting change in habitual patterns of thought, behavior, experience of emotion, and even personality (Hoffer 1967; Sherwood et al. 1962). Although these two models are conceptually distinct, some clinicians and investigators used both, or created hybrid models (Grof 2008; Masters and Houston 2000).

In reaction to the cultural upheaval of the 1960s and concern about the dangers of widespread illicit use of psychedelics during that era, clinical research on hallucinogens came to halt in the early 1970s. The Controlled Substances Act placed LSD, psilocybin, and related compounds in Schedule I, and human research was not allowed to continue. Basic research continued, and many additional compounds were and continue to be discovered, most of which have never been subjected to the most basic pharmacologic study, let alone human laboratory studies or clinical trials. Illicit use for recreational, therapeutic, and/or spiritual purposes continued.

After a hiatus of about two decades, human research on classic hallucinogens resumed in the early 1990s with Rick Strassman's studies of the subjective and physiological effects of intravenous dimethyltryptamine (DMT) on normal volunteers (Strassman and Qualls 1994). Since the beginning of the twenty-first century, there has been a sharp increase in research in this area. The safety of classic hallucinogens (particularly psilocybin) in clinical research settings has been well documented (Johnson et al. 2008). The prosocial and possibly beneficial use of hallucinogens in the context of organized religious activity has also attracted attention in recent years. A considerable body of work has characterized the acute effects of classic hallucinogens on physiology, cognition, emotion, and brain function. All of these factors have motivated the resumption of research into the possible clinical applications of these drugs.

## 2 Use of Classic Hallucinogens in the Treatment of Addiction

### 2.1 LSD

The use of LSD in the treatment of alcoholism was studied extensively in the 1950s through early 1970s [For reviews see Abuzzahab and Anderson (1971); Halpern (1996); Mangini (1998); Dyck (2006); Grinspoon and Balakar (1997)]. The earliest investigations in Saskatchewan, led by the pioneering psychedelic researcher Humphrey Osmond, were based on a model which held that the LSD experience mimicked the experience of delirium tremens, and that this experience of "hitting bottom" could induce abstinence in some cases (Smith 1958). However, based on their experience and the recommendations of A.M. Hubbard, the treatment was modified to facilitate the positive experience of self-surrender, consistent with the psychedelic model (Chwelos et al. 1959). Treatment of alcoholism with LSD

became an accepted clinical treatment in Saskatchewan, and several thousand patients were treated by Dr. Osmond and colleagues using this model. Uncontrolled trials with severe, chronic alcoholic patients using a single high-dose LSD session had variable but generally encouraging results (Abuzzahab and Anderson 1971).

Controlled trials of LSD for alcoholism were underpowered with mixed results, leaving little to definitely be concluded from these studies regarding the clinical efficacy of LSD-assisted treatment for alcohol addiction (Abuzzahab and Anderson 1971; Halpern 1996; Grinspoon and Balakar 1997). However, a recent meta-analysis (Krebs and Johansen 2012) revealed consistent and clinically meaningful effects of LSD over control treatment in the six randomized trials of LSD for alcohol addiction that reported drinking outcomes (Smart et al. 1966; Hollister et al. 1969; Ludwig et al. 1969; Bowen et al. 1970; Pahnke et al. 1970; Tomsovic and Edwards 1970). Across the six studies, 325 participants received active treatment with LSD, and 211 received a control treatment. In all of the studies, LSD was administered in a single high-dose session, in doses ranging from about 210–800 mcg. At the first post-treatment follow-up, LSD-treated patients were more likely to show significant improvements in drinking outcomes (Odds Ratio = 1.96, 95% CI 1.36–2.84,  $p = 0.0003$ ). Treatment effects remained significant at 6 months. The effect of LSD treatment was homogeneous across the six studies, in spite of great variability in the psychotherapeutic components of treatment and the control treatments employed. These promising findings strongly support renewed clinical investigation of LSD for the treatment of alcoholism.

Studies were also conducted using LSD as a component of treatment for opioid addiction. Seventy “post-narcotic drug addicts” at the U.S Public Health Service Hospital in Lexington, Kentucky received a single 2–3 h therapeutic session in which they were randomly assigned to receive one of five treatments: (1) insight-oriented psychotherapy, (2) hypnotherapy (psychotherapy conducted under hypnosis), (3) LSD with no psychotherapeutic intervention, (4) LSD with psychotherapy, or (5) LSD with hypnotherapy (Ludwig and Levine 1965). At 2-month follow-up, all groups showed significant improvement on a questionnaire designed to measure various dimensions of psychopathology, with greater improvement in the group that received LSD with hypnotherapy. Drug use behavior after discharge from the hospital was not investigated. The dose of LSD used in this study (0.2 mcg/kg, or 140 mcg for a 70 kg person) was lower than the doses used in the controlled alcohol trials summarized above. In another trial, Savage and McCabe randomly assigned 78 incarcerated male heroin addicts to outpatient treatment as usual versus psychedelic therapy followed by treatment as usual (Savage and McCabe 1973). The psychedelic therapy included a single high-dose (300–500 mcg) LSD session in the context of 4–6 weeks of residential treatment that included extensive psychotherapy before and after the session. Participants who received psychedelic therapy had better outcomes during the 12-month follow-up period (25% vs. 5% continuous abstinence). The design of this study did not separate the effects of the LSD from other aspects of the residential treatment.

## 2.2 *Dipropyltryptamine*

Dipropyltryptamine (DPT) is a classic hallucinogen, structurally very similar to DMT, which has effects lasting 1–6 h (depending on the dose) when given by intramuscular injection (Grof et al. 1973b). Grof et al. reported highly significant improvements in drinking behavior and other outcomes at 6 months among 47 participants who received between 1 and 6 (mean 1.9) DPT sessions using a psychedelic treatment model (Grof et al. 1973b). A randomized trial conducted by the same group found no difference in outcome between DPT treatment, “conventional treatment” (psychotherapy similar to that received by the DPT group, but without the DPT sessions), and “routine hospital treatment” (Rhead et al. 1977). However, this study suffered from methodological limitations including high attrition both during treatment and in the follow-up period (only 40% of the randomized sample was assessed at follow-up), as well as differential dropout among the groups.

## 2.3 *Psilocybin*

The effects of psilocybin were described over 50 years ago (Isbell 1959; Leary et al. 1963), and at least 2000 individuals received psilocybin in clinical studies using the *psychedelic* and *psycholytic* models of treatment (Passie 2005). However, other than very brief reports of psilocybin used in combination with LSD (Rydzynski et al. 1968; Rydzynski and Gruszczyński 1978), the first trial of psilocybin used to treat alcoholism was completed very recently (Bogenschutz et al. 2015a). In this proof-of-concept study, ten volunteers with DSM-IV alcohol dependence received orally administered psilocybin in 1 or 2 supervised sessions scheduled 4 weeks apart. Psilocybin was administered in the context of a 12-week manualized therapy program, in doses of 0.3 mg/kg and 0.4 mg/kg. Drinking decreased significantly following psilocybin administration, and gains remained significant during 36 weeks of follow-up. The intensity of self-reported effects during the first psilocybin session at week 4 strongly predicted improvement in drinking during weeks 5–8 ( $r = 0.76$  to  $r = 0.89$ ). A double-blind efficacy trial using a similar model of treatment is currently under way, a multicenter trial conducted at the University of New Mexico School of Medicine (NCT02061293) and the New York University School of Medicine.

In the first study of classic hallucinogens administered in the treatment of nicotine addiction, a recent open-label pilot study, utilizing a model of high-dose psilocybin in combination with cognitive behavioral therapy, found remarkably positive outcomes using psilocybin in the treatment of this addiction (Johnson et al. 2014). Fifteen nicotine-dependent smokers received psilocybin (20–30 mg/70 kg in 2–3 sessions) during a 15-week course of manualized therapy. At 6-month follow-up, 12/15 (80%) were abstinent based on self-report and verified by biological measures (urinary cotinine and breath carbon monoxide). This success rate

far exceeds those seen in clinical trials of any currently available pharmacotherapy for tobacco addiction. Measures of mystical experience during psilocybin sessions and of spiritual significance and personal meaning attributed to the sessions were significantly correlated with smoking outcomes (Garcia-Romeu et al. 2014). Based on these very promising results, a comparative efficacy trial (psilocybin vs. nicotine replacement) is now being implemented at the Johns Hopkins School of Medicine (NCT01943994).

In addition, a pilot study is now under way to begin investigation of the effects of psilocybin-assisted psychotherapy in the treatment of cocaine dependence at the University of Alabama School of Medicine (NCT02037126). This study will be the first to use a classic hallucinogen in the treatment of this addiction.

## ***2.4 Mescaline and Peyote***

Mescaline, a phenylethylamine classical hallucinogen, has subjective effects very similar to the tryptamine classic hallucinogens described in this chapter (Wolbach et al. 1962). Mescaline was used interchangeably or in combination with LSD in some of the early work with the treatment of alcohol dependence (Smith 1958, 1959; Sherwood et al. 1962). However, it was never subjected to controlled trials. The peyote cactus (*Lophophora williamsii*), the San Pedro cactus, (*Trichocereus pachanoi*) and a number of other cacti contain mescaline in psychoactive quantities (Ogunbodede et al. 2010; Gabermann 1978). Peyote is used sacramentally by members of the Native American Church (NAC) (Stewart 1987) and the Huichol of northern Mexico (Meyerhoff 1974). Many authors have suggested that taking peyote in the context of NAC ceremonies helps alcoholics achieve and maintain sobriety (Kunitz and Levy 1994; Lu et al. 2009; Albaugh and Anderson 1974; Garrity 2000; Roy 1973), and NAC involvement has been integrated with addiction treatment (Albaugh and Anderson 1974). However, we were unable to find any quantitative data concerning alcohol use among NAC members, or outcomes of treatments including NAC involvement.

## ***2.5 Ayahuasca and DMT***

Ayahuasca is a hallucinogenic tea typically made by boiling the leaves of the shrub *Psychotria viridis*, containing the classic hallucinogen DMT, in combination with the vine *Banisteriopsis caapi*, containing beta carboline alkaloids (principally harmine, harmaline, and tetrahydroharmine), reversible MAO-A inhibitors that render DMT orally active by preventing GI degradation and may have significant effects of their own (McKenna et al. 1984; Callaway et al. 1996). Ayahuasca has been used by indigenous peoples of the Amazon basin for centuries, and is central to the religious practice of organized religions including the União do Vegetal and Santo

Daime (McKenna 2007). Decreased rates of alcohol misuse have been documented among members of both Brazilian and US religious groups using ayahuasca (Halpern et al. 2008; Doering-Silveira et al. 2005; Fabregas et al. 2010). Disapproval of alcohol within these religions may contribute to these low rates of substance use. Ayahuasca is currently being used in treatment centers in Peru and elsewhere for addiction and other conditions (Liester and Prickett 2012; Labate and Cavnar 2011), and many individuals have reported that ayahuasca has facilitated their recovery from addiction. However, with the exception of one observational study (Thomas et al. 2013), to our knowledge neither systematic outcome studies nor clinical trials have been conducted.

### **3 Use of Classic Hallucinogens to Ameliorate Distress Concerning Death**

#### ***3.1 Prevalence and Impact of Psychiatric Disorders (Depression, Anxiety, Adjustment Disorder) and Pain in Cancer***

Psychiatric disorders and psychological distress in individuals with cancer is common, clinically significant, and undertreated. Per year in the US, there are an estimated 1.6 million new cancer diagnoses and approximately 600,000 cancer-related deaths (Siegel et al. 2012). Additionally, in the US, there are approximately 10.5 million Americans with a current or past diagnosis of cancer, and approximately 40% will develop cancer at some point in their lives (Ries et al. 2007). The most common psychiatric disorders in patients with cancer are depressive, adjustment, and anxiety spectrum disorders, with rates of any psychiatric disorder in cancer patients as high as 40% (Zabora et al. 2001; Mitchell et al. 2011). Clinically relevant psychological distress in cancer patients is associated with a variety of poor outcomes if untreated. These include: medication non-adherence, increased emergency room visits and hospital stays, adverse medical outcomes, lower quality of life, decreased social function, increased disability, hastened desire for death, increased rates of suicide, and even decreased survival rates from the cancer (Partridge et al. 2003; Katon 2003; Brown et al. 2003; Kissane 2009; Bultz and Holland 2006; Li et al. 2012). Although a minority of patients with advanced or terminal cancer experience clinically relevant existential/spiritual distress, when it occurs its effects are highly consequential and associated with the following negative outcomes: increased pain perception, decreased quality of life, increased depressive and anxiety symptoms, increased healthcare visits, increased desire for hastened death, and increased suicidal ideation and behaviors (Puchalski 2012; LeMay and Wilson 2008). Pain is a common symptom associated with cancer syndromes, occurs in an estimated one-third to one-half of patients, and is often undertreated and contributes to a variety of adverse outcomes including

fatigue, impaired function, desire for hastened death, and suicide (Carr et al. 2002; Jaiswal et al. 2014). Completed suicide is the worst possible outcome in patients with cancer diagnoses and a diagnosis of cancer increases the risk of suicide and in some estimates increases the risk by a factor of 2 (Allebeck and Bolund 1991; Levi et al. 1991; Yousaf et al. 2005; Storm et al. 1992).

When queried, patients with advanced or terminal cancer very commonly (as high as 90% in some samples) cite spiritual/existential themes as having significant importance to them with the following types of common themes identified: meaning, purpose, hope, seeking forgiveness, increased importance of relationships including wanting a closer connection with God or one's faith, thoughts of death (El Nawawi et al. 2012; Winkelman et al. 2011; LeMay and Wilson 2008). Despite the centrality of spirituality to the needs of patients with advanced or terminal cancer who are facing death, treatment providers do a poor job of diagnosing, referring, or treating this type of distress in patients with cancer (Institute of Medicine 2008; Puchalski 2012). Conversely, increased spiritual well-being in cancer patients has been associated with: increased hope/gratitude/positive outlook relative to a cancer diagnosis, increased quality of life as death approaches, decreased depression, decreased hopelessness, and decreased desire for hastened death (Taylor 2003; Gall and Cornblat 2002; Ferrell et al. 1998; Brady et al. 1999; Nelson et al. 2002; Breitbart et al. 2000; McClain et al. 2003; Greenstein and Breitbart 2000).

### ***3.2 Spiritually/Existentially-Based Interventions for Cancer-Related Psychological Distress***

Victor Frankl (a psychiatrist and holocaust survivor) and Dame Cicely Saunders (the founder of the modern hospice movement in Great Britain) were pioneers in highlighting the importance of spiritual and existential dimensions, both as symptoms of distress and as treatment targets, in patients with terminal cancer (Frankl 1984; Saunders 1988; LeMay and Wilson 2008). Spiritual or existential distress/pain lacks a consistent nosologic framework and has been described in various ways by prominent psycho-oncologists such as: severe distress associated with events that threaten the "intactness" of a person (Cassel 1982), pain caused by the threat of extinction of an individual and meaning of the self (Murata 2003), or mental turmoil experienced by those facing death accompanied by lack of meaning or purpose, powerlessness, hopelessness, remorse, a sense of futility, grief, isolation, loss of dignity, and demoralization (Kissane 2000; Clarke and Kissane 2002).

With limited evidence from randomized controlled trials in cancer populations, currently there are no well-established evidence-based treatment algorithms to guide the optimal pharmacologic or psychosocial treatment of cancer patients with depressive and anxiety spectrum disorders; rather, treatment guidelines have had to be derived from the available research conducted in cancer populations as well as from the more extensive research in psychiatric and other medical illness populations (Traeger et al. 2012; Li et al. 2012). Also, given the relationship between

spiritual well-being and improved psychiatric outcomes in patients with advanced cancer (most importantly decreased depression, decreased hopelessness, decreased DHD and possibly decreased suicide), it would make sense to develop treatment (psychosocial, pharmacologic or combined pharmacologic–psychosocial) paradigms to specifically target such spiritual/existential distress when it manifests. While a handful of manualized existentially oriented psychotherapies have been developed to address the existential/spiritual issues faced by patients with advanced/terminal cancer, with some empirical support from clinical trials (LeMay and Wilson 2008), there are no current FDA approved pharmacologic interventions to treat this type of distress in cancer patients. However, historically and in the last 2 decades in the United States, psychedelic treatment models for end-of-life cancer distress have been empirically studied.

### ***3.3 History of Psychedelic Therapy in Death and Dying***

The first suggestions that classic hallucinogens could be useful for humans in the dying process came from Valentina Wasson and Aldous Huxley (Grof and Halifax 1977). Along with her husband Gordon Wasson, Valentina Wasson, a pediatrician and mycologist, was responsible for introducing psilocybin to western culture and medicine. After being the first known westerners to participate in a psilocybin ritual in Mexico with the Mazatec curandera Maria Sabina, the Wassons wrote about their experience in 1957 in *Life Magazine* (Wasson 1957). Valentina Wasson predicted that psilocybin would one day have medical utility for a variety of illnesses including terminal diseases. The famous writer Aldous Huxley also believed in the power of altered states and hallucinogens to help the dying. While his first wife, Maria, lay dying in 1955, he employed a hypnosis technique to alter her consciousness in an attempt to help with the dying experience and then in 1963 while dying of cancer himself, Huxley had his second wife Laura administer 100 mcg of LSD several hours before his death to facilitate his own dying process (Grof and Halifax 1977).

The first scientific exploration of classic hallucinogens as stand-alone pharmacologic interventions to help the dying in a medical setting occurred in the early 1960s with Eric Kast MD, an internist and psychiatrist at the University of Chicago Medical School. Kast was a specialist in pain medicine and became interested in studying LSD as a novel analgesic agent in patients with terminal cancer and pain syndromes by exploring LSD's ability to alter pain attention and perception (Grof and Halifax 1977). In his first paper on the topic, published in 1964, Kast conducted a blinded comparative efficacy trial of LSD (100 mcg orally) compared to Demerol 100 mg and dilaudid 2 mg in a sample of 50 gravely ill patients, mostly with terminal cancer but also including those with severe burns and infectious illnesses (Kast and Collins 1964). Kast reported that the LSD group had statistically significant reductions in pain compared to the 2 opioid groups, from 3 h post-dosing to up at least 19 h post-dosing. In addition, he noted that the patients in the LSD group appeared to display a type of detachment from the fear of dying that he thought was

useful given their grave medical conditions. Based on this observation, he extended his LSD research by administering oral LSD 100 mcg to over 200 patients with terminal cancer and pain syndromes in an open-label design and paid increasing attention to psychological phenomenon (in addition to pain perception) such as sleep, affective changes, and attitudes toward death and dying. In further published research, Kast confirmed his earlier findings by observing: decreased pain perception acutely and lasting up to 2 weeks post-dosing, improved sleep and mood, improved communication between treatment provider and patients, enhanced morale and outlook on life, reports of mystical-type experiences ('happy, oceanic feelings'), enhanced philosophical and spiritual states, and decreased fear of cancer diagnoses and death (Kast 1966). It is important to note that Dr. Kast viewed LSD treatment in his patients as a type of pure pharmacologic intervention and did not account for or introduce the well-known components of set, setting, dose titration, and psychotherapeutic preparation and integration relative to the dosing sessions (Grof and Halifax 1977).

The other significant historical research utilizing classic hallucinogens to treat psychological distress associated with advanced or terminal cancer occurred from the early 1960s to the mid-1970s at the Spring Grove State Hospital in Maryland, a research affiliate of the Johns Hopkins School of Medicine and the University of Maryland School of Medicine at the time. Starting in 1963, a group of psychiatrists, psychologists, nurses, and social workers began examining LSD-assisted psychotherapy with alcoholics. In 1965, when one of the nurses on the research team became ill with metastatic breast cancer, one of the research psychologists (Sidney Wolf) suggested that a course of psychedelic therapy might help alleviate her anxiety associated with cancer. After she underwent LSD-assisted treatment and reported relief, the researchers at Spring Grove decided to embark on research utilizing LSD-assisted psychotherapy (a pharmacologic–psychosocial paradigm) to help patients with terminal cancer and psychological distress. This research project began in 1967 and was headed by the psychiatrists Stanislav Grof and Walter Pahnke (Pahnke et al. 1969). The treatment model utilized was significantly different from the pharmacologic only model developed by Dr. Kast. It was based on Dr. Grof's LSD research in administering moderate to high doses of LSD to normal volunteers (developed while doing research at the Psychiatric Research Institute in Prague, Czechoslovakia), paying careful attention to set, setting, as well as session preparatory psychotherapy and post-session integrative psychotherapy. The treatment model drew from psychoanalytic theory as well as transpersonal psychology, and Grof commented that "Many individuals who had the experience of death and rebirth sometimes accompanied by feelings of cosmic unity independently reported that their attitudes towards dying and their concepts of death underwent dramatic changes. Fear of their own physiological demise diminished, they became open to the possibility of consciousness existing after clinical death, and tended to view the process of dying as an adventure in consciousness rather than 'the ultimate biological disaster'" (Grof and Halifax 1977). A total of 60 patients participated in the open-label experimental trial with 44 of the patients receiving LSD (200–500 mcg orally) and 19 patients receiving dipropyltryptamine (DPT) (60–105 mg IM).

Systematic, longitudinal analyses performed on a subsample of 31 participants found statistically significant pre–post reductions in the following domains: depression, anxiety, pain, isolation, and fear of death; in addition, a global index of improvement broke down as follows (29% dramatically improved, 42% moderately improved, 23% unimproved, 6% worse) (Grof et al. 1973a).

Of note, from 1965 to 1970, a limited amount of open-label research studying LSD-assisted psychotherapy took place at the UCLA School of Medicine by the psychiatrist Sidney Cohen and the psychologist Gary Fisher. Dr. Cohen, a pioneering psychedelic researcher who also understood and articulated the risks associated with classic hallucinogens, commented: “Death must become a more human experience. To preserve the dignity of death and prevent the living from abandoning or distancing themselves from the dying is one of the great dilemmas of modern medicine” (Grof and Halifax 1977).

### ***3.4 Phase II Trial: LSD-Assisted Psychotherapy for Anxiety Associated with Life-Threatening Disease***

The study of LSD-assisted psychotherapy to treat psychosocial distress associated with life-threatening illnesses has resumed with a trial recently completed in Switzerland. In this double-blind, randomized, crossover study, 12 participants received the experimental condition (LSD 200 mcg orally) and the active control (LSD 20 mcg orally) in random order, in two medication administration sessions separated by 2 months, in conjunction with psychotherapy. Safety of LSD was supported in this small cohort with no reported serious adverse events. Compared to the active control, the experimental group had significant short-term (2 month follow-up) reductions in anxiety as measured by the State-Trait Anxiety Inventory (STAI) (Gasser et al. 2014). A recent 12-month follow-up study of participants from the above trial reported sustained reductions in anxiety (as measured by the STAI), increases in quality of life, and no reports of any adverse psychological or medical sequelae (Gasser et al. 2015).

### ***3.5 Phase II and Phase III Trials: Psilocybin-Assisted Psychotherapy for Cancer-Related Psychological Distress***

Randomized controlled trials utilizing psilocybin-assisted psychotherapy to treat psychosocial-spiritual distress (depression, anxiety, existential suffering) associated with advanced or terminal cancer have resumed in the United States within the last 2 decades at UCLA, NYU, and Johns Hopkins University (JHU). At all 3 sites, the treatment model was similar and was based on the Spring Grove psychedelic

psychotherapy model, developed by Dr. Grof and colleagues. Important similarities among the three sites were as follows: (1) double-blind design methodology; (2) randomization among groups; (3) use of validated outcome measures (i.e., Hospital Anxiety and Depression Scale [HADS], Beck Depression Inventory, STAI); (4) use of exclusion criteria such as major unstable medical illnesses (e.g., cardiac/renal/hepatic failure) and major mental illness in particular psychotic spectrum illnesses (e.g., schizophrenia, bipolar I with psychotic features) or a family history of these disorders; (5) careful preparation of the participants for the experimental sessions by trained psychotherapists (usually as part of a dyad team of treatment providers) after a thorough life review and review of their cancer diagnosis narrative with an emphasis on spiritual/existential themes of distress; (6) conduct of the dosing sessions in a comfortable living room-like setting designed for maximal comfort and safety; (7) instructions to participants intended to increase the likelihood of the induction of mystical states of consciousness (participants instructed to lie down on a couch with eyeshades to reduce external visual distractions, and to focus on their inner experiences while a preselected music program played during the session); and (8) integration of the experience during 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), NYU (0.3 mg/kg); JHU (0.43 mg/kg); (2) single (UCLA, NYU) versus multiple (JHU) dosing schedules; (3) the active control (niacin at UCLA, NYU, low dose psilocybin at JHU); and (4) inclusion of nonterminally ill cancer patients (at NYU and JHU but not at UCLA).

The UCLA study results suggested an acute and short-term sustained antidepressant and anxiolytic effect associated with psilocybin versus placebo (Grob et al. 2011). Two other randomized controlled trials of psilocybin-assisted psychotherapy for patients with cancer and psychosocial distress (NYU  $N = 29$ ; Johns Hopkins  $N = 44$ ) have both recently finished and are at this time in the process of formal data analyses. Preliminary findings from both sites suggest treatment effects of the experimental psilocybin group versus the active placebo condition in terms of acute and sustained reductions in anxiety and depression as well as reports of highly salient mystical-type experiences having sustained personal and spiritual significance to participants (Ross et al. 2016; Griffiths et al. 2016).

## **4 Use of Classic Hallucinogens to Treat Mood and Anxiety Disorders**

Prior to prohibition of clinical research with classic hallucinogens in the 1970s, LSD and, to a lesser extent, psilocybin and mescaline were used in the treatment of mood and anxiety disorders (anxiety neuroses in the parlance of the day) (Grinspoon and Balakar 1997). However, we are unaware of any published outcome data from trials of any of these disorders during that era.

Francisco Moreno and colleagues conducted the first clinical trial of a classic hallucinogen in the treatment of OCD (Moreno et al. 2006). In this study, nine participants with OCD received up to 4 doses of psilocybin at least 1 week apart. The active doses were 0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg in ascending order, with a control dose of 0.025 mg/kg inserted in double-blind fashion at a random point in the sequence. Participants had significant pre–post decreases in OCD symptoms, as assessed with the Y-BOCS, lasting for 24 h or more. However, there was no significant effect of dose, i.e., higher doses did not result in more improvement than the putative control dose of 0.025 mg/kg. Because of the design of the study it is not possible to conclude whether there was a true treatment effect or only a time effect related to expectancy other sources of bias. Further controlled trials of the use of psilocybin-assisted therapeutics for OCD are clearly warranted.

Several researchers on these drugs have proposed the testing of psilocybin for this indication and proposed mechanisms by which such treatment could be effective (Baumeister et al. 2014; Vollenweider and Kometer 2010; Carhart-Harris et al. 2012b; Kraehenmann et al. 2014). Carhart-Harris et al. recently reported results of a pilot study in which 12 patients with treatment-resistant depression received psilocybin-assisted treatment including a low dose (10 mg orally) followed one week later by a high dose (25 mg orally) (Carhart-Harris et al. 2016). Depressive symptoms were markedly reduced following the high-dose session, and remained so at the final follow-up, with an effect size of  $g = 2$  at three months..

## 5 Mechanisms of Clinically Relevant Effects

Detailed reviews of hallucinogen effects at all mechanistic levels are provided elsewhere in this volume. Very little is known about how any of these persisting effects might mediate lasting therapeutic benefits. Possibly relevant mechanisms reviewed in other publications (Bogenschutz and Pommy 2012; Bogenschutz and Johnson 2016) include downregulation of 5HT<sub>2A</sub> receptors, increased expression of neurotrophic factors resulting in increased neuroplastic potential, and persisting psychological changes including changes in personality. There is some evidence that the subjective experience during drug administration may be an important determinant of therapeutic effects. Recent studies in normal volunteers have demonstrated that self-reported ratings of the “mystical” quality of the psilocybin experience significantly predicts the lasting personal significance of the experience (Griffiths et al. 2008) and personality change (Maclean et al. 2011). Recent pilot work with psilocybin for alcohol and nicotine addiction demonstrated that strong mystical-type experiences were associated with greater improvement in substance use (Bogenschutz et al. 2015b; Garcia-Romeu et al. 2014). In the alcohol study, more general measures of the intensity of subjective effects (not limited to mystical-like effects) were associated with improvement in drinking (Bogenschutz et al. 2015b). In both of the two recently published trials of psilocybin-assisted

treatment of depression and anxiety associated with a life-threatening cancer diagnosis, the degree of mystical experience during psilocybin administration was significantly correlated with improvement in mood and anxiety symptoms (Ross et al. 2016; Griffiths et al. 2016).

It is clear that the brain can be persistently (and sometimes permanently) altered and damaged by an overwhelming psychological event, as in the case of post-traumatic stress disorder (Karl et al. 2006). It has been hypothesized that under the right conditions a very intense experience occasioned by a classic hallucinogen can do the opposite, leading to lasting (and sometimes permanent) positive changes in the brain and in behavior (Garcia-Romeu et al. 2014).

## 6 Safety

As with all medications, there are risks associated with administration of classic hallucinogens. Within the context of clinical research, these risks are modest. In the reemergence of psychedelic research since the early 1990s, close to 1000 doses of psilocybin (ranging from low to high doses) have been administered safely in Europe and the United States at major academic medical centers (University Hospital of Psychiatry Zurich, Johns Hopkins University, NYU, UCLA, University of New Mexico, University of Arizona) with no reports of any treatment-related serious adverse events (SAEs), including no reported cases of prolonged psychosis or Hallucinogen Persisting Perception Disorder (HPPD) (see below sections on psychosis and HPPD) (Studerus et al. 2011); personal communications Roland Griffiths, Stephen Ross, Charles Grob, Michael Bogenschutz, Francisco Moreno 2014). In addition, approximately 200 doses of intravenous DMT were administered at the U of New Mexico to normal participants in the early 1990s without any SAEs, and LSD has now been administered to approximately two dozen research participants in Europe in the last year (Switzerland, England) without any SAEs reported (Gasser et al. 2014, 2015; Carhart-Harris et al. 2014a). The key commonality among all these studies is the careful attention to screening, set, setting, dose, and preparation and integration before and after drug administration.

### 6.1 *Medical Toxicity*

Classic hallucinogens possess remarkably low physiological toxicity and are not associated with end organ damage, carcinogenicity, teratogenicity, lasting neuropsychological deficits, or overdose fatalities (Johnson et al. 2008; Hasler et al. 2004; Cohen 1960; Halpern et al. 2005, 2008; Strassman 1984; Gable 2007; Barbosa et al. 2012). The classic hallucinogens produce sympathomimetic effects and can moderately increase pulse as well as diastolic and systolic blood pressure, although this has not been associated with cardiac, neurologic or other organ

damage. (Hasler et al. 2004; Passie et al. 2002; Griffiths et al. 2006; Grob et al. 2011). Common physiological side effects of the classic hallucinogens include: mydriasis, blurry vision, dizziness, tremors, weakness, paresthesias, and increased deep tendon reflexes (Johnson et al. 2008).

## 6.2 *Psychiatric Toxicity*

### 6.2.1 *Acute Effects*

The acute psychological and behavioral effects of the classic hallucinogens are greatly influenced by set (personality and expectations of the individual), setting (environmental conditions and context of use) and dose, with the factors combining to influence the valence (positive or negative) of the experience. Affective changes can range from euphoric or ecstatic spiritual states to anxiety, terror and panic. Perception is intensified and amplified with alterations in time, space, and boundaries between self and others. Synesthesia (the mixing of various sensory stimuli, e.g., hearing colors) is common. Sensory illusions (e.g., walls breathing) are common, and frank hallucinations can occur, though less frequently. Thought processes are loosened, with effects ranging from increased creativity to thought disorder. Cognition is altered and can range from sudden and deeply felt insight (“noetic” effect) to confusion and disorientation (Wilkins et al. 2014). The sum total of the experience can range from positive mystical-type experiences associated with enduring positive changes in affect/cognition/behavior (Griffiths et al. 2008) to very unpleasant experiences dominated by fear and dysphoria. Severe adverse psychological experiences (‘bad trips’) tend to occur in poorly prepared individuals who use the substance in an uncontrolled setting and who have psychological risk factors (e.g., severe mental illness, recent trauma). These experiences typically include anxiety, panic, dysphoria, depersonalization, paranoid ideation, fear that the experience will never end, and fear of losing one’s mind. Despite such adverse reactions, users usually retain insight into the fact that their symptoms are related to drug ingestion, and they usually respond to verbal reassurance. Classic hallucinogens can acutely engender frank psychosis marked by hallucinations, thought disorder and delusions, although this is rare in individuals without underlying psychotic spectrum illness (Wilkins et al. 2014). Such adverse psychological experiences can potentially lead to dangerous behavior toward self or others especially when used by vulnerable individuals without proper preparation and supervision. (Strassman 1984). In a review of LSD research conducted during the 1950s including thousands of research participants, the reported suicide attempt and completed suicide rates were very low at 1.2 and 0.4, respectively, per 1000 psychiatric patients, and no completed suicides or attempts among 1200 non-patients (Cohen 1960).

## 6.2.2 Prolonged Effects

### Psychosis

The serotonergic hallucinogens have long provided evidence implicating the serotonergic system, as one of several neurotransmitter systems (the other main ones being the dopaminergic, glutamatergic, and endocannabinoid systems), in the pathophysiology of schizophrenia and related psychotic disorders (Murray et al. 2013; Beringer 1923; Halberstadt and Geyer 2013; Szara 1956). After LSD became widely used as a recreational drug in the 1960s, it was increasingly recognized that its use could trigger psychosis, a common example being first used by a teenager or young adult (during the age of typical onset of schizophrenia) who developed the onset of schizophrenia and went on to develop a chronic course of the illness. However, although it is the case that classic hallucinogen use can cause transient psychotic-like positive symptoms in normal volunteers and can provoke sustained psychosis in vulnerable people with psychotic spectrum illnesses (i.e., schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features), there is little to no evidence linking classic hallucinogen use to prolonged psychosis in individuals without a psychotic diathesis (Ross and Peselow 2012). Estimates of the prevalence of LSD-induced psychosis as assessed by early psychedelic researchers and clinicians (many working with and administering LSD to psychiatric *inpatients*) were as follows from 2 reports: 0.8/1000 research volunteers (a single case out of 1250, where the volunteer was the identical twin of an individual with schizophrenia) and 1.8/1000 psychiatric patients (seven cases out of approximately 3850 patients) (Cohen 1960); and 0/170 research volunteers and 9/1000 psychiatric patients (37 out of 4300 patients) (Malleon 1971). A recent cross-sectional study evaluating data taken from years 2001–2004 of the National Survey on Drug Use and Health with a sample of 130,152 (representing a random sample of the US population living in households) did not find any significant associations between lifetime use of any psychedelic or past year use of LSD and increased rates of any psychiatric symptoms (including psychosis) or mental health outcomes (Krebs and Johansen 2013). Given that the classic hallucinogens are known to exacerbate psychosis in individuals with psychotic spectrum illnesses, in the modern era of psychedelic research in the last 20 years, all human trials at academic medical centers in the US and Europe have excluded individuals with psychotic spectrum illness or those who are at risk of such illnesses because of a known positive family history of psychotic illnesses. As mentioned above, no cases of persisting psychosis have been reported across these studies.

### Hallucinogen Persisting Perception Disorder (HPPD)

Descriptions of persisting perceptual abnormalities (“flashbacks”) following the use of the SHs were first described over 100 years ago with mescaline (Ellis 1898). The next reports of this condition occurred in the 1950s and 1960s, mostly in relation to

LSD ingestion, and described prolonged changes in normal perception that were similar in nature to the perceptual effects experienced under the influence of the hallucinogen, persisting subacutely (weeks to months), and chronically after use of the hallucinogen (Cooper 1955; Smart and Bateman 1967). In addition to the classic hallucinogens, cases of persisting perceptual disturbances have been reported and attributed to the use of MDMA, ketamine, and cannabis (Litjens et al. 2014). The symptoms can occur spontaneously or be triggered by stress, anxiety, exercise, or use of another drug (e.g., cannabis) (Abraham 1983). The term “flashback” has sometimes been used synonymously with HPPD but is distinguished from HPPD in that flashbacks do not necessarily persist or cause clinical distress or impairment, and can even be experienced as pleasurable by the individual (Lerner et al. 2002; Frecska and Luna 2006). Unlike flashbacks, HPPD tends to be recurrent with a continuous or intermittent/paroxysmal pattern of symptoms that is either a slowly reversible or a chronic permanent condition experienced as highly distressing by patients (Lerner et al. 2002). It is important to note that HPPD is not a psychotic spectrum illness, and patients have intact reality testing and awareness that the illusions and hallucinations are not real.

Although the exact prevalence of HPPD is unknown due to a lack of rigorous epidemiologic studies, it is thought to be a rare (but highly distressing) condition given the relatively few cases reported out of the tens of millions of doses of hallucinogens used over the last 50 years, and it appears to be significantly less common in research settings with careful screening and preparation (Studerus et al. 2011; Johnson et al. 2008; Halpern and Pope 2003). In two recent web-based surveys of hallucinogen users, visual distortions and illusions were quite commonly reported, but only 4–11% were distressed by these experiences (Baggott et al. 2011; Carhart-Harris and Nutt 2010). Data from the above-mentioned population study derived from the 2001–2004 National Survey on Drug Use and Health found no association between lifetime use of psychedelics or past year use of LSD and past year visual phenomena consistent with HPPD (Krebs and Johansen 2013).

### Addictive Liability of the Serotonergic Hallucinogens

A commonality among all drugs that are capable of producing addiction is their ability to substantially increase extracellular DA levels in the nucleus accumbens, either directly by enhancing DA transmission through reuptake inhibition or facilitating presynaptic DA release (e.g., cocaine, amphetamine, MDMA), or by indirect GABAergic, cholinergic or glutamatergic mechanisms that affect DA-cell firing (e.g., alcohol, sedatives, opioids, cannabis, nicotine, NMDA antagonists such as PCP) (Baler and Volkow 2006).

In contrast to all other drugs of abuse, classic hallucinogens are not considered to be capable of producing sufficient reinforcing effects to produce addiction (O’Brien 2001). Animal models (i.e., self-administration, conditioned place preference) have failed to reliably demonstrate addictive liability of the classic hallucinogens, suggesting that they do not possess sufficient pharmacologic properties to initiate or

maintain dependence (Nichols 2004). Almost all of the classic hallucinogens (with the exception of LSD) (Watts et al. 1995; Giacomelli et al. 1998) lack affinity for DA receptors or the DAT and do not directly affect dopaminergic transmission. Interestingly, despite the evidence that classic hallucinogens have been shown to increase DA transmission in striatal areas in humans, they fail to significantly activate the nucleus accumbens in PET imaging studies consistent with the lack of evidence linking classical hallucinogens with dependence syndromes (Vollenweider et al. 1998, 1999; Geyer and Vollenweider 2008). Although problematic or disordered use of classic hallucinogens certainly occurs, it is uncommon, and very rare in people over 25 years of age (Substance Abuse and Mental Health Services Administration 2013). The National Institute on Drug Abuse does not consider the classic hallucinogens drugs of “addiction” as they do not produce compulsive drug-seeking behavior or chronic addiction, and most recreational users decrease or stop their use over time (National Institute on Drug Abuse 2014).

## 7 Case Studies

Because the process of treatment with classic hallucinogens is so different from other pharmacotherapies, it may be useful to provide descriptions of the process in specific cases. Below we provide two brief case reports from the authors’ clinical trials: one of a patient treated for alcohol dependence, the other of a cancer patient struggling depression and anxiety in relation to a cancer diagnosis. Details of these cases have been altered to obscure the identity of these individuals.

### 7.1 *Psilocybin-Assisted Treatment of Alcoholism*

C is a 59 year-old divorced mother of 2 who had struggled with alcohol since age 15. Her drinking had led to problems including recurrent physical violence, multiple arrests, poor work history, and intermittent homelessness. She had suffered severe abuse in the context of relationships with partners who also drank, including being beaten unconscious and suffering from intracranial bleeding on at least one occasion. She had made several past attempts to stop drinking, with little success. When she volunteered for the psilocybin trial, she had been sober for 11 days, and had been drinking 7 out of the past 84 days, an average of 16.9 standard drinks per drinking day.

During the preparatory phase of treatment in the study, she stated a goal of total abstinence, and rated the importance of abstinence as high and her readiness for abstinence as high, but her confidence in achieving it was low. She said that she wanted to understand why she drank, and hoped that this would help her stay sober. She listed God’s will, forgiveness, humility, (to be) loved, and self-control as her

most important values, and saw clearly that her drinking was in conflict with these values.

During her first psilocybin session, she reported that she experienced powerful feelings of sorrow and remorse regarding the course of her life, and particularly concerning her perceived failures as a parent as a result of her drinking. This experience was quite painful, and she believed that she was sobbing uncontrollably during much of this time, although she was actually lying quietly on the couch at the time. After the session, she felt a sense of relief, and said that she had been able to let go of these feelings and experience a sense of forgiveness. She was hopeful that the experience would help her stay sober, and had no desire to drink after the session.

C remained sober between the first and second psilocybin session. During the second session, she reported that she experienced a visual image of a small child lying “broken” on the floor. She realized that this child was her, and experienced herself as a 3-year-old child, devastated by abandonment by her father, an issue that she had not discussed in the preparatory sessions. After this, she began to perceive a white light, which she called “God’s healing light,” and felt a profound sense of love. She felt that she had been healed by this experience, and that she now felt “whole” and worthy of love.

In discussing these experiences afterwards, C said that she thought her drinking had been an attempt to escape the painful feelings of being unworthy of love, as well as the painful feelings of shame and loss related to her life as an alcoholic. She had avoided these feelings, believing that she would “fall apart” if she faced them. Following the sessions, she now felt that she was strong enough to face these feelings, and that she was a whole person, worthy of love. At her most recent follow-up, 5 months after the first psilocybin session, she remained abstinent and continued to feel that her life had been transformed, in spite of the unexpected death of a close family member during the interim.

## ***7.2 Psilocybin-Assisted Treatment of Cancer-Related Psychological and Existential Distress***

E is a 22-year-old woman, a first year law student, with recent diagnosis of leukemia. She had no prior medical or psychiatry history. She was treated successfully for her leukemia with chemotherapy and was told by her oncologist that she had a very good prognosis and was likely cured of her cancer. For the first 6 months following diagnosis and treatment, she did not experience any adverse psychological effects of the cancer diagnosis. However, at the 6-month point of remission, E started to become frightened that the cancer could recur. Even though she understood the good prognosis, she experienced increasing anxiety about the cancer returning and what that would mean for her. These thoughts continued to get worse to the point where E started experiencing panic attack-like events related to an acute

fear of death. She had always thought of death as a distant event, something that she would not have to contend with for decades. However, the cancer provoked a kind of crisis and she began to feel that there was now a short distance between herself and death. She began to experience a dysphoric and anxious mood accompanied by anhedonia, poor concentration, preoccupation with death, and a desire for a hastened death because she felt that the end was imminent. From a Catholic faith background, she became angry at God for allowing her to get cancer and started for the first time in her life to have doubts about the existence of God. She stopped attending church and felt she had lost access to the nurturing parts of her religion and spirituality. She told her oncologist about these symptoms, and her oncologist referred her to the NYU Psilocybin Cancer Project. E was a casual user of alcohol and had no prior use of other drugs including hallucinogens and marijuana. She was intrigued by the use of psilocybin to treat anxiety but admitted that she was skeptical that it would actually do anything to decrease her anxiety or fear of death related to her cancer diagnosis. She felt it was worth a try given her level of distress and because she trusted her oncologist's judgment.

E underwent her first dosing session and happened to be randomized to the group that received psilocybin (0.3 mg/kg) first. On the day of the session, she reported having some trouble sleeping the night before and being somewhat apprehensive about the dosing session. She wanted to make sure that she would return to normative reality when the session ended. Her treatment dyad team did some deep breathing with her before the session and reassured her of all the ways the team would address any difficult or anxious psychological experiences. E received her psilocybin capsule at 9 AM. The treatment team checked in every hour to assess E's mental state. For the first 3 h, E reported nothing suggestive of a psychoactive experience (unusual for those that receive psilocybin whose effects usually are experienced in the first hour post-dosing). She told the dyad team that she was sure she must have gotten the placebo. At approximately 12:30, E sat up and took off her eye shades. She reported that the music sounded "trippy." When the dyad team inquired more, she said that she felt anxious and wondered if she would feel normal again. After verbal reassurance, E lay back down and placed the eye shades on. At approximately 2 PM, she sat up and reported the following visions: she journeyed back to parts of her childhood and came upon multiple scenes of her and her family (2 parents, and younger brother) joined together in laughter and love that made her feel a sense of unity and support; she reported a scene where she saw herself standing in front of a hospital and saw a cauldron of black, hot smoke circling inside of her body (which she interpreted as her cancer), followed by her boyfriend and family forming a loving circle around her which caused the black smoke inside of her to disappear outside of her body and into the sky (she interpreted this as a cathartic experience of the fear of cancer leaving her); she reported seeing her cancer-riddled body die in front of her eyes while the treatment providers and a transcendental entity together solved a complicated mathematical equation (she interpreted this as God and the treatment team working together to figure out the biological nature of her cancer-related anxiety). At the end of the experience, E declared that she felt "re-born" and freed from the anxiety and

fear of death caused by her cancer diagnosis. Her scores on the main outcome measures of anxiety and depression (i.e., HADS, STAI, Beck Depression) dropped dramatically from high clinically significant values at baseline to almost zero, 7-h post-dosing with psilocybin. Her follow-up distress scores on all of these scales remained close to zero for the next 6-months until the final follow-up point. It is now 1.5 years after her treatment, and she continues to report no anxiety or distress associated with her cancer diagnosis. She is flourishing as a law student and reports a sense of calmness and psychological well-being that she continues to attribute to the psilocybin dosing experience. She has taken up a meditation practice and still can remember salient aspects of the experience that have stuck in her memory.

## 8 Discussion

Although classic hallucinogens have been used by humans for millennia, known to science for over a century, and subjected to extensive basic research for decades, the rigorous study of their clinical use is in its infancy. Promising early phase research conducted from the 1950s through the early 1970s was discontinued before any conclusions could be reached concerning the efficacy of any of the classic hallucinogens for any clinical condition. However, the research that was conducted in that era strongly suggests that classic hallucinogens have clinically relevant effects, particularly in the case of LSD treatment of alcoholism. In the past decade, clinical trials have resumed investigating the effects of classic hallucinogens in the treatment of existential distress in the face of cancer, and in the treatment of addictions including alcoholism and nicotine addiction. The studies that have been completed to date are small, and not sufficient to establish efficacy. However, they strongly suggest that the administration of psilocybin in the therapeutic context produces therapeutic benefit in both patients with addictions and cancer patients with existential distress. Only time will tell if hallucinogen-assisted treatments for addiction and cancer-related psychological/existential distress will prove to be safe and effective in large scale double-blind, placebo-controlled clinical trials. If the data supports their efficacy, they would constitute a novel psychopharmacologic–psychosocial treatment paradigm to treat these disorders.

The clinical safety of classic hallucinogens, well documented by extensive research in the 1950s through early 1970s, has been confirmed in the rigorous clinical work which began again in the 1990s. Although physical and psychological risks exist, they can be minimized through the safety procedures followed in recent clinical studies, including careful screening of participants, thorough training of therapists, close attention to dose, set, and setting, preparation, support and monitoring, and follow-up of participants, and predetermined procedures for dealing with medical and psychiatric emergencies (Johnson et al. 2008). Since the resumption of clinical research with classic hallucinogens in the 1990s to date, there have been no reported treatment-related serious adverse events or cases of persistent harm to participants. Although no medication is harmless, this fact is encouraging.

Future research must continue to make every effort to maximize safety. Should a classic hallucinogen be approved for clinical use in the future, it will also be critical that rigorous safety procedures be built into the approved conditions of clinical use.

Although research has elucidated many of the acute neurobiological and psychological effects of classic hallucinogens on humans, animals, and in vitro systems, the mechanisms of clinically relevant persisting effects remain poorly understood. At this point, the causal mechanisms with the strongest support are intensely memorable and personally meaningful experiences, particularly those of a mystical quality. Much more work is necessary to better understand the mechanisms by which such experiences, and their neurobiological correlates, can lead to persisting psychological, behavioral change, and neurobiological change.

Given the early stage of clinical research on classic hallucinogens, relative to other classes of drugs, many avenues of research could be explored that would advance the field. Among them, several topics appear particularly promising. First, well-designed and adequately powered efficacy trials should be conducted testing the efficacy of classic hallucinogens (particularly psilocybin and LSD) for the indications where the existing evidence strongly suggests efficacy: addiction to drugs including alcohol and nicotine, and existential crisis in the face of death among cancer patients or in other patients facing life-threatening illness. Phase II trials for psilocybin-assisted psychotherapy for cancer-related psychological distress were recently completed and a phase III trial for this same indication is currently being planned which potentially could lead to the historic partial rescheduling of psilocybin to become a prescribable medication. Furthermore, controlled trials are already under way testing the efficacy of psilocybin in the treatment of alcohol use disorders, tobacco addiction, and cocaine addiction.

Second, a broader range of classic hallucinogens and possible indications should be studied. The encouraging results that have been seen with classic hallucinogen treatment across alcohol, nicotine, and opioid dependence suggest the possibility that other chemical and behavioral addictions may also respond to treatment with these agents. While it cannot be assumed that addictions are interchangeable or that classic hallucinogen all have comparable efficacy in the treatment of addiction, it seems reasonable to pursue additional indications. One such possibility will be explored in a pending trial that will be the first to evaluate the effects of psilocybin-assisted treatment of cocaine dependence. Given the remarkable short-term efficacy of ketamine (an NMDA antagonist hallucinogen with biological and psychological effects overlapping those of classic hallucinogens), in the treatment of depression (Serafini et al. 2014), the efficacy of classic hallucinogens in depression should be studied as well (Baumeister et al. 2014).

Third, it will be important to investigate the mechanisms of action of classic hallucinogens in the treatment of specific disorders. Although neuroimaging studies have begun to characterize the acute effects of psilocybin on brain function (Tagliazucchi et al. 2014; Carhart-Harris et al. 2012a, 2013, 2014b; Kraehenmann et al. 2014), the persisting effects of classic hallucinogens on brain function have not been characterized. Changes in 5HT<sub>2A</sub> receptors, serotonin transporters, neurotrophic factors, and other relevant brain chemicals have not been measured in the

context of clinical studies of classic hallucinogen treatments. Although the small trials that have been conducted have provided some information concerning the psychological processes that may underlie behavior change, future trials should continue to characterize both the acute medication effects and the longer term psychological changes that are associated with desired clinical outcomes.

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