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## THE USE OF PSILOCYBIN IN PATIENTS WITH ADVANCED CANCER AND EXISTENTIAL ANXIETY

CHARLES S. GROB

### INTRODUCTION

Major advances in the medical and surgical treatments of many types of cancers have occurred over the past several decades. Our knowledge of pathophysiological mechanisms of tumor genesis and growth has evolved significantly, along with new and innovative treatment regimens, some of which have had success in prolonging survival time. Unfortunately, addressing the psychological and spiritual needs of patients with end-stage cancers has often received far less attention. Even with the lengthening life span of some patients, the final months for individuals dying of cancer are often burdened with extreme levels of suffering, both physical and mental. Along with the physical pain often associated with the spread of cancer, the patient approaching death frequently encounters variable degrees of anxiety, depression, and psychological isolation. The inevitable and impending death often provokes feelings of defeat, helplessness, and despair not only in the patient but also in family members and even among attending medical personnel. Our modern system of medical care is often successful in increasing the amount of time a terminal cancer patient has to live, but very little is customarily done to enhance the quality of intra- and interpersonal life during the patient's final months (Derogatis et al. 1983; Cochirov 2000).

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a mystical experience. Pahnke reported that two-thirds of his treated cancer patients reported improvement, with decreased "tension," depression, pain, and fear of death. In the *Harvard Theological Review*, Pahnke described that he observed

an increase in serenity, peace and calmness. Most striking was a decrease in the fear of death. It seems as if the mystical experience, by opening the patient to usually untapped ranges of human consciousness, can provide a sense of security that transcends even death. Once the patient is able to release all the psychic energy which has tied him to the fear of death and worry about the future, he seems able to live more meaningfully in the present. He can turn his attention to the things which have the most significance in the here and now. This change of attitude has an effect on all the people around him. The depth and intensity of interpersonal closeness can be increased so that honesty and courage emerge in a joint confrontation and acceptance of the total situation. (Pahnke 1969, p. 12)

One of the final studies exploring the therapeutic potential of hallucinogens before clinical research was shut down for a thirty-year hiatus was led by Stanislav Grof, one of the most accomplished psychiatric investigators in Europe and the United States from the 1950s to early 1970s. Before his program was terminated by political pressure, Grof studied 60 terminal patients with either LSD or dipropyltryptamine, of whom 29% improved dramatically and 41.9% moderately. Grof described that "probably the most surprising of the findings were the changes in the attitude toward death and in the concept of death itself. Increased acceptance of death usually followed sessions in which the patients reported deep religious and mystical experiences, whereas improvement of the emotional condition of the patients and relief of pain was frequently observed even after sessions with predominantly psychodynamic content" (Grof et al. 1973, p. 143).

## PSILOCYBIN

Psilocybin is 4-phosphoryloxy-*N,N*-dimethyltryptamine and occurs in nature in many species of mushrooms, including the genera *Psilocybe*, *Conocybe*, *Gymnopilus*, *Panaeolus*, and *Stropharia*. Psilocybin mushrooms grow in many 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). Employed for religious purposes by the Native peoples, the use of mushrooms was condemned under the laws of the Holy Inquisition in the early 17th century following European conquest and domination of the New World. Driven underground by repression and forced conversion to Christianity, the ceremonial use of psilocybin-containing mushrooms was believed to be extinct until their "rediscovery" in 1955 by New York banker and amateur mycologist R. Gordon Wasson. Permitted to attend a healing ritual conducted in the hills of Oaxaca,

Mexico, by a native curandera, Maria Sabina, Wasson was allowed to ingest samples of a mushroom later identified as *Psilocybe mexicana*. Wasson would later write an account of his profound experience with the legendary magic mushrooms of Mexico for Life magazine, in 1957, and in so doing stimulated interest among other Westerners in this previously unknown phenomenon (Riedlinger 1990; Metzner 2004).

Several years after Wasson's discovery, specimens sent to the Basel, Switzerland, laboratory of Sandoz medicinal chemist, Albert Hofmann, yielded the isolation of the two active indole alkaloids, identified as psilocybin and psilocin. As is the case with LSD and mescaline, psilocybin is an extremely potent agonist at 5-HT(2A) and 5-HT(2C) receptors, and their binding potency to these receptors is directly correlated with their human potency as hallucinogens (Presti and Nichols 2004). Although not provided the extensive degree of investigation received by the prototype hallucinogen, LSD, psilocybin was subjected to a variety of research studies during the 1960s employed to establish its psychopharmacological profile of action. Psilocybin was determined to be active in the 10 to 20mg range and was found to be about thirty times stronger than mescaline and approximately 1/200 as potent as LSD. The experience lasts from four to six hours. Physiologically, psilocybin was observed to be similar to LSD but gentler. Psychological effects were also observed to be very similar to LSD, with psilocybin evaluated as more strongly visual, less intense, more euphoric and with fewer panic reactions and less chance of paranoia than LSD.

### Contemporary Psilocybin Research

After almost three decades of inactivity, the hallucinogen treatment model is again being examined in formal psychiatric settings. Essential physiological and psychological examinations of the effects of psilocybin have been conducted in healthy normal volunteer subjects at the Heffter Research Center and the University of Zurich in Switzerland. Effects on cardiovascular function, blood chemistries, and neuroendocrine secretion were all determined to be modest and within normal limits. Overall, the investigators concluded that psilocybin was not hazardous to somatic health (Hasler et al. 2004). A recent study conducted at Johns Hopkins administered high dose (30mg/70kg) psilocybin to 36 healthy volunteer subjects, with no sustained deleterious physiological or psychological effects. The investigators also corroborated findings from previous decades that psilocybin could reliably catalyze mystical experiences in prepared subjects (Griffiths et al. 2006).

Groundbreaking work has also been done, exploring the effects of psilocybin on the central nervous system. Franz Vollenweider and his colleagues at the University of Zurich have administered psilocybin to research subjects undergoing PET (positron emission tomography) scans of their brain. These PET studies found that psilocybin produced a global increase in cerebral metabolic rate of glucose with significant and most marked increase in the frontomedial and

frontolateral cortexes, anterior cingulate cortex, and dorsolateral prefrontal cortex. These findings suggest that psilocybin-induced hyperfrontality in patients with OCD and derealization phenomena may be related to the neurophysiologic effects of hallucinogens on the functional substrate of major depressive disorder (Vollenweider et al. 2006).

The first approved psilocybin treatment in the United States was recently reported in the direction of Francisco Moreno with severe, refractory OCD. Due to its difficulty, research has established an important precedent for its use. In 2006, Chapter 6, this volume also describes how investigators are exploring psilocybin for the recognition that the drug may be a better system should theoretical and unpublished research also published and unpublished research (the apparently successful use of psilocybin and LSD) to treat OCD. Two pilot studies were that psilocybin may be associated with improved outcomes (Moreno et al. 2006; also see

### The Harbor-UCLA Cancer Anxiety Proj

Since 2004, work has been done at the Los Angeles Biomedical Research Institute. The efficacy of psilocybin in anxiety disorders in this population is the first approved study in more than 40 years. A double-blind, placebo-controlled study in the 1960s had not found the same methodological standards of scrutiny. Each subject in the study was participating in two research sessions, psilocybin (0.2mg/kg) and placebo. The treatment sessions are supervised by research staff and are voluntary. For these reasons, it was decided that the experimental medicine for a threatening disease, would

frontolateral cortexes, anterior cingulate, and temporomedial cortex. This metabolic hyperfrontality in particular may be related to states of ego disintegration and derealization phenomena. Such work not only elucidates the range of neurophysiologic effects of hallucinogens but also provides valuable knowledge of neurotransmitter function needed to advance our knowledge of the neurobiological substrate of major mental illnesses and their psychopharmacological treatment (Vollendweider et al. 1997).

The first approved psilocybin treatment study in several decades in the United States was recently conducted at the University of Arizona under the direction of Francisco Moreno. Examining the effects of psilocybin on patients with severe, refractory OCD (obsessive-compulsive disorder), a disorder notorious for its difficulty responding to conventional treatments, Moreno's study has established an important precedent demonstrating that it is possible once again to conduct sanctioned clinical treatment research with hallucinogens (see also Chapter 6, this volume). Interestingly, what motivated these mainstream investigators to explore psilocybin's potential efficacy treating OCD was both the recognition that the drug's specific effects on the serotonergic neurotransmitter system should theoretically ameliorate the disorder and the examination of published and unpublished anecdotal accounts over the past half-century describing the apparently successful self-medication use of hallucinogens (psilocybin and LSD) to treat OCD. The conclusions of the recent University of Arizona pilot study were that psilocybin is safe and well tolerated in subjects with OCD and may be associated with "robust acute reductions" in core OCD symptoms (Moreno et al. 2006; also see Chapter 6, this volume).

#### **The Harbor-UCLA Psilocybin Treatment of Cancer Anxiety Project**

Since 2004, work has been under way at Harbor-UCLA Medical Center and the Los Angeles Biomedical Research Institute studying the potential therapeutic efficacy of psilocybin in advanced-stage cancer patients with anxiety. Given that this is the first approved study using a hallucinogen as treatment for this patient population in more than thirty years, it was considered prudent to include a double-blind, placebo-controlled research design. Although investigators from the 1960s had not found the need for placebo controls, adhering to contemporary methodological standards at this point in time is necessary to pass scientific scrutiny. Each subject in this approved study functions as his or her own control, participating in two research sessions, on one occasion receiving the active medicine, psilocybin (0.2 mg/kg), and the other occasion receiving a placebo. Actual treatment sessions are spaced several weeks apart, and neither the subject nor the research staff is aware of what order the sessions will occur. For ethical reasons, it was decided that all subjects would have an opportunity to receive the experimental medicine and that none of the subjects, all with grave life-threatening disease, would be denied the active treatment.

Prospective subjects are rigorously screened to exclude those with central nervous system involvement, either primary or metastatic disease to the brain, severe cardiovascular illness, and lifetime history of severe mental illness. Several preparatory meetings are arranged for the subject to establish rapport with the investigators and to examine the intention and purpose of their participation in the treatment study. Sessions take place on the GCRC (General Clinical Research Center) at Harbor-UCLA Medical Center, where a single room has been allocated and prepared for the study. Sessions are six hours in length, during which time the investigators remain continuously with the subject. The treatment model is similar to that developed by the Spring Grove research team in the 1960s and early 1970s, with the subject instructed to lie down on a bed with eyeshades on and listening with headphones to preselected music. Subjects are encouraged to relax and go deeply into their experience. At every hour point, the subject's blood pressure is taken and the investigators check in and inquire about their experience. Short reports are encouraged, and then the subject is instructed to put on the eyeshades and head phones again, lie down, and go deeply back into their experience. Toward the end of the session, usually around the five-hour point, more extensive discussions of the subject's experience and associations to it are elicited.

In the days, weeks, and months following the sessions, investigators stay closely in touch with the research subjects, providing assistance with integrating the experience and evaluating the effects of treatment. Prior to the actual treatment sessions, subjects are asked to complete questionnaires examining their level of anxiety, depression, general psychological status and level of physical pain perception, as well as additional measures exploring questions of religion and spirituality and quality of life specific for patients with cancer. Questionnaires are again administered at various intervals following treatment, up to the six month follow-up point.

The study was developed and supported with funding from the Heffter Research Institute. Contact information as well as details on inclusion/exclusion criteria can be found at [www.canceranxiestudy.org](http://www.canceranxiestudy.org).

#### CASE VIGNETTE

P. is a 58-year-old Japanese-American woman, who presented with stage IV colon cancer. P. had been in good health until two years previously, when routine colonoscopy identified and resected a polyp. Histopathological inspection of the polyp revealed adenocarcinoma. Further examination of the polyp revealed that the resection had not yielded cancer-free margins. Inexplicably, P.'s health maintenance organization refused to authorize further intervention. Several months later, the cancer had spread to her lungs, peritoneum, and diffuse lymph nodes.

In the previous year, P. had had to undergo surgical excision of the primary tumor in the colon, as well as extensive cancer chemotherapy. P. and her husband had also filed a malpractice law suit against the health maintenance organization

and the physicians who had removed the polyp. In several meetings with P., she expressed considerable anger toward her physicians and the health maintenance organization from its primary site. Although she had a fairly sizable court settlement, she remained distressed, her life being severely damaged.

P. was the only child of a family with a history of intense xenophobia from their homes and families until the end of World War II. P. had never seen her father in business and had never seen her mother. She had had good physical health until her physical pain and discomfort from her physician-recommended treatment.

During what is presented here, P. reported experiencing a profound improvement of affect after four and a half-hour point. She cried, which she continued during the session. P. stated that she was experiencing a psychological state with whom she had had a relationship that in this experience, she felt the tremendous pain of death.

In the months following the session, P. sustained a positive mood. In particular, she has had a good relationship with her husband as well as great relationships with important friends in her community. P.'s participation in the research and psilocybin treatment study was a "booster" session (or two) to her experience with the session.

#### IMPLICATIONS FOR

Since earlier efforts have been made in ameliorating the advanced cancer were for

and the physicians who had elected to forego further excision of the cancerous polyp. In several meetings with research staff prior to her treatment with psilocybin, P. expressed considerable distress over the ordeal she had experienced, and in particular the anger she had directed towards the poor judgment employed by her physicians and the health system which had allowed the cancer to metastasize from its primary site. Although she expressed some gratification at having won a fairly sizable court settlement from her HMO (Health Maintenance Organization), she remained distraught that their ineptitude had resulted in her health being severely damaged.

P. was the only child of second-generation immigrants who during the period of intense xenophobia following Pearl Harbor had been arrested and then taken from their homes and forced to live in internment camps where they remained until the end of World War II. P. had had long-term employment in a computer business and had never sought mental health treatment. Until her colon cancer, she had had good physical health. She reported no substance use history, except for physician-recommended use of "medical cannabis" to help her with her physical pain and discomfort and cancer chemotherapy-induced nausea.

During what is presumed to have been her experimental psilocybin session, P. reported experiencing a pleasant and sustained reverie with noticeable improvement of affect and relaxation of tension. However, at approximately the four and a half-hour point, she appeared distressed and spontaneously began to cry, which she continued for approximately twenty minutes. Later, when processing the session, P. stated that her tearfulness was in response to internally experiencing a psychological state of very powerful empathic rapport with her husband, with whom she had had a very close long-term relationship. She further explained that in this experience, she had "become" her husband, and in particular could feel the tremendous pain of loss he would inevitably have to undergo upon her death.

In the months following her single active session treatment, P. has reported sustained positive mood, less anxiety, and greater acceptance of her situation. In particular, she has described a further strengthening of her bond with her husband as well as greater interest and motivation in spending "quality time" with important friends in her life. The only criticism she has had regarding her participation in the research study was that the protocol only allowed for one psilocybin treatment study. P. strongly expressed her viewpoint that an additional "booster" session (or two) might further amplify the positive effects she attributes to her experience with the psilocybin treatment model.

## IMPLICATIONS FOR PSYCHO-ONCOLOGY

Since earlier efforts investigating the safety and effectiveness of hallucinogens in ameliorating the psychospiritual distress seen in individuals with advanced cancer were forced to halt over three decades ago, significant advances

have been achieved within mainstream culture, sensitizing the medical system to the needs of dying patients. Development of the hospice movement and the field of palliative care have provided greater and more humane attention to the treatment of physical pain, as well as to providing a supportive structure, often within the home, for the dying process itself. Nevertheless, it is an unavoidable fact that innumerable individuals approaching the final phase of their life experience terrible psychosocial anguish that precludes a peaceful, tranquil, and dignified death (Rousseau 2000). This profound spiritual suffering shares many features of depression, including hopelessness, worthlessness, and meaninglessness. Indeed, depression and hopelessness are associated with poorer survival rates in cancer patients and with dramatically higher rates of suicide, suicidal ideation, desire for hastened death, and interest in physician-assisted suicide (Breitbart et al. 2000; Cochirov 2000).

The psychotherapeutic approach to working with end of life issues often emphasizes the significance of spirituality and meaning as important resources for coping with the emotional and existential suffering encountered as one nears death. The crisis of dying may include overwhelming fear, panic, anxiety, anger, and dependency which must be addressed. Acquiring meaning and purpose become pivotal existential resources for helping patients reconcile with their past, come to terms with their present, and accept an uncertain future (Breitbart et al. 2004). Indeed, there is no greater existential crisis than of facing one's own death. One of the founders of the existential psychiatry movement, Victor Frankl, himself a survivor of Auschwitz Concentration Camp, has emphasized that "meaning can be found in life up to the last moment, up to the last breath, in the face of death" (Frankl 1988, p. 76). The goal and outcome of finding meaning at the end of life is to transform anxiety, despair, and hopelessness into new ways of exploring relationship to self and others, and to promote emotional and spiritual well-being.

The hallucinogen treatment model for the existential anxiety crisis often encountered at the end of life was first suggested by the expatriate British writer Aldous Huxley, who during the final decade of his life, ending in 1963, devoted considerable attention to closely examining the implications of psychedelics to society. Huxley, according to his close colleagues, often said that "the last rites should make one more conscious rather than less conscious, more human rather than less human" (Huxley 1977, pp. 257-258), and true to his personal vision received from his personal physician an injection of 100 micrograms of LSD several hours prior to his demise from cancer. Subsequently, medical and psychiatric investigators explored the capacity of hallucinogens to reduce the intensity and tenacity of physical pain without the mental dulling and awareness constricting effects often observed with narcotic analgesia. The transcendent state of expanded consciousness frequently reported in patients undergoing psychedelic experiences was also found to enhance their capacity to maintain interest in their lives, and helped create, in the words of early researcher Eric Kast, "a new will to live and a zest for experience which against a background of dismal darkness and

preoccupying fear produces terms the short but profound" (Kast 1966b, p. 85).

A remarkable opportunity by the dying is offered by this model. Recent research on psilocybin administered under a mystical experience in non-use of hallucinogens with such treatment may be to intervene and ameliorate. Under the influence of hallucination with their bodies actual physical demise, a transcendence of the life constant and with a new equilibrium ceases. This implicitly altered approach to and dependency that were

The facility which has in catalyzing genuine mystical Reports of patients with a transition between heightened and subsequent improvement. Finally, there are serious dangers of using hallucinogens in Walter Pahnke, in his 1969 study suggested that "although it is a tantalizing enigma, there is more to the range than we assume. Because the answer is certainly no cause for people, each person must ultimately experience can prepare one to" (Pahnke 1969, pp. 20-21).

## CONCLUSIONS

During the 1960s an exploration of the use of hallucinogens in isolation often associated with highly encouraging, descriptive actual epiphanies, often with

preoccupying fear produces an exciting and promising outlook. In human terms the short but profound impact upon the dying patient is impressive" (Kast 1966b, p. 85).

A remarkable opportunity to address the universal existential dilemma faced by the dying is offered by careful examination of the hallucinogen treatment model. Recent research contributions by Griffiths et al. (2006) demonstrate that psilocybin administered under optimal conditions may reliably induce legitimate mystical experience in normal volunteers, strengthening the case for the judicious use of hallucinogens with patients in profound psychospiritual crisis. Indeed, such treatment may be considered as *existential medicine* designed to directly intervene and ameliorate the emotional and spiritual suffering of dying patients. Under the influence of hallucinogens, individuals transcend their primary identification with their bodies and experience ego-free states before the time of their actual physical demise, and return with a new perspective and profound acceptance of the life constant, change. Experiencing oneself in a transitional state and with a new equilibrium and consciousness, identification with the dying body ceases. This implicit acceptance of the inevitable cycles of life leads to a drastically altered approach to what time is remaining without the panic, fear, pain, and dependency that were previously so overwhelming (Fisher 1969, 1970).

The facility which hallucinogens, when taken under optimal conditions, have in catalyzing genuine mystical experiences provides a rich area for further study. Reports of patients with advanced-stage cancer suggest a strong positive correlation between heightened spiritual consciousness induced by these compounds and subsequent improved psychological status during their remaining time. Finally, there are serious transpersonal and ontological implications of administering hallucinogens to individuals approaching the end of life. On this matter, Walter Pahnke, in his Ingersoll Lecture to the Harvard Divinity School, elegantly suggested that "although the questions of human immortality may always remain a tantalizing enigma, the psychedelic mystical experience at least teaches that there is more to the range of human consciousness than we might ordinarily assume. Because the answer cannot be definitely proved either way, there is certainly no cause for pessimistic despair. Perhaps it is not so unfortunate that each person must ultimately find out for himself. The psychedelic mystical experience can prepare one to face that moment with a sense of open adventure" (Pahnke 1969, pp. 20-21).

## CONCLUSIONS

During the 1960s and early 1970s, investigators initiated research studies exploring the use of hallucinogens to treat the existential anxiety, despair, and isolation often associated with terminal cancer. Reports from that time were highly encouraging, describing critically ill individuals undergoing psychospiritual epiphanies, often with powerful and sustained improvement in mood and



anxiety regulation, as well as diminished pain perception and need for narcotic pain medication. Unfortunately, the political and cultural turmoil of that historical period led to the inevitable shut-down of all clinical research with hallucinogens. In spite of the promising preliminary studies of Eric Kast (1962, 1966a,b, 1970; Kast and Collins 1964), Walter Pahnke (1969), Stanislav Grof (1980; Grof et al. 1973), William Richards (Grof et al. 1973), Gary Fisher (1969, 1970), and Sidney Cohen (1965), several decades would have to pass before the work of these pioneer investigators would be reexamined.

Beginning in the early 1990s, a few Phase I research investigations of hallucinogens were permitted in the United States, followed a decade later by several pilot clinical treatment trials. Psilocybin in particular has recently been explored in an adjunctive therapeutic model, with promising preliminary reports. Questions have been raised; however, concerning the choice of psilocybin in these studies over other classical or novel hallucinogens. One important advantage psilocybin has over the better known LSD is that it carries less political baggage and consequently has a far less sensationalized reputation. The more recently prominent drug MDMA (methylenedioxymethamphetamine), popularly known as Ecstasy, has also been suggested as a possible treatment for cancer anxiety, however, the clear advantage of psilocybin over MDMA is its far safer range of cardiovascular effects. While MDMA has demonstrated therapeutic potential with people suffering from post-traumatic stress disorder, these are usually individuals in good physical health. On the other hand, patients with advanced cancer often have multiple organ system failures, and are consequently more sensitive to the sympathomimetic effects of MDMA. Furthermore, psilocybin's greater capacity than MDMA to catalyze transcendent and psychospiritual states of consciousness would, according to the early investigators, lead to a more therapeutic outcome.

As clinical research with hallucinogens experiences renewed activity, great sensitivity will have to be utilized in selecting the psychotherapists who will do the actual work. It is imperative that, in addition to the requisite psychological acumen, therapists will also need to possess sufficient emotional maturity, psychological stability, and ethical integrity to be able to conduct their work effectively and safely. Patients under the influence of hallucinogens are exquisitely sensitive to environmental stimuli, including the individual and collective input of the therapy team. Consequently, as both past and recent history attest, attentiveness to set and setting remains paramount when conducting clinical investigations with hallucinogens.

After a hiatus of several decades, there are encouraging signs that hallucinogen research is beginning to receive the sanctions necessary to move forward again. The promising findings of a previous generation of researchers now need to be replicated using contemporary state-of-the-art research methodologies. Early work with advanced-stage cancer patients in particular demonstrated the promise of effective intervention for psychospiritual crises often observed at the end of life. A critical element that is necessary to support such a program of

research, which was no degree today, is a stable versatility of the essential-conducted hallucinogen the end of life period, the demonstrate the utility o

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research, which was not available to our predecessors but is to an increasing degree today, is a stable political and professional environment. Given the universality of the essential existential dilemma, and the potential for the optimally conducted hallucinogen treatment model to significantly enhance the quality of the end of life period, there is clearly a need to develop further research that will demonstrate the utility of this field of hallucinogen medicine.

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