Psycho-existential distress in cancer patients: A return to "entheogens"

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The palliation of clinically significant psychological and existential distress in cancer patients remains a challenging problem. Cancer patients have a higher prevalence of anxiety and depression, approximately 30–40% (Mitchell et al., 2011), compared with 7–10% in the general population (Kessler et al., 2005, 2009). Cancer patients who suffer from anxiety or depression often have worse outcomes: higher healthcare utilization, worse pain, decreased quality of life, and decreased survival (Arrieta et al., 2013; Brown et al., 2003; Jaiswal et al., 2014). Unfortunately, pharmacotherapy and psychological interventions used to treat anxiety and depression in cancer patients have limited efficacy (Faller et al., 2013; Grassi et al., 2014). Existential distress, or demoralization, a syndrome characterized by hopelessness and helplessness due to a loss of purpose and meaning, is common among patients at the end of life (Robinson et al., 2016). Indeed, in states where physician-assisted dying is legal, some of the common reasons for using a lethal prescription are existential in nature, for example losing autonomy, loss of dignity, and being a burden to others (Ganzini et al., 2008). To date, there are no approved pharmacotherapies or evidence-based psychosocial interventions for existential distress, though some approaches show promise and are associated with improvement in patients' sense of meaning and purpose, for example dignity therapy (Chochinov et al., 2011; Faller et al., 2013) and meaning-making therapy (Breitbart et al., 2010).

Naturally occurring hallucinogenic compounds, described by some botanists as "entheogens" (ancient Greek: ἔνθεος [entheos—"full of god"] and γενέσθαι [genesthai—"to come into being" or "generate"]) have unique physiologic and psychological properties, including the altering of consciousness and the induction of what may be described as "mystical" experiences.

Entheogens, such as peyote, ayahuasca, and psilocybin-containing mushrooms, have been used by shamans and spiritual healers throughout human history in religious and spiritual-healing ceremonies. Indigenous peoples have known about the potential health benefits of such substances, incorporating their use to heal themselves, to cultivate physical and spiritual well-being, and ultimately to seek liberation—a state of freedom that many of our myths and ancient writings teach us is both within our grasp and a goal of human existence.

In the last century, "psychedelic drugs" (e.g., lysergic acid diethylamide [LSD]) were studied in a range of conditions, including alcoholism, depression, obsessive–compulsive disorder, autism, schizophrenia, and others. Though the studies were of poor quality by today's standards, they were groundbreaking in their attempts to find some therapeutic use for these novel compounds. However, after the popularization of LSD by Timothy Leary and others, and the "counterculture" embrace of psychedelics in the 1960s, Richard Nixon signed the Controlled Substance Act of 1970, placing such serotoninergic psychedelics into the DEA's Schedule 1 classification: "drugs with no currently accepted medical use and a high potential for abuse." So by the early 1970s, this novel research project, which was starting to focus on psycho-spiritual distress in advanced cancer (Grof et al., 1973), came to an end.

In recent years, a renewed interest in psilocybin, a tryptamine serotoninergic psychedelic, has emerged. Researchers, in a more rigorous, scientifically disciplined fashion than their predecessors, embarked on exploring the role of these powerful drugs for the treatment of depression, anxiety, and psycho-existential distress in terminally ill cancer patients (Grob et al., 2011).

In this issue of the *Journal of Psychopharmacology*, Griffiths et al. (2016) and Ross et al. (2016) have published the largest randomized controlled trials of psilocybin for depression and anxiety in cancer patients to date. The studies were double-blinded, randomized, placebo-controlled (low-dose psilocybin and niacin, respectively), crossover trials, which followed subjects for months after the active psilocybin dose. The researchers used multiple validated psychological tools and other metrics to examine a range of effects and to assess the safety. The primary outcomes in both studies were depression and anxiety. Secondary outcomes were broad and included measurements to assess spirituality, existential distress, death anxiety, death transcendence, mystical experience, and quality of life. The psilocybin intervention and control groups both received guided psychotherapy during the monitoring of the intervention. Efforts were made to decrease the effect of expectancy by obscuring the actual psilocybin dose conditions to facilitate blinding (Griffiths et al., 2016) or by use of an active placebo, niacin (Ross et al., 2016).

Both studies demonstrated that a single "high" dose of psilocybin (~0.3 mg/kg) could be safely administered to patients with cancer-related psychological distress (anxiety and depression).

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The effect on depression and anxiety in both studies was rapid, clinically significant, and sustained for at least weeks (five to seven weeks, respectively, prior to the crossover) and possibly longer (six to six-and-a-half months after the crossover). While the limited pre-existing data on psilocybin's potential effect on psychologic outcomes did not permit a power calculation, the consistent results in both groups, before and after the crossover, and the correlation of many of the secondary outcome metrics with the effect on the primary outcomes supports the validity of the authors' findings. The limitations of the studies, as the authors point out, include the crossover design, which limits the interpretation after the crossover, such that only the outcomes prior to the crossover at five to seven weeks, respectively, can be reliably due to the psilocybin administered to subjects. In the Griffiths et al. (2016) study, the very low dose of psilocybin (1 mg/70 kg) may have had potential activity and thus could have affected the double-blind assessment of the efficacy of the higher dose. In the Ross et al. (2016) study, the use of a control (niacin) with limited blinding may have contributed to some bias of the results. The psychiatric exclusion criteria limit the findings only to those patients with depression and anxiety disorders, but not with a family history or patient history of other psychiatric disorders (particularly schizophrenia and bipolar disorder) Additionally, the relatively small sample size, made up of a largely white, educated population, precludes generalizability.

If these findings are confirmed, or other therapeutic effects are demonstrated, in large, powered, randomized controlled studies in a diverse population of patients, then the classification of psilocybin as a Schedule 1 drug should be challenged, for this would represent a treatment modality unlike anything in psychiatry: a rapid and sustained reduction in depression and anxiety with a single dose of a psychoactive compound (combined with guided psychotherapy). The closest example is the immediate effect ketamine has been shown to have in the treatment of refractory depression (Zanos et al., 2016). However, even in the case of ketamine, the enduring effect last for days to perhaps weeks, not weeks or months.

While the studies' primary outcomes did not include existential distress, the studies both showed improvement in this domain that was enduring for weeks, possibly months. Indeed, when we consider the lack of evidence for the treatment of psycho-existential distress and the ethical dilemma in palliative care of when (and whether) to use intermittent or terminal sedation for "refractory" and/or severe existential distress (Anquinet et al., 2014), psilocybin may offer a potential therapeutic modality to offer before embarking on such a final and ethically controversial decision.

Lastly, one of the more interesting findings in these two studies is the significant association or correlation between the subjects' mystical-type experience and the therapeutic outcomes of the reduction in depression and anxiety. The link between ineffable spiritual experiences and our capacity for psychological well-being may point to a model for therapeutic modalities that have hitherto not been considered for depression and anxiety, for example interventions that awaken our inner capacity for meaning and transcendence. The potential of entheogens to awaken our (dormant) spiritual self through a mystical-type experience may show more promise for cancer patients suffering from depressed mood and anxiety than selective serotonin reuptake inhibitors, which to this date have not shown compelling results in cancer patients. A return to entheogens for the treatment of psycho-existential suffering may signal that medicine has come full circle to embrace the earliest known approach to healing our deepest of human agonies—by "generating the divine within."

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