



The role of psychedelics in palliative care reconsidered: A case for psilocybin

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Psychiatric research with classic hallucinogens has enjoyed a resurgence of late. While studies performed in the late 1960s and early 1970s with lysergic acid diethylamide (LSD) and psilocybin demonstrated therapeutic promise by producing a rapid and sustained reduction in anxiety, improvement in mood, and enhanced quality of life in patients with terminal cancer (Grof, 1973), a fuller exploration of their use in palliative medicine was curtailed by the establishment of a strict federal regulatory environment. Now, after decades of research inactivity, the potential of psychedelics to alleviate the distress associated with a terminal illness has been significantly advanced by the results of two recent studies investigating the efficacy of psilocybin in the treatment of anxiety and depression in patients with life-threatening cancer. Using double-blind, placebo-controlled, crossover designs, the studies conducted at Johns Hopkins University (JHU) and New York University (NYU) were methodologically rigorous and broad in the scope of their outcome variables. Both studies demonstrated that a single-dose of psilocybin can produce both an acute and enduring reduction in depression symptoms, anxiety, and existential distress in patients with life-threatening cancer.

That the studies replicated one another is a source of confidence in their findings. However, there were also informative differences between the studies. The group at JHU led by Griffiths et al. investigated the effects of a very low dose (1–3 mg/70 kg, placebo-like) versus high dose (22 mg/70 kg) of psilocybin administered five weeks apart in 51 patients diagnosed with life-threatening cancer and suffering with symptoms of depression and/or anxiety (Griffiths et al., 2016). The group at NYU led by Ross et al. compared the effect of high-dose psilocybin (0.3 mg/kg, ~21 mg/70 kg) with niacin (used as an “active” control) in 29 patients, and both groups received targeted psychotherapy (Ross et al., 2016). All patients were screened and prepared for the study intervention through several meetings with staff who established rapport and provided an understanding of the range of altered states of consciousness that might be encountered during their treatment sessions. The psilocybin experience was well tolerated by all patients, and there were no serious medical or psychological adverse events.

Both studies evaluated a broad range of outcome measures, including the common measures of anxiety and depression, as well as quality of life, spirituality, and mystical experiences. In the Griffiths et al. trial, high-dose psilocybin produced large and sustained decreases in clinician- and patient-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning and optimism, and decreases in anxiety related

to death. In the NYU trial, psilocybin produced rapid, substantial, and enduring reductions in cancer-related anxiety and depression, improved quality of life, increased spiritual well-being, and improved measures of existential distress, and was associated with improved attitudes toward death. At follow-up at six-and-a-half months, the initial robust clinical effects observed after the administration of a single dose of psilocybin endured in 60–80% of the patients, and when patients were asked (six-and-a-half months post drug administration) to reflect on what they thought of their psilocybin session, 52% and 70% rated the psilocybin experience as the singular or top 5 most spiritually significant, or the singular or top 5 most personally meaningful experience of their entire lives, respectively, while 87% reported increased life-satisfaction or well-being attributed to the experience (Ross et al., 2016). The findings that single-dose psilocybin can produce acute and sustained improvements in cancer-related anxiety and depression is perhaps the most important and novel finding of the two studies, and add to and extend the findings of a similarly designed trial in patients with terminal cancer where a single low dose (0.2 mg/kg) of psilocybin showed non-significant trends for benefit compared with placebo (Grof et al., 2011).

In both studies, mediation analysis indicates that the mystical experience was a significant mediator of the effects of psilocybin dose on therapeutic outcomes. Mystical experience is defined as encountering a profound sense of unity, transcendence of time and space, deeply felt positive mood, noetic quality (sense of understanding), ineffability, transiency, and paradoxicality infused with a renewed sense of purpose and meaning (Griffiths, 2006, 2008, 2011; Grof et al., 2013). Further evidence for the

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role of the mystical experience and/or higher doses in therapeutic outcomes comes from two open-label trials for addiction where the mystical experience was correlated with improved smoking cessation (Garcia-Romeu et al., 2014) and drinking outcomes (Bogenschutz et al., 2015). Furthermore, Carhart-Harris et al. (2016) recently investigated the safety and efficacy of psilocybin in treatment-resistant depression, and showed that a higher dose correlated with a better treatment outcome. The association between psychedelic-induced mystical experience and therapeutic outcome, while not new, requires further exploration, as when induced under optimal conditions and in a controlled setting, it could provide a valuable therapeutic intervention for disorders that are otherwise difficult to treat.

Although not the primary aim of these studies, directionality of the relationship between the pharmacology of the drug, mystical experiences, and clinical outcome remains inconclusive. We do not know for certain whether these mystical experiences are a cause, consequence or corollary of the anxiolytic effect or unconstrained cognition (see below). For instance, it is possible that mystical experiences associated with psilocybin serve as a measure of adequate drug effects rather than mediating an antidepressant and/or anxiolytic effect. Perhaps future studies could shed some light on this relationship by employing other drugs, such as Salvinorin A and other kappa opioid receptor agonists, capable of producing perceptual alterations and mystical experiences similar to serotonergic hallucinogens but pharmacologically different (Johnson et al., 2011; Ranganathan et al., 2012). Also intriguing is whether the psychoactive effects of psilocybin influence its efficacy through, not yet fully understood, psychological mechanisms that continue to exert their effect well beyond the acute pharmacological effects. Rapid alleviation in mood is also reported with a single administration of ketamine, a dissociative anesthetic known to occasion mystical experiences. However, the antidepressant effects are relatively transient and typically disappear after a week. Moreover, not all the psychotropic substances (e.g., scopolamine and nitrous oxide) that induce dissociative and/or mystical experiences produce an acute and enduring clinical benefit. Is there a differentially unique characteristic about the pharmacology of psilocybin and its enduring clinical effects compared with other serotonin receptor (5-HT_{2A}) agonists such as dimethyltryptamine or dipropyltryptamine?

Imaging studies in healthy controls indicate that psilocybin decreases blood flow to regions of the brain regions collectively known as the default mode network (DMN) and promotes unconstrained cognition (Carhart-Harris et al., 2012, 2014). Increase in metabolic activity in the DMN has been associated with increase in ruminative thinking and has been implicated in depression and anxiety but normalized by a range of effective treatments (Carhart-Harris et al., 2014). One theoretical framework that might link mystical experiences to a new, more positive outlook through changes in brain function is Predictive Processing (Friston, 2005). This theory posits that the brain is a prediction machine and its hierarchically organized neuroanatomy is geared toward predicting future inputs based on prior experiences. Any mismatches or prediction errors (coded glutamatergically) can gather new learning based in their precision (implemented by slower neuromodulators such as dopamine, acetylcholine, or serotonin, depending on the inferential hierarchy) (Corlett et al., 2009). We have previously argued that psychotomimetic drugs may induce their psychedelic or

mystical effects by altering the balance between predictions and prediction errors such that errors are registered inappropriately and perceptual inferences become deranged (Corlett et al., 2009). These experiences can gather new learning, expanding the possibility space for future inferences (Corlett et al., 2010). This may be reflected in the significantly elevated trait openness, which persists for 14 months following a single infusion of psilocybin (MacLean et al., 2011). Future work will need to discern how and why these drugs can have psychotomimetic effects in some individuals and antidepressant effects in others. The environmental setting and individual's baseline are clearly crucial to the effects a psychedelic drug can have (Zinberg, 1984). Thus expectations and environments may enhance the drug's potential to foster religious and spiritual experiences. In his book *Heaven and Hell*, Aldous Huxley observes, "Many schizophrenics have their times of heavenly happiness; but the fact that (unlike the mescaline taker) they do not know when, if ever, they will return to the reassuring banality of everyday experiences causes even heaven to seem appalling."

These studies have demonstrated a critical advancement in this field. Psilocybin may offer a novel and potentially valuable approach for addressing the psychological suffering of dying often observed in this patient population, particularly given the limited efficacy of extant treatments. These studies also raise a number of important questions that warrant further research. How necessary are the acute psychedelic effects of psilocybin for its antidepressant and anxiolytic effects? What are the predictors of beneficial effects and adverse effects? Would moderate doses have similar effects? How specific are the effects? For a single dose of a drug to have effects that are still detectable six months later opens a new era of potential psychopharmacological treatments. But it also begs the question about what is/are the mechanism/s underlying the sustained beneficial clinical effects of psilocybin.

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