Commentary

Psilocybin in end of life care: Implications for further research

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This issue of the *Journal of Psychopharmacology* contains two important randomized controlled studies on the use of psilocybin to treat mood and anxiety (including adjustment disorders) in carefully selected and supervised patients with later stage malignancies.

Ross et al. (2016) studied 29 cancer patients using a two-session, double-blind, crossover (seven weeks after administration of dose 1) design employing psilocybin first then niacin second, or niacin first and psilocybin second. Both groups had extensive orientation to the trial and psychotherapy with supportive, psychodynamic, and existential elements. They found that psilocybin produced an immediate and ongoing anxiolytic and antidepressant response, with 83% in the psilocybin-first group (vs. 14% in the niacin-first group) meeting criteria for antidepressant response seven weeks after dose 1. Pre-crossover results were significant post initial drug administration, although Beck Depression Inventory between groups was significant at the $p<0.05$ level one day prior to initial drug administration but not at baseline. At follow-up at six and a half months (after both groups received psilocybin), antidepressant or anxiolytic response rates were in the 60–80% range depending upon measure. Subjects' mystical or spiritual experiences were highly correlated with clinical response and mediated four out of six primary outcome measures.

Griffiths et al. (2016) studied 51 cancer patients using a two-session, double-blind, crossover (five weeks after administration of dose 1) design employing high-dose psilocybin first then very low-dose (placebo-like) psilocybin second, or very low-dose (placebo-like) psilocybin first and high-dose psilocybin second. The use of low-dose psilocybin as its own control, instructional language to subjects and that which aimed to minimize the placebo response, and extensive supportive meetings with study personnel (but not formalized psychotherapy) were distinctive element of the study design. It was found that high-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety. Five weeks after session 1, 92% in the high-dose psilocybin-first group (vs. 32% in the low-dose-first group) showed a clinically significant response and 60% versus 16% symptom remission. At follow-up at six months (after both groups received high-dose psilocybin), these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Subjects' mystical or spiritual experiences were highly correlated with clinical response and mediated seven of the primary outcome measures.

In both studies, adverse events were limited and included expected increases in blood pressure, pulse, nausea and vomiting, and transient anxiety or occasional psychotic symptoms, which remitted rapidly. Improvements in attitudes toward death and the experience of deeply meaningful spiritual experience were likewise reported in both studies.

These studies build on prior smaller studies, including a psilocybin study that found a trend to decreased psychological distress in people with life-threatening illness (Grob et al., 2011). While there are several methodological issues in the Ross et al. (2016) study, including changes in cancer severity, recruitment criteria, and a larger number of agnostic/atheist subjects in the niacin-first group, and changes in the high- and low-dose regimens shortly after initiation in the Griffiths et al. (2016) study, analyses showed these did not contribute to the outcomes. More substantial is the difficulty of blinding subjects or study personnel to the effects of a drug with such dramatic effects as psilocybin. The study instructions and use of low-dose psilocybin as the control drug in the Griffiths et al. (2016) study was a creative way to address these issues. It is, however, unclear how effective blinding procedures were.

Placebo responsiveness and expectations are of course complex issues to isolate. This is especially true in studies that included a significant percentage of participants with prior psychedelic use and who were facing serious medical and existential issues. Nevertheless, the rate and speed of response to an active drug, its intensity and duration, is decidedly more substantial than one sees in placebo responses in moderately depressed patients, even with highly committed and engaged research groups.

What are the implications of these studies for ongoing research and clinical care with psychedelic agents? If the agents used in these studies were new investigational compounds, given the paucity of agents that have rapid effects on depressed mood, there would likely be rapid dissemination of the results, expansion of trials to larger and other clinical populations, and attempts to develop additional compounds with similar mechanisms of action. If, after further study, initial findings were confirmed, discussions of compassionate use

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for individuals with severe and unremitting illness or rapid movement to approve for clinical use would likely occur.

The history of psychedelics and their legal status as highly restricted compounds of course make this a more complex issue. While the use of psilocybin and related compounds in spiritual ceremonies has a very long history in many traditional and non-Western cultures, the more recent history of widespread non-clinical use, or even more disturbingly their use in unethical and dangerous research designs surreptitiously funded by national security authorities, makes the status of these compounds more complex and suspect (Nichols, 2015; Select Committee on Intelligence, 1977). Despite extensive evidence of the safety of these compounds in well-selected individuals under careful supervision, as in these studies, their prior history and the general history of expansion of indications for clinical agents, including their clinically questionable use after approval for specific indications, is an important cautionary tale.

Beyond the clinical utility of these agents in individuals who are facing critical existential issues in end-of-life settings, it is likely that studies will expand into other important clinical populations such as those with treatment-resistant depression, where an initial proof of concept study showed similar responses to those reported in these studies (Carhart-Harris et al., 2016).

There are, however, other important considerations in research with psychedelic agents. Psychiatric illnesses are both highly complex neurobiologic conditions and among the most intimate of human illnesses, touching as they do on our deeply held sense of self and human agency. Both of these issues are highlighted in research with psychedelic agents. These compounds have important value in understanding the neural networks that support a well-delineated sense of self and other, and potentially in antidepressant or anxiolytic mechanisms of action. Psilocybin neuroimaging studies have suggested changes in the coupling of the posterior cingulate cortex and the medical prefrontal cortex (Carhart-Harris et al., 2012) and coupling of the medial temporal lobe and the neocortex (Lebedev et al., 2015). However, neuroimaging studies with psilocybin and other psychedelics agents are in their early stages.

As important as these imaging studies may become for our understanding of these mechanisms, is the experience of these agents by the study participants. Many participants rated their psilocybin experience as among the most profound and meaningful of their lives. The benefit of these experiences on mood and anxiety seemingly continued to affect them months later, despite only a single administration of psilocybin and their serious medical conditions. It is unclear at present to what degree this benefit is due to the power of these experiences, ongoing changes in neural mechanisms, or other causes.

The experiences of salience, meaningfulness, and healing that accompanied these powerful spiritual experiences and that were found to be mediators of clinical response in both of these carefully performed studies are also important to understand in their own right and are worthy of further study and contemplation. None of us are immune from the transitory nature of human life, which can bring fear and apprehension or conversely a real sense of meaning and preciousness if we carefully number our days. Understanding where these experiences fit in healing, well-being, and our understanding of consciousness may challenge many aspects of how we think about mental health or other matters, but these well-designed studies build upon a recent body of work that confronts us squarely with that task.

These two studies demonstrate the efficacy of using a classic psychedelic agent, psilocybin, to treat psychologically distressed late-stage cancer patients with depressed mood and anxiety. Both studies found acute, substantial, and enduring (six-month follow-up) antidepressant and anxiolytic effects in 60–80% of study participants. They also found that the spiritual effect of psilocybin on the session day mediated the improvement in therapeutic outcomes. Given the strength of these findings, more extensive studies to replicate these outcomes are called for, as are studies in more diverse clinical populations. Since, as the authors note, it is difficult to blind these agents adequately, consideration should be given to including research groups that have had less prior involvement in this area to minimize placebo responsiveness. Finally, the complex history and legal status of psilocybin and related agents suggests that additional thought should be given as to how to deal with the unique legal, ethical, and regulatory issues surrounding clinical use of these agents. Careful discussion now with ethicists, regulatory, legal, and clinical research authorities may be helpful to understand how psilocybin and potentially related agents can be provided to select clinical populations should more extensive trials confirm the work reported in these studies.

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