Psychedelic Studies: Implications for Psychiatric Research and Care

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The December 2016 issue of the *Journal of Psychopharmacology* contained 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. 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. These findings were sustained for most subjects at six months. Subjects' mystical or spiritual experiences were highly correlated with clinical response.

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. High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety. At follow-up at six months about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Subjects' mystical or spiritual experiences were also highly correlated with clinical outcomes.

In both studies, adverse events were limited and there were improvements in attitudes toward death and the experience of deeply meaningful spiritual experience. 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).

The February 2017 issue of *Clinical Pharmacology and Therapeutics* published an article about the potential psychiatric uses for MDMA. The article summarized the results of a series of published and unpublished Phase 2 studies (Mithoefer et al., 2011; Mithoefer et al., 2013; Oehen et al. 2013) into the use of MDMA-assisted psychotherapy for subjects with chronic, treatment-resistant posttraumatic stress disorder (PTSD),

reporting that "In phase II PTSD studies, 2 months after two to three active-dose MDMA treatments, 55% of chronic PTSD subjects no longer met the PTSD Diagnostic Criteria (N = 100) and 66.2% were in remission at least 12 months postdrug (N = 65)."

The difficulty of blinding subjects or study personnel to the effects of drugs with such dramatic effects as psilocybin or MDMA is an ongoing issue in these studies.

What are the implications of these and similar studies with other agents 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 or on chronic, treatment-resistant PTSD, 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 for individuals with severe and unremitting illness or rapid movement to approve for clinical use would likely occur.

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.*

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 or who are suffering from PTSD, 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), while studies of MDMA's mechanism of action implicate the medial temporal lobes (Carhart-Harris et al., 2015; Gamma et al., 2000). However, neuroimaging studies with psilocybin, MDMA, and other psychedelic agents are in their early stages.

As important as these imaging studies may become for our understanding of these mechanisms, so 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. Participants who received MDMA reported profound experiences that catalyzed durable healing from PTSD. 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 these carefully performed psilocybin studies, and the experiences of fear extinction that were catalyzed by MDMA, 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.

Given the strength of these recent reports, more extensive studies to replicate these outcomes are called for, as are studies in more diverse clinical populations. Since, 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 com-

plex history and legal status of psilocybin, MDMA 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, MDMA and potentially related agents can be provided to select clinical populations should more extensive trials confirm the work reported in these studies.

Disclosure

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Declaration of conflicting interests

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The author receives personal fees from CME Outfitters, Pharmasquire, and universities and associations for non-promotional speaking; royalties from Harvard University Press, Springer, and American Psychiatric Press; and consulting fees from Owl, Inc. and Quartet Health, Inc., all outside the submitted work.

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