Psilocybin and palliative end-of-life care

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Commentary

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Cancer is among the leading causes of death worldwide, and annual cancer cases are expected to increase from 14 million in 2012 to 22 million within the next two decades (Stewart and Wild, 2014). As depression and anxiety are prevalent among individuals diagnosed with cancer, the treatment of psychological distress in this population is a mental-health priority. Of course, depression and anxiety associated with the end of life are not limited to individuals diagnosed with cancer (Cochinov et al., 2016), and according to the prominent terror management theory, fear secondary to the awareness of the inevitability of death drives much of human behavior (Greenberg et al., 1997). Treatments for death distress may therefore be considered a universal need.

Unfortunately, evidence supporting the efficacy of existing interventions for depression and anxiety among individuals diagnosed with cancer is scarce. Indeed, there are very limited data supporting the effectiveness of antidepressants, anxiolytics, or psychotherapy for the management of cancer-related depression or anxiety (Faller et al., 2013; Ostuzzi et al., 2015). Papers by Griffiths et al. (2016) and Ross et al. (2016) in this journal are notable in that they suggest a rapid, clinically robust, and sustained effect of the 5HT2A agonist psilocybin on depression and anxiety among individuals with advanced-stage cancer. The latter was a very small scale (N=29) crossover study comparing psilocybin treatment to the active control niacin, chosen for its ability to mimic some psilocybin side effects. The benefits were remarkable, consisting of both acute and enduring (six-and-a-half months) antidepressant and anti-anxiety effects. Griffiths et al. (2016) showed similar shorter- and longer-term antidepressant and anti-anxiety benefits of psilocybin in a study that compared a very low (placebo-like) dose (1 or 3 mg/70 kg) versus a high dose (22 or 30 mg/70 kg) of psilocybin administered in counterbalanced sequence with five weeks between sessions in a somewhat larger sample (N=51). The results of these studies are very encouraging, given the limited evidence-based treatment options for cancer-related psychological distress.

Functional unblinding—the ability of participants to ascertain treatment assignment based on drug effects—is the principal limitation of the studies. Both projects attempted to deal with this problem by using active placebo controls (niacin or low-dose psilocybin) and certain study procedures. However, neither study used a direct assessment of the integrity of the blinding procedure—that is, neither directly asked participants to estimate treatment assignment. It would be prudent to collect this information in future studies. However, it should be noted that the salience of psilocybin's effects may render complete blinding unfeasible, as is often the case with studies of psychoactive drugs and behavioral interventions. Nonetheless, the results of these studies and the relative lack of serious side effects of administering psilocybin in a controlled setting support moving forward into Phase III clinical trials.

How does psilocybin produce these benefits? Possible mechanisms of action may include increases in glial cell line–derived neurotrophic factor and brain-derived neurotrophic factor, downregulation of 5HT2A receptors, alterations in pyramidal cell dendritic spine organization, and normalization of the default mode network (Carhart-Harris et al., 2014; Vollenweider and Kometer, 2010). It is unlikely that the benefits result from identical mechanisms of action of established antidepressant therapies or more recent treatments such as ketamine that target the glutamate NMDA receptor. In the case of ketamine, the putative mechanism of action is the release of brain-derived neurotrophic factor, which stimulates neural synaptogenesis (Li et al., 2010). These effects occur rapidly and are sustained over several days. However, ketamine has to be administered repeatedly to maintain the effect, which does not appear necessary with psilocybin. In both studies, the mystical experience associated with psilocybin, as assessed by the Mystical Experience Questionnaire (MEQ30), was associated with improvements in depression and anxiety. In both studies, a formal test of statistical mediation was conducted. While statistical mediation does not necessarily imply causation, it does support the notion that the mystical experience induced by psilocybin could be a causal factor in the improvement in distress.

Should Phase III study confirm the effectiveness of psilocybin for advanced-stage cancer distress, psilocybin may ultimately represent a viable treatment in palliative end-of-life care. Notable advantages of this approach include a supervised

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administration of the drug on only one or a few occasions, obviating concerns about medication adherence, and transient acute and adverse effects. However, the path forward is not a simple one—larger-scale, controlled, Phase III studies are expensive, and moving psilocybin from the most restrictive controlled substance schedule to an Food and Drug Administration–approved therapy is highly atypical, and not without obstacles.

Considering the ubiquity of affective disturbance across mental-health conditions, the results of Griffiths et al. (2016) and Ross et al. (2016) suggest that psilocybin may also hold promise outside of palliative end-of-life care, a contention supported by several recent investigations (Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Hendricks et al., 2015; Johnson et al., 2015). Moreover, if the terror created by the awareness of death's inevitability is indeed a universal human experience, the psilocybin treatment paradigm may, in due course, prove useful from the perspective of positive psychology. The scientific community invites further exploration.

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