Commentary

Psilocybin for depression and anxiety associated with life-threatening illnesses

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Life-threatening and terminal illnesses are accompanied by substantial stressors that encumber both patients and their families. Faced with a life-threatening diagnosis such as late-stage cancer, these factors can compound the existential crisis of impending mortality and produce or exacerbate major depressive and anxiety symptoms (Silverstone, 1990; Vergo et al., 2016). Addressing depression and anxiety in the unique context of life-threatening illnesses has been a significant problem for palliative psychiatric care. In this regard, two recent studies suggest that the one-time use of the naturally derived psychoactive compound psilocybin could have the potential to alleviate these symptoms for up to six months.

Two independent studies by Griffiths et al. (2016) and Ross et al. (2016) demonstrate that psilocybin, a serotoninergic psychedelic, can produce a rapid and clinically significant decrease in the symptoms of depression and anxiety, which can persist for up to six months. Each study utilized a double-blind design and employed different active control compounds to address design-based confounds associated with the use of a psychoactive drug. Griffiths et al. (2016) used a low dose (1–3 mg) of psilocybin, while Ross et al. (2016) selected niacin. It is worth noting that the placebo effect is a major confound in the development of novel antidepressant drugs, as placebos can produce antidepressant effects in 30–40% of individuals (Papakostas et al., 2016). Psilocybin treatment was associated with statistically significant antidepressant and anxiolytic effects in both studies. The use of two separate control compounds (including a subclinical dose of psilocybin as control) minimizes the potential outcome that the effects are due to placebo rather than an active drug effect.

Additionally, these studies utilized a crossover design, where patients receiving placebo for the first administration were given psilocybin in the second half of the study. When patients in this latter group were given psilocybin, they also exhibited marked reductions in depression and anxiety-related symptoms beyond that which may have occurred following administration of the control compounds. Together with their larger sample of participants compared with prior trials (51 and 29, respectively), these studies provide support for definitive trials designed to test the hypothesis that psilocybin may have therapeutic effects with what appear to be minimal side-effects.

A prior open-label study also showed apparent efficacy of psilocybin in treatment-resistant depression (Carhart-Harris et al., 2016), and although other studies have suggested a role for psychedelics such as psilocybin and lysergic acid diethylamide (LSD) as adjuncts to psychotherapy (Carhart-Harris et al., 2012; Gasser et al., 2014; Grob et al., 2011), these prior studies have been criticized for their small sample size and open-label design. The current studies represents a significant advance over these prior studies by virtue of larger sample sizes and the use of comparator compounds as controls.

Serotonin selective reuptake inhibitors (SSRIs) and other antidepressants are thought to exert many of their actions, in part, by augmenting the concentration of serotonin at the neuronal synapse. Indeed, direct activation of serotoninergic nuclei in the dorsal raphe can produce antidepressant-like effects in animal models (Urban et al., 2016). The antidepressant effects of SSRIs and other conventional tricyclic antidepressants, however, require at least three to six weeks to achieve clinical efficacy (Frazer and Benmansour, 2002), which may not be optimal for individuals with terminal illness.

Although SSRIs and psilocybin presumably both work via modulating central nervous serotonin, psilocin, the active hydroxy metabolite of psilocybin, directly activates serotonin receptors, including 5-HT2A receptors located on prefrontal cortical neurons (Willins et al., 1997). Elevated cortical 5-HT2A receptor expression has been implicated in depression-related suicide (Pandey, 2013; Pandey et al., 2002), and SSRIs have been reported to reduce cortical 5-HT2A receptor expression (Yamauchi et al., 2006) via a process termed receptor downregulation. Considering that both 5-HT2A antagonists and agonists have been found to induce 5-HT2A downregulation (Yadav et al., 2011), and that several newer generation antidepressants such as mirtazepine (Nutt, 1998) possess 5-HT2A antagonist activity, it is conceivable that psilocin may possess such sustained antidepressant effects with one-time use via downregulating serotonin receptors, although further studies are needed to test this hypothesis directly. It should be noted, though, that psilocin has actions at essentially all other serotonin receptors (http://kidbdev.med.unc.edu/databases/kidb.php), and its actions could be due to a

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combination of actions at many serotonin receptors in addition to its agonist actions at 5-HT2A receptors.

Over the past 50 years, the use of psychedelic drugs such as psilocybin and LSD as potential therapeutics has remained controversial (Nichols, 2016). The Griffiths et al. (2016) and Ross et al. (2016) studies, as well as previous studies (Griffiths et al., 2006), suggest that the mystical experience stemming from psilocybin sessions may be an integral part of the antidepressant process. Given the complex pharmacology of these compounds, however, it would be essential to extend these findings, for instance by attempting to abrogate the hallucinatory actions via pretreatment with a 5-HT2A-selective antagonist. Alternatively, more selective 5-HT2A agonists exist (e.g., 2,5-dimethoxy-4-iodoamphetamine), and it would be interesting to see if they have similar apparent antidepressant actions. This is particularly relevant given the recent finding that the antidepressant actions of ketamine may be due to metabolites, which lack the NMDA-like pharmacology associated with the parent compound (Zanos et al., 2016).

Nonetheless, the findings of Griffiths et al. (2016) and Ross et al. (2016)—that one-time use of psilocybin can produce clinically relevant and apparently long-lasting effects on depressive and anxious symptoms—are remarkable, and they underscore the potential for psilocybin as an alternative to first-line antidepressants.

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