Role of psilocybin in the treatment of depression

Ther Adv Psychopharmacol
2017, Vol. 7(1) 54–56
DOI: 10.1177/2045125316676092

Ananya Mahapatra and Rishi Gupta

Abstract: Psilocybin is a naturally occurring alkaloid, pharmacologically similar to the classic hallucinogen lysergic acid diethylamide (LSD). Although primarily used as a recreational drug or an entheogen in particular cultural settings, recent population based studies have shown that it does not lead to serious physical or mental health problems or dependent use. In view of recent work demonstrating psilocybin's potential to increase subjective sense of wellbeing and because of its novel mechanism of 5-HT_{2A} serotonin receptor agonism, it is being explored for possible therapeutic utility in mood and anxiety disorders.

Keywords: depression, hallucinogen, psilocybin, treatment

Classical hallucinogens have been categorized into three groups: tryptamines, such as psilocin, the psychoactive metabolite of psilocybin; lysergamines (a subgroup of tryptamines), prominently lysergic acid diethylamide (LSD); and phenethylamines, such as mescaline [Geyer *et al.* 2009]. Psilocybin is a naturally occurring alkaloid. Though primarily considered a recreational substance, recent population-based studies have shown that it does not lead to serious physical or mental health problems, including dependence [Krebs and Johansen, 2013; Johansen and Krebs, 2015]. The psychopharmacological action of psilocybin is thought to be mediated *via* binding to serotonergic 5-HT_2 receptors, primarily 5-HT_{2A} receptors, although non-5-HT_2 receptors are probably also involved [Tylš *et al.* 2014]. Downregulation of 5-HT_{2A} receptors is purported to mediate antidepressant and antianxiety effects of antidepressants and atypical antipsychotics [Van Oekelen *et al.* 2003]. Because of the high binding affinity of psilocybin to the 5-HT_{2A} receptor, its effects are thought to be mediated through modulation of 5-HT_{2A} receptors, in addition to second messenger signalling and gene-expression effects [Gonzalez-Maeso *et al.* 2007].

In view of recent work demonstrating psilocybin's potential to increase subjective sense of wellbeing [Griffiths *et al.* 2008] and because of its novel mechanism of 5-HT_{2A} serotonin receptor agonism, it is being explored for therapeutic utility in mood and anxiety disorders [Vollenweider and Kometer, 2010].

A recent study made an attempt to investigate the feasibility, safety and efficacy of psilocybin in treatment-resistant unipolar depression, when administered along with psychological support [Carhart-Harris *et al.* 2016]. This was the first open-label study in patients with moderate to severe unipolar depression who had not responded to two or more adequate trials of antidepressants from different pharmacological classes. The authors administered 10 mg (low dose) oral psilocybin, followed 1 week later by another dose of 25 mg (high dose). Psilocybin was well tolerated by all patients, and no serious or unexpected adverse events were reported. Relative to baseline, depressive symptoms were markedly reduced at 1 week and at 3 months after treatment. This study paves the way for more rigorous trials in the future to further investigate the therapeutic potential of psilocybin in depression.

The foremost requirement for any pharmacological agent to be used as a medicinal drug is that it should be acceptably safe when administered to humans. The doses of psilocybin used in the present study have been shown to be safe previously when administered to both healthy individuals, and patients with medical and psychiatric illness. A study in 36 healthy individuals who received 30 mg of psilocybin found no sustained deleterious physiological or psychological effects [Griffiths

Correspondence to:
Ananya Mahapatra, MBBS, MD
Department of Psychiatry, 4th floor Academic Block, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India
nnyaa09@gmail.com

Rishi Gupta, MBBS
Junior Resident, Department of Psychiatry and National Drug-Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS), New Delhi, India

et al. 2006]. Another study exploring the effects of psilocybin on anxiety in 12 patients with advanced-stage cancer reported no clinically significant adverse effects [Grob *et al.* 2011].

Second, for a psychedelic drug to be feasibly used as a pharmacologic agent in humans, its acute effects themselves should be well tolerated, and easily managed. Psilocybin has been found to have mild, pleasurable and nonthreatening effects in 110 healthy individuals in a pooled analysis of eight double-blind placebo-controlled experimental studies [Studerus *et al.* 2011]. This study concluded that administration of moderate doses of psilocybin in well-prepared subjects in a carefully monitored environment was associated with an acceptable level of risk.

There is a growing evidence base suggesting a neurobiological basis for the possible efficacy of psilocybin in unipolar depression. A functional magnetic resonance imaging (fMRI) study showed that the medial prefrontal cortex (mPFC) was consistently deactivated by psilocybin [Carhart-Harris *et al.* 2012a]. Medial PFC has been shown to be hyperactive in fMRI studies in depression, and effective treatment of depression has shown to normalize this hyperactivity [Holtzheimer and Mayberg, 2011]. Thus, the deactivation of mPFC by psilocybin is consistent with its proposed effect in depression. The fact that the magnitude of deactivation of mPFC was found to be correlated with the drug's subjective effects further supports this assumption [Carhart-Harris *et al.* 2012a]. Other fMRI studies have found that psilocybin attenuates amygdala activation in response to threat-related visual stimuli [Kraehenmann *et al.* 2015a], and decreases threat-induced modulation of top-down connectivity from the amygdala to the primary visual cortex [Kraehenmann *et al.* 2015b]. Both of these mechanisms are proposed to induce positive affect states. Given that the amygdala plays a central role in the perception and generation of emotions, and given that amygdala hyperactivity in response to negative stimuli has consistently been related to negative mood states in depressed patients [DeRubeis *et al.* 2008], the effect of psilocybin strongly points at a therapeutic mechanism in depression. Though psychedelics have historically been used to assist psychotherapy, recently a neurobiological basis for the same is emerging. Psilocybin has been found to robustly facilitate activation of various areas of the brain, including the limbic system, in response to autobiographical memory cues [Carhart-Harris *et al.* 2012b]. Such facilitation of the recall of salient memories during psychotherapy may be of significance. In addition, ayahuasca, a naturally occurring hallucinogen with a pharmacological profile similar to psilocybin, has been shown to significantly reduce depressive symptoms [Osório Fde *et al.* 2015], and increase blood perfusion in brain areas implicated in regulation of mood [Sanches *et al.* 2016].

The study by Carhart-Harris and colleagues [Carhart-Harris *et al.* 2012b] suffered from a few methodological issues. As it was an open-label, non-placebo-controlled study, it is not possible to differentiate between pharmacological action and the placebo effect of administering psilocybin, as the placebo effect has been shown to have a significant beneficial effect on depression on its own. However, designing double-blind, controlled studies with agents such as psilocybin is difficult, given the ease with which its psychotropic actions are recognizable. Also, as 5 of the 12 participants reported previous psilocybin use, it is possible that a predisposition towards the pleasurable effects of the substance may have contributed to the improvement in symptoms, thus confounding the results. Adverse effects such as paranoia, as described by one of the participants, may also hamper the effectiveness of such drugs. In addition, patient compensation may influence outcomes in such studies, and this information is not adequately elucidated in the paper in question. Finally, the authors have declared support from one of the many private foundations which finance research into hallucinogens [Dakwar, 2016]. Since detailed information on conflicts of interest has not been provided, skepticism may arise as to the role of such foundations in study design and execution, potentially biasing the results. Such studies also face practical issues, such as procuring supplies of hallucinogens. By overcoming limitations such as unclear information on the conflicts of interest, such studies may gain more acceptance in the medical community.

Thus, although limited, the current evidence base suggests that psilocybin may prove to be a safe, feasible, and efficacious pharmacological agent for depression, at least in patients not responding to conventional therapies.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

Carhart-Harris, R., Bolstridge, M., Rucker, J., Day, C., Erritzoe, D., Kaelen, M. *et al.* (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* 3: 619–627.

Carhart-Harris, R., Erritzoe, D., Williams, T., Stone, J., Reed, L., Colasanti, A. *et al.* (2012a) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci U S A* 109: 2138–2143.

Carhart-Harris, R., Leech, R., Williams, T., Erritzoe, D., Abbasi, N., Bargiotas, T. *et al.* (2012b) Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. *Br J Psychiatry* 200: 238–244.

Dakwar, E. (2016) The death and rebirth of hallucinogens. *Drug Alcohol Depend* 165: 293–297.

DeRubeis, R., Siegle, G. and Hollon, S. (2008) Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nat Rev Neurosci* 9: 788–796.

Geyer, M., Nichols, D. and Vollenweider, F. (2009) Serotonin-related psychedelic drugs. In: Squire, L. (ed.), *Encyclopedia of Neuroscience*. Oxford: Academic Press.

Gonzalez-Maeso, J., Weisstaub, N., Zhou, M., Chan, P., Ivic, L., Ang, R. *et al.* (2007) Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 53: 439–452.

Griffiths, R., Richards, W., McCann, U. and Jesse, R. (2006) Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacol (Berl)* 187: 268–283.

Griffiths, R., Richards, W., Johnson, M., McCann, U. and Jesse, R. (2008) Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol* 22: 621–632.

Grob, C., Danforth, A., Chopra, G., Hagerty, M., McKay, C., Halberstadt, A. *et al.* (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry* 68: 71–78.

Holtzheimer, P. and Mayberg, H. (2011) Stuck in a rut: rethinking depression and its treatment. *Trends Neurosci* 34: 1–9.

Johansen, P. and Krebs, T. (2015) Psychedelics not linked to mental health problems or suicidal behavior: a population study. *J Psychopharmacol* 29: 270–279.

Kraehenmann, R., Preller, K., Scheidegger, M., Pokorny, T., Bosch, O., Seifritz, E. *et al.* (2015a) Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. *Biol Psychiatry* 78: 572–581.

Kraehenmann, R., Schmidt, A., Friston, K., Preller, K., Seifritz, E. and Vollenweider, F. (2015b) The mixed serotonin receptor agonist psilocybin reduces threat-induced modulation of amygdala connectivity. *NeuroImage Clin* 11: 53–60.

Krebs, T. and Johansen, P. (2013) Psychedelics and mental health: a population study. *PLoS One* 8: e63972.

Osório Fde, L., Sanches, R., Macedo, L., Santos, R., Maia-de-Oliveira, J., Wichert-Ana, L. *et al.* (2015) Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Rev Bras Psiquiatr* 37: 13–20.

Sanches, R., de Lima Osório, F., dos Santos, R., Macedo, L., Maia-de-Oliveira, J., Wichert-Ana, L. *et al.* (2016) Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression. *J Clin Psychopharmacol* 36: 77–81.

Studerus, E., Kometer, M., Hasler, F. and Vollenweider, F. (2011) Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *J Psychopharmacol* 25: 1434–1452.

Tylš, F., Paleníček, T. and Horáček, J. (2014) Psilocybin – summary of knowledge and new perspectives. *Eur Neuropsychopharmacol* 24: 342–356.

Van Oekelen, D., Luyten, W. and Leysen, J. (2003) 5-HT_{2A} and 5-HT2C receptors and their atypical regulation properties. *Life Sci* 72: 2429–2449.

Vollenweider, F. and Kometer, M. (2010) The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. *Nat Rev Neurosci* 11: 642–651.