

Return of the psychedelics: Psilocybin for treatment resistant depression



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ABSTRACT

Psilocybin, the clinically most researched classic psychedelic has recently been tested for its safety and efficacy in a clinical population of treatment resistant depression. The efficacy of psilocybin in clinical depression previously demonstrated in the electrophysiologic and neuroimaging findings as also in neuropsychological assessments is further validated by the findings of this rigorously conducted randomized trial. Mechanism of action of psilocybin and efficacy in treatment resistant depression are discussed in this paper. Ethical issues of conducting clinical trials with psychedelics are also discussed with particular emphasis on their relative safety and absence of addiction potential. Implications of these issues for conduct of larger trials for establishing risk benefit ratio in treatment resistant depression are further suggested.

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Psilocybin (4-phosphoxy-*N,N*-dimethyltryptamine), the best known classic psychedelic is a monoamine/indole alkaloid naturally occurring in psilocybe genus of mushrooms (Mithoefer et al., 2016). A serotonin agonist in the human brain psilocybin acts like a hallucinogen and has profound effect on cognition, perception and emotion producing transient psychosis like symptoms (Nichols, 2016). Known as a recreational drug of abuse and viewed pejoratively by the medical community, clinically significant positive results in a recent phase II trial in treatment resistant depression have renewed interest in its therapeutic potential (Carhart-Harris et al., 2016).

Serotonergic hallucinogens are the oldest recreational drugs dating back to the prehistoric era and continue being used. The Aztecs used 'god's flesh' (psilocybe mushrooms) in various religious healing ceremonies (Nichols, 2016). In youths hallucinogens caused 'social perversion' and 'insanity' perceived as a social rebellion and resulted in the political decision of schedule I categorization.

Continuing research into their therapeutic and adverse effects has generated an intense debate on this stringent categorization. No definite harm has been proven; these do not act on dopaminergic system so cannot cause dependence or addiction rather have anti-addictive properties. Positive findings of their

therapeutic effectiveness have further intensified this debate (Mithoefer et al., 2016).

Hallucinatory action of psilocybin is due to indole ring at 4th position of its simple tryptamine structure. (Fig. 1) Upon ingestion rapid hydrolysis dephosphorylates it into psilocin (4-hydroxy-dimethyltryptamine), its active ingredient. The oral effective dose of psilocybin is 0.045–0.429 mg/kg body weight. The plasma half life upon oral ingestion is 2.5 h and onset of action of hallucinogenic effect is within 1–2 h of oral intake which lasts for about 3–4 h (Tylš et al., 2014).

Psilocybin use is perceived as a pleasant positive spiritual and mystical experience; which users reminisce as personally meaningful. Positive effect on behavior and attitude last longer than the duration of use. Effect of psilocybin is influenced by mental state, prior experience with use, personality dimension and environmental conditions (Griffiths et al., 2011).

Naturally occurring serotonergic hallucinogens are physiologically safe. Physical side effects reported include headache and cortical blindness due to vasoconstrictive property (Nichols, 2016). However, concerns of psychological problems during psilocybin administration require administration under clinically supervised structured settings. Safety guidelines for psychedelic research recommend adequate subject preparation, environmental setting and presence of clinician with sufficient knowledge and experience of administering psychedelics (Fischman and Johanson, 1998).

Psilocybin has positive influence on mental health in terms of reduction of psychological distress and suicidal thoughts (Hendricks et al., 2015). Phase II clinical studies of effectiveness

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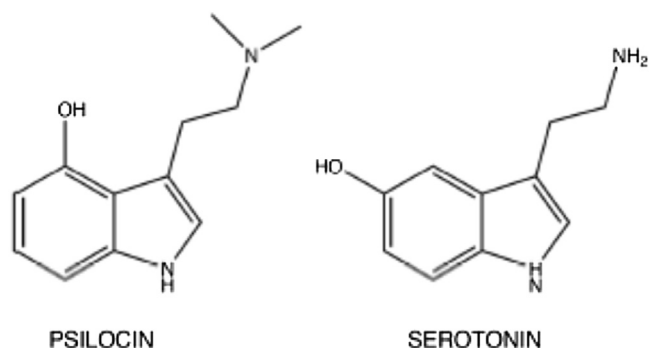


Fig. 1. Psilocybin: structural resemblance to serotonin.

Source: adapted from Tittarelli et al. (2015).

of psilocybin in obsessive compulsive disorder, depressive disorders, cancer anxiety, and alcohol and tobacco dependence have shown preliminary positive results (Nichols, 2016).

The inhibitory effect of psilocybin on amygdala is the biological basis of positive affective state observed in BOLD (Blood Oxygen Level dependent) fMRI changes. Psilocybin has attenuating effects on right amygdala with resulting decrease in amygdala reactivity to neutral and negative images which causes increase in positive affective state (Kraehenmann et al., 2016). Recently phase II trial has demonstrated feasibility and effectiveness of psilocybin in patients of treatment resistant depression (Carhart-Harris et al., 2016) with clinically meaningful improvement in Hamilton Depression Rating Scale (HDRS) scores of 10 points in one week.

This trial has heralded a new era in clinical research adhering to psychedelic research guidelines.

Psilocybin is proving a true psychedelic, meaning ‘of benefit to mind.’ Carefully conducted double blind placebo controlled trials with adequate power can predict whether effect of psilocybin outweighs its risks in treatment resistant depression.

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