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Spotlight

Is psilocybin an effective antidepressant and what is its Mechanism of action?

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Goodwin et al.[1] report a single 25 mg dose of psilocybin has an antidepressant effect short-term in medication-resistant depression. Unanswered questions include drug blood level as a guide to dose, psychedelic effects relationship to antidepressant benefit, and potential suicide risk of psilocybin.

Idiographic reports that psychedelic drugs like psilocybin (an active ingredient of some psilocybe mushroom species) may have antidepressant properties have captured public imagination and spurred efficacy studies. To date, such studies were mostly sponsored by purpose-driven, venture capital-funded entities instead of traditional large pharmaceutical companies. This race to market has left many basic questions unanswered. The first major study came from Carhart-Harris et al.[2] and used a complex dosing plan that involved either two 25 mg doses of psilocybin given 3 weeks apart, overlapping with 6 weeks of placebo, or two 1 mg doses of psilocybin 3 weeks apart, overlapping with 6 weeks of a selective serotonin reuptake inhibitor (SSRI) antidepressant. The study failed to find efficacy using its primary outcome measure at 6 weeks, but secondary outcomes favored psilocybin. A study by Goodwin et al.[1] included outpatients with treatment-resistant depression and employed single doses of 1 mg, 10 mg, or 25 mg of psilocybin. The primary outcome was measured at 3 weeks. Individuals who participated in the study were asked to stay off other psychotropic medications for the first 3 weeks and most complied. The 25 mg dose showed efficacy compared with 1 mg daily at 3 weeks, and this continued until 12 weeks, even though many patients started other antidepressants after week 3. The 25 mg dose group showed a 12-point mean improvement at 3 weeks compared with 5.4 in the 1 mg group. Most side effects (nausea, headache) were comparable between the 10 mg and 25 mg dose groups, but surprisingly, the paper is silent about psychedelic effects even though it reports such effects lasted about 6 h after taking psilocybin. Of note, suicidal ideation and behavior history were comparable in all three dose groups prior to the study, but *emergent* suicidal ideation and behavior was observed in the 25 mg and 10 mg groups and not in the 1 mg group (employed as an active comparator instead of a placebo).

Psychedelics like psilocybin are 5-HT_{2A} receptor agonists, and this action is considered to mediate both their psychedelic and antidepressant effects.[3] Positron emission tomography (PET) brain imaging using the 5-HT_{2A} agonist PET tracer [11C]Cimbi-36 finds 43% receptor occupancy at a dose of about 3.5 mg,[4] and higher occupancy with higher doses in healthy volunteers, ranging to over 60% occupancy for 14 mg or higher doses. This study showed that blood level correlates more strongly than oral dose with brain occupancy, not surprising given 20-fold inter-individual variation in blood levels on the same oral dose of many drugs. The findings support use of drug plasma levels to optimize psilocybin doses and to analyze dose-dependent variance in clinical response, instead of using oral dose. In this study of brain 5-HT_{2A} receptor occupancy, the lowest psilocybin dose of about 3.5 mg showed robust occupancy because the PET tracer employed was an agonist. An antagonist PET tracer binds to the high and low agonist-affinity receptor conformational states with equal affinity. Such a PET tracer would underestimate receptor occupancy of psilocybin because the psilocybin would not compete for binding at the low agonist-affinity receptor. Other psychotropic medications, like SSRIs or antipsychotics, appear to require more than 70% occupancy to exert a therapeutic effect. But those drugs work by blockade, an effect requiring most sites to be occupied. In contrast, agonists may produce effects with much lower levels of receptor occupancy. Perhaps the receptor binding levels of the 1 mg dose is below what is required for benefit, but 14 mg and above have occupancy levels of above 60% and would be expected to have therapeutic benefit and psychedelic side effects. This prediction is supported by this PET study, because intensity of psychedelic effects strongly correlated with 5-HT_{2A} receptor occupancy.

A comparison of the Carhart-Harris et al. and Goodwin et al. studies is instructive. Carhart-Harris et al. found an 8-point MADRAS score decline at week 6 in the psilocybin group compared with a 6-point decline in the SSRI group. Goodwin et al. found a 12-point decline in the 25 mg group compared with a 5.4-point decline in the 1 mg group at 3 weeks. The Goodwin study showed 50% more improvement in the 25 mg group psilocybin group despite giving only one dose, studying treatment-resistant depression, and measuring response after only 3 weeks. Perhaps the clinical samples were different or there is another explanation. In the STAR*D study,[5] the response rate to two initial 6-week clinical trials was 56%, but the response rate for the third and fourth clinical trials was only 11%. If the STAR*D and Goodwin study populations were comparable, then the 37% response rate in the Goodwin 25 mg group is more than three times better than expected.

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These results should be compared with ketamine, which has psychotomimetic effects, and one dose works rapidly and robustly, even in antidepressant-resistant depression. The Goodwin study indicates the initial response to psilocybin was already apparent in full at day 2, and so psilocybin is rapidly acting and worked in medication-resistant depression. Psilocybin works via the 5-HT_{2A} receptor, and ketamine is an NMDA receptor antagonist and thought to work via AMPA receptor-mediated glutamate trophic effects, although some suggest it works via mu opioid receptors. Milak et al.[6] found that the psychotomimetic symptoms of ketamine were not quantitatively related to antidepressant benefit, raising the possibility that an effective NMDA antagonist antidepressant can be developed without psychotomimetic effects. Is the same true for psilocybin? Finally, ketamine is robustly effective in diminishing the severity of suicidal ideation,[7] but psilocybin in the Goodwin study was associated with emergent suicidal ideation and behavior in the 10 mg and 25 mg groups. Other psychedelics, like LSD, have idiographic evidence of the risk of a bad trip with suicidal urges. These side effect differences may reflect pharmacologic differences in these two antidepressants.

Future research must examine the role of drug levels to optimize dosing, examine the best way to use psilocybin given its apparent rapid onset of action, evaluate its safety in terms of suicide risk, and consider alternative chemical structures that may retain its therapeutic effect without the accompanying psychedelic effects.

DECLARATION OF INTERESTS

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