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Question-based Drug Development for psilocybin

In *The Lancet Psychiatry*, Robin Carhart-Harris and colleagues[1] conclude that there is preliminary support for the safety and efficacy of psilocybin for treatment-resistant unipolar depression. This finding is important because more effective pharmacological treatments with acceptable side-effects are urgently needed for patients suffering from depression. We support the limitations the authors have pointed out about the study population and trial design. We also recognise the paucity of well-designed trials in psychiatry that are based on the principles of clinical pharmacology. Nonetheless, the study raises several crucial questions regarding its pharmacological aspects. At our institute, we apply the so-called Question-based Drug Development (QBD)[2] approach in the design of trials with innovative CNS drugs, which has enabled us to guide the development of various new CNS drugs along a rational path in the past 25 years. Essentially, the QBD approach requires reliable answers to six crucial questions to understand the pharmacological effects of CNS drugs, as illustrated below for psilocybin.

(1) Does psilocybin or its active metabolites reach the site of action? Psilocybin is administered orally, after which it is systemically absorbed, distributed across the blood–brain barrier and, at the same time, metabolised and excreted.[3] Additionally, psilocybin is a prodrug and is converted to the biologically active psilocin. Because the authors do not expand on these issues in their study, it is uncertain how psilocybin's pharmacokinetics relate to mood-elevating pharmacodynamic properties.

(2) Does psilocybin cause its intended pharmacological or functional effects? Psilocybin is thought to exert its primary pharmacological action through $5HT_{2A}$ receptor ($5HT_{2A}R$) agonism. To verify whether psilocybin actually has central serotonergic effects, establishing the effect of psilocybin on validated biomarkers for serotoninergic stimulation, such as cortisol and prolactin release[4] and pupil dilatation,[5] could be informative.

(3) Does psilocybin cause undesired pharmacological effects? Information about in-vitro receptor binding affinity or preclinical experiments with psilocybin is not provided, so it is unclear whether psilocybin has off-target or secondary pharmacological effects that might cause clinical side-effects or raise safety issues in patients with depression. Also, abuse potential after prolonged exposure is not addressed.

(4) Does psilocybin have beneficial effects on the disease or its clinical pathophysiology? $5HT_{2A}R$ agonism has been linked to enhanced cognitive flexibility, associative learning, cortical neural plasticity, and putative mood improvement in animals. Because these functional processes could be involved in the pathophysiology of depression, it might be useful to evaluate whether psilocybin has such functional effects in a population of patients with depression. Alternatively, the neuroimaging data that are yet to be presented might, therefore, provide interesting findings in terms of neuronal network biomarkers.

(5) What is the therapeutic index of psilocybin? The rationale for the selected doses is unclear because no previous dose-ranging has been done. Also, the relationship between psilocybin's presumed favourable mood-enhancing effects and toxic CNS effects remains obscure. Therefore, the presented clinical adverse effects might have been the result of unintended toxic CNS concentrations, which actually might have attenuated psilocybin's potential effects on mood.

(6) How do the sources of variability in response to psilocybin in patients with depression affect its application? Variability relating to both pharmacodynamic (such as population characteristics in terms of depression or tolerance due to previous antidepressant use) and pharmacokinetic (such as absorption, clearance, and gender) issues should be identified, to understand differences between individuals in terms of response or the occurrence of side-effects.

In our opinion, future trials with psilocybin in patients with depression will benefit from the QBD approach. After all, such a systematic approach is expected to yield information that would facilitate understanding of psilocybin's pharmacodynamic effects in relation to its pharmacokinetics, and as a consequence, increase the reliability of data generated in trials with patients.

We declare no competing interests.

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Authors' reply

We are grateful to Colin Hendrie and Alasdair Pickles, and Francis Dijkstra and colleagues for their letters.

First, a comment on the title of Hendrie and Pickles' letter: *psilocybin: panacea or placebo*. Poetics aside, psilocybin is, of course, neither of these things. Although Hendrie and Pickles are not suggesting the former, they seem to imply that our clinical outcomes were unimpressive and no greater than what can be achieved with placebo. They offer two citations to support the claim that placebo can account for 40% remission rates in major depression, equivalent to what we observed 3 months on from only two exposures to psilocybin in treatment-resistant depression. Crucially, however, remission rates are not reported in either of the papers cited. Khan and Brown[1] do not, in fact, mention remission rates once in their 4000-word review and Iovieno and colleagues's review[2] on bipolar depression only mentions response rates, which were 25–40% for placebo, compared with our 75% reduction 1 week after treatment with 25 mg psilocybin (measured by Beck Depression Inventory [BDI]). In the review by Khan and Brown,[1] percentage symptom reduction data are presented for placebo and a range of active treatments. Percentage symptom reduction with placebo was 30–40%, whereas, in our trial, it was a 74% reduction 1 week after treatment with 25 mg psilocybin (BDI). If Hendrie and Pickles propose that psilocybin's effects can be accounted for by mere placebo-like expectation, then it is most appropriate to gauge this 1 week after treatment, when expectation is likely most influential. Placebo conditions in depression trials typically involve the daily intake of capsules for several weeks (eg, 56 daily doses in a typical 8-week trial), whereas, we had just two doses in our psilocybin trial. Even when we compare results with placebo 3 months after treatment, psilocybin was associated with a 55% symptom reduction (BDI), superior to most of the active treatments in the meta-analysis by Khan and Brown.[1] Finally, it is important to re-emphasise that patients in our trial met criteria for treatment-resistant depression; they had a mean duration of illness of 18 years, did not improve with an average of five different medications and 11 of 12 patients had also tried at least one form of psychotherapy. In such a context, 67% remission rates at 1 week after treatment and 42% at 3 months, should be considered promising in the very least.

To address Dijkstra and colleagues' questions in turn: (1) Does psilocybin or its active metabolites reach the site of action? The evidence suggests so. Pretreatment with serotonin 2A receptor antagonists effectively abolishes the principal psychedelic effects of psilocybin,[1] even at lower doses than we gave in our trial. Future research could assess this relationship in a patient population, but it would be surprising if the outcome were any different. An important scientific question for our ongoing research is what accounts for the long-term effects of psilocybin after the drug has been metabolised and excreted? We are currently seeking grant money to address this under-researched topic. (2) Does psilocybin cause its intended pharmacological or functional effects? Our answer would be consistent with that given above. The evidence that psilocybin elicits its effects via serotonin 2A receptor agonism is strong.[3] (3) Does psilocybin cause undesired pharmacological effects? Psilocybin is not associated with any known toxicity. The transient anxiety[4] and headaches[5] might be caused by serotonin 2A receptor agonism and future work could test this, but these side-effects are short-lived (eg, minutes for anxiety and 1–2 days for headaches) and were often dismissed by patients relieved about the alleviation of their depressive symptoms. (4) Does psilocybin have beneficial effects on the disease or its clinical pathophysiology? Our forthcoming report on pretreatment versus post-treatment functional MRI in an extended sample from this study will shed light on this matter, but the short answer is, probably both. (5) What is the therapeutic window index of psilocybin? Dose finding has been done previously[6] and these data informed our dose selection for this trial. (6) How do the sources of variability in response to psilocybin in patients with depression affect its application? This is a very interesting question and one that we are keen to address in future work. We suspect a combination of psychological state and trait, as well as environmental and genetic factors contribute to this variability.

We declare no competing interests.

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