The speed with which psilocybin and other psychedelics have gone from pariah status to being widely seen as mental health’s next great pharmacological hope is nothing short of remarkable. To give a sense of this, in 2016, there were three entities engaged in psychedelic drug development programmes under the ‘commercial sponsor’ designation. As of mid-2020, at least 20 organisations, including large pharmaceutical companies, have either entered or invested in the psychedelic space. Most studies of psilocybin and other psychedelics to date have used high doses that reliably induce a full psychedelic experience. Although interest in the repeated use of low doses (i.e., ‘micro-dosing’) of psychedelics is intense, this strategy awaits its first formal human studies.

To highlight key study design decisions that any high-dose psychedelic drug development programme will have to face, this article examines several of the most pressing considerations in the development of psilocybin for major depressive disorder (MDD) and treatment resistant depression (TRD). This focus allows us to leverage the fact that these development efforts are further along than others in the psychedelic space and thus have had to wrestle more thoroughly with how to design and implement studies that meet regulatory licensing expectations. To date, the success of these design choices – as imperfect as they are – is reflected in the fact that the two drug development sponsors working in this area have both received breakthrough therapy designation from the FDA for these indications.

Major Depressive Disorder: The Need for Novel Treatments and the Evidence for Psilocybin

Despite many available pharmacological and behavioural...
treatments, rates of MDD – and its most worrisome symptom, suicide – has increased over the last several decades in much of the developed world, such that MDD is now the leading worldwide cause of medical disability (1). Multiple factors contribute to this state of affairs, but none more so than the fact that current treatments, despite helping many patients, are inadequate. In particular, antidepressant medications take weeks to fully work, and only provide optimal symptom relief in two-thirds of patients – even after these patients have undergone multiple trials of different agents (2). In patients who achieve remission, relapse rates are high even when medication is continued, and higher still when medication is withdrawn (3). Many patients stop using antidepressants or tolerate a reduced quality of life due to side effects. Perhaps of most concern, some evidence suggests that prolonged antidepressant use may actually worsen disease course in MDD and/or may promote treatment resistance (4).

Although far from definitive, five small academic studies paint a very different picture of the effects of psilocybin in depressive conditions (5-9). Unlike standard antidepressants, psilocybin produces an antidepressant effect that is apparent within a day following a single treatment and that lasts, in at least some patients, for an extended period of months to years without the need for additional dosing (8,10). Although the six- to eight-hour psychedelic experience induced by psilocybin can be emotionally challenging for many patients, when dosed in a psychotherapeutically supportive clinical setting psilocybin elicits strikingly low rates of long-term adverse physical or psychological adverse events (11).

The First Study Design Challenge: Is Psilocybin Even an Antidepressant?

In all recent studies of psilocybin as a therapeutic agent, the drug has been administered within a protocol most frequently referred to as ‘set and setting’ (SaS), with ‘set’ referring to the mindset a person brings to the psychedelic experience and ‘setting’ referring to the physical and interpersonal environment in which the experience occurs. Although varying somewhat between research groups and development programmes, the SaS universally comprises:

1. A significant preparation period prior to drug dosing
2. Dosing in an aesthetically pleasing room with at least one (typically two) trained psychotherapists in attendance
3. One or more post-dosing psychotherapeutic integration sessions conducted with the patient by the same therapists

This approach is widely considered essential for both efficacy and safety, and is consistent with the increasingly accepted theory that psilocybin is not an antidepressant in and of itself, but rather produces therapeutic effects in dependence upon the occurrence of transformative psychedelic experiences, which, in turn, require
an appropriate psychotherapeutic context to reliably occur (11-12).

The SaS has been lauded as a biopsychosocial intervention that might help heal the rift between pharmacology and psychotherapy that bedevils mental health treatment in the US. However, it also poses unique challenges in terms of study design. Foremost is the question of what exactly is being studied in psilocybin trials, and by implication, what might eventually be approved by the FDA or other regulatory agencies. In the context of MDD/TRD, is psilocybin best conceptualised as a pharmacological treatment, or as a catalyst for therapy? Might it be the case that psilocybin and its context of delivery are synergistic in ways that make separating them therapeutically meaningless?

Both of these possibilities suggest different study design approaches. For example, if psilocybin is a pharmacological treatment, drug delivery contexts might be best designed to provide safety but not additional psychotherapeutic elements that – even if not extraneous – may introduce unhelpful variability into study outcomes. On the other hand, if psilocybin is a catalyst to psychotherapy in general, an optimal design might compare psilocybin and psychotherapy to placebo and psychotherapy. Finally, if psilocybin and psychotherapy are seen as an inseparable synergistic intervention, then rather than testing psilocybin in isolation or accepting current SaS approaches ‘as gospel’, it might be most prudent to first evaluate whether psilocybin synergises more effectively with one type of psychotherapy or psychological support framework than another.

Challenges with Study Blinding and Choice of Placebo

When we say that a medication works, we often fail to appreciate the question of ‘works compared to what?’, because placebo effects contribute so greatly to symptomatic improvements in MDD trials, the gold standard comparator for antidepressants is some type of placebo intervention that seeks to isolate direct biologic effects of the active agent from as many non-specific aspects of the treatment as possible.

When it comes to psilocybin, however, this strategy faces unique challenges. Like other psychedelics, psilocybin induces an acute experience characterised by a suite of perceptual, cognitive, and emotional effects so profound that many study participants rate the experience as among the five most significant and meaningful events of their lives. How would one fully blind research subjects or staff in the dosing room to this type of experience without rendering subjects unconscious? Further complicating this situation is that the subjective quality of the psychedelic experience induced by psilocybin strongly predicts the drug’s later therapeutic effects, not just in depression, but in anxiety and substance use disorders also. This means that were one to find a comparator that fully blinded subjects and staff by producing similar acute effects, it would likely also be a powerful antidepressant, and for those same reasons as psilocybin.

Although it is probably impossible to fully blind subjects to their randomisation status, several steps can mitigate this challenge, at least to some extent.

First, it is essential for both subjects and study personnel (especially those attending subjects during the dosing session) to be educated in, and committed to, the importance of not assuming they know which substance a given subject received. In fact, there are individuals who have minimal responses to psychedelics and others who have profound mystical experiences in response to placebo when administered in a SaS context. Encouraging subjects to make the most of their dosing experience may also help avoid unintended nocebo effects in subjects who believe they received placebo, although this might also enhance placebo response rates, which would need to be countered by larger study sample sizes.

Second, it is of utmost importance for symptom raters to be as removed as possible from any other knowledge regarding the subjects they assess. This can be optimally accomplished using off-site ‘centralised raters’ who have limited knowledge of the study design, do not know where in the study process a given patient is during any assessment, and do not engage with any given subject often enough to personally identify him or her.

Third, despite obvious limitations in relation to psilocybin, registration trials may require the use of a comparator substance. The choice of this comparator for two-arm studies is especially challenging. The use of a low (and presumably inactive) dose of psilocybin has been associated with enhanced blinding, but doesn’t allow a safety comparison of psilocybin with a biologically inactive substance (7). Moreover, even low doses of psilocybin may have relevant behavioural effects, as evidenced by the micro-dosing trend (13). Use of a fully inactive substance or a substance with biological effects unrelated to depression avoids these issues, but increases the risk of nocebo effects from frustrated subject expectations and provides no information on potential dose-response relationships that might provide additional confirmation that psilocybin does have direct pharmacological antidepressant effects.

Study Duration: How Long is Long Enough?

New antidepressants typically receive approval based on outperforming a placebo comparator over a
Identifying the degree to which psilocybin is a pharmacological antidepressant that requires a safe setting for administration vs being an element in a truly biopsychosocial intervention

2. Determining optimal strategies for blinding subjects and research personnel to randomisation status (including selection of the most appropriate comparator strategies)

3. Determining how to design studies to best identify long-term dosing strategies

What is more certain is that if results from studies conducted to date are replicated in larger sponsored studies designed to support regulatory approval, psilocybin will likely transform how we think about, and treat, MDD.

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