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Psilocybin: promising results in double-blind trials require confirmation by real-world evidence

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Historically the role of the medicines regulator has been to decide whether scientific and manufacturing data submitted by the medicine developer were valid and, if so, whether the clinical benefits of a product outweighed its risks in the intended population. Increasingly regulators now work with other stakeholders including patients, health technology assessors and payers to ensure that clinical trials provide the evidence required for all stakeholders to minimise uncertainty while providing timely access to new treatments for unmet needs. This collaboration has led to a number of regulatory and methodological innovations including new trial methodologies and sources of evidence (European Medicines Agency, 2016).

The studies from the Johns Hopkins and New York University (NYU) teams presented in this journal demonstrate rapid, substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer with a single administration of psilocybin compared with placebo in a supervised, clinical setting (Griffiths et al., 2016; Ross et al., 2016). These findings are very promising. They also raise important regulatory and methodological questions as regulators consider approving follow-on studies leading to general patient access. More specifically, the question is what research is needed now to be able to move the treatment from a randomised controlled environment to larger numbers of patients in a real-world care setting.

To address this question, a number of considerations made by regulators to release treatment with psilocybin for subsequent use in clinical practice need to be addressed.

To what extent might psilocybin be considered a ‘repurposed’ drug?

Psilocybin is not a new drug. A serotonergic hallucinogen acting as a 5-hydroxytryptamine receptor 2 (5-HT_{2A}) receptor agonist, it was first synthesised in 1958, and marketing approval was granted to Sandoz for use in psychiatric research and psychodynamic psychotherapy (Passie et al., 2002). But social and political pressure resulted in it being reclassified as a Schedule 1 drug in 1970 and Sandoz surrendered its licence. Limited clinical research on psilocybin in a variety of clinical conditions was resumed in the 1990s, and more recent interest in its therapeutic potential, has made reassessment of its regulatory status necessary. This is consistent with other medicines that have been repurposed for new indications.

What is its abuse potential and likelihood for dependency?

The previous reputation of hallucinogens used in recreational setting, has left them with an unfavourable reputation. Recent work

has shown psilocybin can be administered safely to patients with treatment-resistant depression, psychological distress associated with life-threatening diagnosis, in addition to alcohol and tobacco dependency, and obsessive compulsive disorder (OCD). Both animal models and human studies showed psilocybin to be non-habit forming and not capable of producing sufficient reinforcing effects to cause dependence (Fantegrossi, 2004).

Is the present knowledge on its clinical pharmacology sufficient for use with confidence in a broader range of patients?

Clinical pharmacology provides the physiological basis for the benefit-risk assessment of any drug and is thus an important part of any marketing authorisation submission.

Pharmacokinetic, pharmacodynamic and toxicological standards have changed greatly in the past 50 years, and much of the previous preclinical data on psilocybin is no longer admissible. The metabolic profile of psilocybin has now been elucidated using new analytical methodology. Its toxicology has been re-assessed and it has been shown to have extremely low toxicity; all modern clinical research uses doses within a large margin of clinical safety.

But to date, reproductive, genetic and carcinogenic toxicology information is limited mostly to ethnographic and population health evidence, and will have to be brought up to modern standards before repeated, multiple administrations or long-term use could be considered in clinical settings. For the current research with one or two psilocybin sessions in a patient population confronting life-threatening diagnoses, long term use has limited relevance.

In humans, after oral consumption psilocybin is converted by first-pass metabolism to psilocin which produces most of its pharmacological activity. The initial effects after oral administration occurs in approximately 20–30 min with peak effects 60–90 min

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post-drug administration, and effects lasting 4–6 h. Elevations of heart rate of 10–20 beats/min and in blood pressure of 10–30 mm Hg are seen in man. However, these effects only occurred within the supervised environment of the trial, were not clinically significant and did not persist beyond the supervised session.

Psilocybin produces an alteration in perception, thought and mood in a dose-dependent manner, typical of a hallucinogen. Alterations in visual perception and self-awareness are common, but reality testing remains intact. Most subjects describe their experiences as enriching, yet not something that they would regularly repeat. Dysphoric experiences appear to be rare, dose-dependent and are often associated with long-term therapeutic benefit in a supported setting (Griffiths et al., 2011). Studies in larger and more heterogeneous groups of patients are needed to find clinically useful predictors of response in individuals.

Is there a precedent for its use in the current healthcare delivery model, considering the proposed psilocybin-assisted treatment protocol?

Unlike most drugs, the request for marketing authorisation and eventually reimbursement of psilocybin is not merely for drug administration but for a model of psilocybin treatment administration as utilised in the two studies. In regulatory terms, this is unusual. The treatment protocol requires specially trained healthcare professionals to prepare and support patients during and after drug administration for which there is no precedent in the current mental healthcare delivery model. This will have to be spelled out in any risk management plan in the European Union and as part of a risk evaluation minimisation strategy (REMS) in the USA. Future protocols also call for careful design of research to incorporate the full spectrum of treatment support components as they would be an inseparable part of its use in routine care.

What is the optimal methodology to investigate further the effectiveness of psilocybin?

A renewed interest in pragmatic trials has fuelled discussions about the appropriate selection of patients and outcomes, supported the relevance of comparisons to usual care rather than placebo, and questioned the relevance of the conventional paradigm of double-blind tightly controlled trials even in the pre-launch setting (Zuidgeest et al. 2016). At the same time, diverse stakeholder perspectives demand a new vision on ethical constraints of such trials (Kalkman et al., 2015).

The initial proposed indication sought is the benefit to cancer patients with anxiety or depression; in particular, whether patients with a cancer diagnosis experience lasting reduction of symptoms when compared with usual care which does not include psilocybin.

While psilocybin treatment may be effective and well-tolerated under tightly controlled double-blind conditions, an important question is whether the observed benefits are sustained when applied under real-life conditions in a broader range of patients. To answer this question, the logical next step would be to conduct a pragmatic trial to explore the effectiveness of psilocybin-treatment in usual care. As there is no single widely accepted standard treatment for anxiety or depression in this clinical population, the relevant comparator in such a study is usual care.

An argument can be made that in order to define more precisely the contribution of psilocybin, protocol-driven psychotherapy should also be offered as a standard component of usual care in the control group. However, recent work would suggest that currently available psychotherapeutic treatments show minimal efficacy. In two double-blind trials published in this issue of the Journal, psychoeducation prior to the psilocybin session and support during and after treatment, appeared to play an important role. Therefore, the marketing authorization application should specify the mode of administration, rather than approval for the drug alone.

Conclusion

The results of two well-controlled blinded trials, showing persisting improvements in depression and anxiety in patients with life-threatening cancer with a single administration of psilocybin-assisted therapy, provide an important opportunity for the clinical management of such patients. Given additional circumstantial data on safety and tolerability of psilocybin, this paves the way for larger pragmatic trials in less selected patients under real-world conditions, including routine care as a comparator, to promote the use of this treatment in clinical practice with confidence.

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