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EDITORIAL

The psychedelic renaissance: the next trip for psychiatry?

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The psychedelic research renaissance is gaining traction. Preliminary clinical studies of the hallucinogenic fungi, psilocybin, with psychological support, have indicated improvements in mood, anxiety and quality of life. A seminal, open-label study demonstrated marked reductions in depression symptoms in participants with treatment-resistant depression (TRD). The associated neurobiological processes involve alterations in brain connectivity, together with altered amygdala and default mode network activity. At the cellular level, psychedelics promote synaptogenesis and neural plasticity. Prompted by the promising preliminary studies, a randomized, double-blind trial has recently been launched across Europe and North America to investigate the efficacy of psilocybin in TRD. One of these centres is based in Ireland – CHO Area 7 and Tallaght University Hospital. The outcome of this trial will determine whether psilocybin with psychological support will successfully translate into the psychiatric clinic for the benefit of patients.

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Four thousand metres above sea level, in Lípez Altiplano, Bolivia, a recent discovery of ancient artefacts, provided further evidence of the ever-present human desire for self-transcendence. Chemical residues of psychoactive plants, including psilocin, the active metabolite of psilocybin, were found on paraphernalia, dating back 1000 years (Miller *et al*. 2019). The altered states of consciousness evoked by these psychoactive plants in the brains of our ancestors were likely to have given them a different perspective on their relationship with themselves and their environment. Brain research is now throwing light on the processes involved in such altered states of consciousness.

What has also emerged is that psilocybin may be a potential therapeutic intervention for major depressive disorder. Following three decades of a psychedelic research embargo, Roland Griffiths at John Hopkins, and others, have conducted several double-blind placebo-controlled trials, using psilocybin in a supportive therapeutic setting. These studies have predominantly focused on healthy controls and those with anxiety related to cancer. In the group diagnosed with cancer, the psilocybin experience reduced anxiety (including death anxiety), improved mood, optimism and imbued a sense of meaning (Grob *et al*. 2011; Griffiths *et al*. 2016). Moreover, these effects were sustained at 6-month follow-up in 80% of the participants (Grob *et al*. 2011; Griffiths *et al*. 2016). The findings in terminally ill cancer patients have been reproduced by other research groups (Ross *et al*. 2016; Reiche *et al*. 2018). Griffiths and colleagues reported that, in healthy hallucinogen-naive adults, psilocybin led to profound experiences of personal 'meaning' and 'spiritual' significance (Griffiths *et al*. 2006). These subjective experiences generally related to feelings of greater interconnectivity with the environment and with others (Erritzoe *et al*. 2018).

Other research groups have utilized the altered perspective induced by psychedelic-assisted psychotherapy to help people overcome tobacco (Johnson *et al*. 2014; Johnson *et al*. 2017) and alcohol addiction (Krebs and Johansen, 2012; Bogenschutz *et al*. 2015; Dyck and Farrell, 2018; Garcia-Romeu *et al*. 2019). Preliminary evidence also suggests that obsessive–compulsive disorder may also benefit from psilocybin administered in a controlled environment (Moreno *et al*. 2006).

A ground-breaking study from Carhart-Harris and colleagues at Imperial College London has once again compelled psychiatry to re-appraise its ambiguous relationship with psychedelics. Sixty-seven percent of participants with treatment-resistant depression (TRD) had significantly reduced depression symptoms at 1 week, with 40% of participants showing a sustained response at 3 months post-dose (Carhart-Harris *et al*. 2016a). Furthermore, there were lasting benefits at 6-month follow-up in some participants (Carhart-Harris *et al*. 2018a). Notwithstanding the open-label design, with a small sample size, this study showed

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marked clinical improvements, rarely seen in the field of psychiatry. No doubt the Food and Drug Administration was influenced by their work when psilocybin was given 'breakthrough therapy' status last year. The Imperial College group are now comparing psilocybin to escitalopram in the treatment of depression (ClinicalTrials.gov Identifier: NCT03429075), *et al*. the results of which have the potential to introduce psilocybin into clinical psychiatry. Furthermore, an open-label pilot study to investigate the safety and efficacy of psilocybin in people with chronic anorexia nervosa has just started (NCT04052568).

Unravelling the neurobiological processes underlying the 'mystical experience' or ego dissolution evoked by psychedelics is an important endeavour for neuroscience. At the pharmacological level, psilocybin acts as a serotonin 2A receptor subtype agonist (Carhart-Harris, 2019). Compared to other recreational substances, psilocybin is among the least harmful, with minor physiological side effects and minimal reinforcing effects (Krebs and Johansen, 2013; Hendricks *et al*. 2015; Johansen and Krebs, 2015; Johnson *et al*. 2018). At the cellular level, psychedelics act as 'psychoplastogens', a relatively new class of fast-acting therapeutics capable of rapidly promoting structural and functional neural plasticity (Catlow *et al*. 2013, Ly *et al*. 2018). Indeed, the antidepressant effects of psilocybin have been demonstrated 1 day post-dose (Carhart-Harris *et al*. 2017). Interestingly, these cellular effects are comparable to those produced by the fast-acting antidepressant ketamine.

At the neuroimaging level, psychedelics alter brain connectivity (Carhart-Harris, 2019), and activity in the amygdala (Roseman *et al*. 2018) and default mode network (DMN) (Carhart-Harris *et al*. 2017). DMN integrity has been linked to many complex psychological processes, including depressive rumination (Hamilton *et al*. 2015). A 'reset' mechanism has been proposed by which a decrease in DMN integrity during the psychedelic experience (Carhart-Harris *et al*. 2012; Palhano-Fontes *et al*. 2015; Carhart-Harris *et al*. 2016b) may increase or normalize in the post-acute period (1 day post-dose) accompanied by improvements in mood (Carhart-Harris *et al*. 2017). Indeed, increased ventromedial prefrontal cortex–bilateral inferior lateral parietal cortex resting state functional connectivity, 1 day post-dose, predicted treatment response (measured by the Quick Inventory of Depressive Symptoms scale) at 5 weeks post-dose (Carhart-Harris *et al*. 2017). However, larger studies will be required to confirm this intriguing theory.

The scarcity of successful translation into the clinic is a major challenge for psychiatry (Kelly *et al*. 2016; Kelly *et al*. 2017a). A rare, but successful example of translation into clinical utility is the re-purposing of ketamine, first synthesized in 1956 (Li and Vlisides, 2016). The unfulfilled promises of translational breakthroughs from neuroscience, and of paradigms shifts that fail to deliver discernible benefits to patients, are understandably frustrating for clinicians. Apart from ketamine, and the recently approved brexanolone, an analogue of the endogenous hormone allopregnanolone, for the treatment of postpartum depression (Meltzer-Brody *et al*. 2018), very little research has translated into tangible clinical benefits for patients in recent decades. Of note, neither ketamine nor brexanolone is currently available in Ireland.

Will the psychedelic renaissance deliver translational benefits for patients or launch psychiatry into another round trip? This renaissance, and the enthusiasm among the general population (Polito and Stevenson, 2019), has left some professionals nonplussed. They await the scientific evidence. Some of the hesitations about psilocybin relate to previous 'trips' into psychedelic use in psychiatry that did not involve consistent rigorous scientific study, such as Timothy Leary's Harvard Psilocybin Project (Moreno, 2016) or R. D. Laing's experiments with psychotic patients in Kingsley Hall in the 1960s (McGeachan, 2014). Clearly, psychedelics are not universally beneficial. In vulnerable brains, especially in uncontrolled and unsupported environments, psychedelics can induce or exacerbate paranoid and disordered thinking.

However, there are key differences between recreational and therapeutic uses. In contrast to recreational use, therapeutic use is conducted in a controlled, supportive environment, with trained therapists who prepare participants before the experience, provide guidance and support during the experience (if required) and assist with the integration process afterwards. The building of a trusting relationship with the team and particularly with the therapist, who encourages and supports the participants, is pivotal to maximize the therapeutic effect, while minimizing the risk of adverse events (Carhart-Harris *et al*. 2018b). A survey of 1,993 people, conducted by Roland Griffiths' group, showed that 7.6% of recreational users had a difficult psychedelic experience and subsequently sought treatment for psychological symptoms; whereas, in carefully screened, well-prepared and closely monitored volunteers the rate was only 0.9% (Carbonaro *et al*. 2016).

Spurred by the above-mentioned studies at Imperial, a multi-centre, phase 2b (dose finding), double-blind clinical trial of psilocybin with psychological support in TRD has been commenced (ClinicalTrials.gov Identifier: NCT03775200). Tallaght University Hospital was the first centre to assist a participant through the psilocybin experience in this large-scale randomized-controlled trial (RCT) which aims to recruit 216 participants, across Europe and North America. By

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synergistically combining psychotherapy and psychopharmacology, this RCT has the potential to evolve treatments beyond the regrettable, but lingering, dichotomy of 'biological' and 'psycho-environmental' (Bracken *et al*. 2012; Dunlop *et al*. 2019). It will be fascinating to see whether psilocybin with psychological support will play a role in a systems-based personalized psychiatry paradigm (Insel *et al*. 2010; Drysdale *et al*. 2017; Kelly *et al*. 2017b; Kelly *et al*. 2019a; Kelly *et al*. 2019b; Tokuda *et al*. 2018). Irrespective of psychiatry's future trajectory, psychedelic research, provided it progresses in a scientific and evidenced-based manner, will advance our understanding of the human brain. In parallel, and of greater importance, psychedelic-assisted psychotherapy, or psychotherapy-assisted psychedelic treatment, may offer a powerful therapeutic tool that, if used correctly, may benefit many people.

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Conflict of Interest

None of the authors have conflicts of interest to disclose.

Ethical Standards

The Cork Clinical Research Ethics Committee approved this trial. The authors assert that all procedures contributing to this work comply with the ethical standards of the Cork Clinical Research Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2008.

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