European College of Neuropsychopharmacology – press release

Study shows psychedelic drug psilocybin gives comparable long-term antidepressant effects to standard antidepressants, but may offer additional benefits

- **Psilocybin as good as SSRI for depression, but doesn't lower sex drive, gives better sense of well-being and psychosocial functioning**

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- Type of research: peer reviewed/experimental study/people

A direct comparison between the experimental psychedelic drug psilocybin and a standard SSRI antidepressant shows similar improvement of depressive symptoms, but that psilocybin offers additional longer-term benefits.

The comparison, between psilocybin (the active ingredient in "magic mushrooms") and the SSRI escitalopram gave similar long-term improvements in depressive symptoms over a 6-month period, however patients taking psilocybin also reported better psychosocial functioning including experiencing a greater sense of meaning in life and psychological connectedness.

The work is presented for the first time at the ECNP Congress in Milan. A related peer-reviewed paper will appear in the peer-reviewed journal *Lancet eClinicalMedicine*[1] to coincide with the conference presentation (see details below). Lead researcher Mr Tommaso Barba (PhD candidate from Imperial College, London) said:

"This is the first work to compare the long-term effects of these two drugs in the context of overall well-being, not just freedom from depression. In previous work we had *found that both treatments led to comparable improvements in alleviating symptoms of depression at the 6-week mark, such as sadness and negative emotions. However, this work shows that psilocybin outperformed escitalopram in several measures of well-being, meaning in life, work and social functioning. These results appeared to be maintained over a 6-month follow-up period. In addition, in previous work* we had found that psilocybin also improves sexual drive, in contrast to SSRIs which tend to lower libido in many patients. So overall it seems psilocybin might give additional positive mental health benefits.*

SSRI drugs (selective serotonin reuptake inhibitors), such as Prozac, Paxil and Zoloft, are one of the main types of drugs used to treat depression. However, around a third of patients don't respond to SSRI treatment, so for them psilocybin may offer an alternative, although this was not studied in this trial.

Tommaso Barba continued:

"SSRIs work well, but not for everyone. They are also associated with some side effects. However this work implies that psilocybin generally seems to offer a real

alternative, and perhaps additional benefits, to people who are worried about taking conventional antidepressants".

The researchers, from Imperial College in London, undertook a 6-month study (phase 2, double-blind, randomised controlled trial) with 59 patients with moderate to severe depression. 30 were treated with a single dose of psilocybin, 29 patients were given a six-week course of escitalopram. Each group received similar psychological support of around 20 hours in total. Both groups showed significant improvement in depressive symptoms, even up to 6 months after treatment (the researchers stopped monitoring at 6 months). However those given psilocybin reported greater improvements in social functioning and psychological 'connectedness with large effect sizes.

Co-first author Dr David Erritzoe , Clinical Director and Deputy Head of the Centre for Psychedelic Research, Imperial College, commented:

"This is important because improving connectedness and having greater meaning in life can significantly enhance a person's quality of life and long-term mental health. The study suggests that psilocybin therapy might be a more holistic treatment option for depression, addressing both the symptoms of depression and overall well-being. This could make a substantial difference in the overall happiness and daily activities of those suffering from depression, providing a more joined-up approach to mental health treatment".

The researchers note that the patients were only treated for 6 weeks, and that many of the patients received additional treatments over the 6-month follow up.

Dr Erritzoe cautioned*:*

"Psilocybin is still an experimental drug; it has not yet been approved for general use. It is administered in highly controlled and protected environments: these precautions are not found in recreational psychedelic use, which is known for having unpredictable and potentially harmful effects, especially for vulnerable people struggling with mental health issues".

Commenting, Johan Lundberg (Adjunct Professor of Psychiatry at the Department of Clinical Neuroscience, Karolinska Institute, Stockholm) said:

"This report is an important attempt to compare the clinical value of psilocybin compared to a state-of-the-art treatment of major depressive disorder. The results come with several caveats, including the lack of a non-inferiority analysis and failure to report other interventions given during the follow-up period. That said, as a hypothesis generating piece it may benefit the field substantially. For now, we don't know if psilocybin will be approved for the treatment of major depression, but if so, it won't be for everyone. Some future patients might prefer psychedelic treatment over SSRI, but some patients may be intimidated by the dramatic alterations in perception and confrontations with challenging emotions that psychedelic drugs promote".

This is an independent comment, Professor Lundberg was not involved in this work.

Notes:

1. Publication details: *Effect of psilocybin versus escitalopram on depression symptom severity in patients with moderate-to-severe major depressive disorder: observational 6-month follow-up of a phase 2, double-blind, randomised, controlled trial*. In press at *Lancet eClinicalMedicine.* Authors: David Erritzoe, Tommaso Barba, Kyle T. Greenway, Roberta Murphy, Jonny Martell, Bruna Giribaldi, Christopher Timmermann, Ashleigh Murphy-Beiner, Michelle Baker Jones, David Nutt, Brandon Weiss, and Robin Carhart-Harris. Paper reference 10.1016/j.eclinm.2024.102799
2. See Psychedelic experiences linked with improved sexual function | Imperial News | Imperial College London

Notes for Editors

This work is presented at the 37th ECNP Congress, taking place in Milan and online 21-24 September 2024, see https://www.ecnp.eu/Congress2024/ECNPcongress. With more than 6,000 participants the ECNP Congress is Europe's leading platform for the latest research in disease-related neuroscience.

Conference Abstract: P1423 ***Psilocybin vs Escitalopram for depression: 6-month follow-up***

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Background: *Psilocybin therapy (PT) produces rapid and persistent antidepressant effects in major depressive disorder (MDD). A recent phase 2 clinical trial [1] comparing two doses of psilocybin with 20 hours of psychological support with a 6 weeks course of the SSRI escitaliopram (and the same amount of psychological support) found that the two treatments produced comparable reductions in depressive symptoms at the primary 6-weeks endpoint (as measured with the Quick Inventory of Depressive Symptompathology (QIDS-SR-16). Psilocybin performed better than escitalopram in measures assessing wellbeing, work and social functioning, anhedonia, meaning in life, etc. However, the long-term effects of PT have never been compared with gold-standard treatments for MDD such as pharmacotherapy or psychotherapy alone or in combination.*

Methods: *This is a 6-month follow-up study of the phase 2, double-blind, randomized, controlled trial involving 59 patients with moderate-to-severe MDD. 30 patients were treated with 25 mg of the psychedelic drug psilocybin administered orally combined with psychological support ('psilocybin therapy' or PT) versus a 6-week course of the selective serotonin reuptake inhibitor (SSRI) escitalopram (administered daily at 10 mg for three weeks and 20 mg for the subsequent three) plus matched psychological support ('escitalopram treatment' or ET). The primary outcome measure was the QIDS-SR-16, and, explicitly, depressive symptom severity changes from baseline to follow-up timepoints. Measures of work and social functioning, connectedness, and meaning in life constituted the study's secondary outcomes during follow-up. The study used linear mixed-effects models to investigate changes over the follow-up period, together with secondary sets of analyses using different imputation methods in order to account for the impact of missing data. The randomized trial was registered at ClinicalTrials.gov, number NCT03429075.*

Outcomes: *Both PT and ET conditions yielded sustained improvements in depressive symptom severity at follow-up, without clinically significant between-condition differences at the 6-month follow-up period (Cohen's d range for PT: 1.24 – 1.55; for ET: 0.74 – 1.70), except for a greater response among PT patients at 1-month follow-up (F(7, 279) =7.33, pFDR= .02); Cohen's d for PT: 1.55; for ET: 0.74). Patients receiving PT did, however, exhibit greater sustained improvements in work and social functioning F(3,143 =6.05, pFDR<.001), psychological 'connectedness' (F(3,147) = 5.93, pFDR=.003), and meaning in life (F(3,143) =5.31, pFDR =.004) over the full follow-up period.*

Interpretation: *Six-week intensive treatments with either PT or ET for MDD were associated with long-term improvements in depressive symptoms. The greater degree of improvement in the PT arm at FU on psychosocial functioning, meaning in life and psychological connectedness suggests potential additional long-term benefits with PT versus SSRIs. The superior enhancements in functioning in the PT condition carry particular importance, as clinical guidelines for MDD prioritize the restoration of functioning as a key objective, and symptom remission frequently*

does not coincide with functional recovery. While some future patients might prefer psychedelic treatment over SSRI , it remains unclear what proportion of patients will find the prospect of psychedelic therapy aversive e.g., due to the dramatic alterations in perception and confrontations with challenging emotions that psychedelic drugs promote.

References

[1] Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of Psilocybin versus Escitalopram for Depression. New England Journal of Medicine. 2021;384(15):1402-11.

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