

# The Therapeutic Potential of Psilocybin for Depression

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SEPTEMBER 2024

[doi.org/10.33548/SCIENTIA1082](https://doi.org/10.33548/SCIENTIA1082)



PSYCHOLOGY &  
NEUROSCIENCE

 Scientia





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Depression is a debilitating mental health condition affecting millions worldwide. While antidepressant medications are widely prescribed, they often come with significant side effects and limited efficacy. Tessa Watford, a researcher in the field of neuroscience, has conducted a systematic review exploring the therapeutic potential of psilocybin, a naturally occurring psychedelic compound, for the treatment of depression. Her work sheds light on a promising alternative approach that could revolutionise the way we treat this prevalent mental health disorder.

## The Personal and Social Burden of Depression

Depression is a common, complex mental health disorder characterised by persistent feelings of sadness, hopelessness, and loss of interest in daily activities. It affects an individual's thoughts, emotions, and behaviours, often leading to significant impairments in social, occupational, and personal functioning. Despite the availability of various treatment options, including antidepressant medications and psychotherapy, many people continue to struggle with the debilitating symptoms of depression on a daily basis. This can have a negative impact both on the affected individuals themselves and on their wider ability to participate in social and professional life.

## Limitations of Current Antidepressant Treatments

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant medications. While they have been shown to be effective for some individuals, they often come with a range of side effects, such as sexual dysfunction, emotional blunting, and even an increased risk of suicidal ideation in certain populations. Moreover, a significant proportion of individuals with depression do not respond adequately to SSRIs, highlighting the need for alternative treatment options. SSRIs, while effective at alleviating symptoms, do not treat depression on their own. Another important limitation is that SSRIs usually take a few weeks to properly kick in, contrasting to the fast action of psilocybin.

## The Therapeutic Potential of Psilocybin

Psilocybin is a naturally occurring psychedelic compound found in certain species of mushrooms (colloquially known as 'magic

mushrooms'). In recent years, it has gained increasing attention as a potential therapeutic agent for depression. Tessa Watford's systematic review aimed to synthesise the available evidence on the efficacy and safety of psilocybin in treating depression. She conducted a comprehensive search of scientific databases, identifying six high-quality studies that met the inclusion criteria. These studies involved a total of 319 participants and employed various study designs, including randomised controlled trials and open-label trials.

## From Ancient Remedy to Modern Medicine

Psilocybin has a long history of use in traditional medicine and spiritual practices. The Aztecs referred to psilocybin-containing mushrooms as 'God's flesh', highlighting their reverence for these fungi. However, it wasn't until the mid-20th century that Western science began to take notice. Albert Hofmann, the chemist who first synthesised LSD, isolated and identified psilocybin as the active compound in these mushrooms.

Initially, there was great interest in psilocybin's potential therapeutic uses. However, this research was abruptly halted in the 1970s when psilocybin was classified as a Schedule I substance in many countries, severely restricting its study. It's only in recent years that scientific interest has been rekindled, with researchers like Tessa Watford leading the charge to understand psilocybin's potential as a treatment for depression.

## Psilocybin's Mechanism of Action

Ms Watford's review highlights the potential mechanisms through which psilocybin may exert its antidepressant effects. One key finding is that psilocybin appears to modulate the default mode



network (DMN) activity, a network of brain regions involved in self-reflection and rumination – the repetitive negative thinking common in depression. Hyperactivity of the DMN is thought to contribute to symptoms, so by temporarily disrupting DMN activity, psilocybin may help break patients out of rigid thought patterns.

Psilocybin also seems to increase connectivity between different brain networks rich in serotonergic 5HT<sub>2a</sub> receptors, which may allow for more flexible thinking and new perspectives. Additionally, psilocybin appears to enhance neuroplasticity – the brain's ability to form new neural connections. This could help 'rewire' dysfunctional circuits involved in depression. Importantly, these brain changes seem to persist long after the acute effects of psilocybin wear off. This may explain why just one or two sessions can produce lasting benefits, unlike traditional antidepressants, which must be taken daily.

### Promising Results from Clinical Trials

The studies consistently demonstrated significant reductions in depressive symptoms following psilocybin treatment. Participants reported improved mood, increased well-being, and a renewed sense of purpose. Notably, the antidepressant effects of psilocybin were observed rapidly, often within a few days to weeks after treatment, and persisted for several months in many cases. This rapid onset of action stands in contrast to traditional antidepressant medications, which typically require several weeks of continuous use (often accompanied by unwelcome side effects) before significant improvements are observed. The vast majority of participants had treatment-resistant depression, meaning that previous treatments had failed where psilocybin had now been effective.

### The Role of Psychological Support

An important aspect of psilocybin treatment highlighted in Ms Watford's review is the integration of psychological support. In all the included studies, psilocybin administration was conducted in a supportive therapeutic setting, with trained therapists or psychologists present to guide and support participants throughout the experience. This psychological support is considered crucial for maximising the therapeutic potential of psilocybin and minimising the risk of adverse effects. The therapists help participants navigate the profound psychological experiences induced by psilocybin, facilitating the processing of emotions, insights, and personal growth.

The included studies reported few adverse effects, with the most common being mild and transient, such as headaches, nausea, and temporary anxiety during the acute effects of the drug. Importantly, no serious or long-lasting adverse effects were observed, suggesting that psilocybin treatment, when administered in a controlled and supportive setting, has a favourable safety profile compared to traditional antidepressant medications.

### Future Directions and Challenges

While the findings of this systematic review are promising, Ms Watford acknowledges that further research is needed to fully understand the therapeutic potential of psilocybin for depression. The included studies had relatively small sample sizes, and more large-scale, well-controlled clinical trials are necessary to establish the efficacy and safety of psilocybin treatment.

Another challenge that is highlighted is the current legal status of psilocybin. As a Schedule I substance, psilocybin is currently



^ Ms Watford provides an analogy to explain how psilocybin might work. 'If you imagine your brain to be a mountain, covered in snow and very steep, every nerve impulse is a sled sliding down from the top to the bottom. When the same thought occurs, the sled takes the same path, which in turn makes it deeper and more pronounced in the snow. Because of this, it becomes easier for the sleds to take this pathway, which is how negative rumination occurs. When you take psilocybin, it covers the mountain in a fresh sheet of snow, meaning there are no indented pathways for the sleds to fall into by default. It's like a mental refresh.'

illegal in most countries, which poses significant barriers to research and clinical application. Efforts are underway to revise the legal classification of psilocybin, recognising its therapeutic potential and the need for further scientific exploration.

### A New Era in Depression Treatment?

Ms Watford's systematic review provides a comprehensive overview of the current state of research on psilocybin for depression. The results are promising, suggesting that this ancient compound could have a significant role to play in modern mental health treatment. The research to date suggests that psilocybin therapy could represent a paradigm shift in how we approach mental health treatment. However, psilocybin is not a magic bullet – it requires careful administration in controlled settings with appropriate support. That said, it represents an exciting development in efforts to expand the toolkit available for helping people with depression.

The story of psilocybin's journey – from an ancient spiritual tool to a prohibited drug to a potential up-and-coming depression treatment – reminds us to keep open minds and continue exploring new possibilities in our quest to alleviate human suffering. As research on psilocybin continues to advance, it may open up new frontiers in our understanding of consciousness, mental health, and human potential. Whatever the ultimate outcome, Ms Watford is already challenging us to think differently about depression and how we treat it.



## MEET THE RESEARCHER

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**Tessa Bo Watford** is currently undertaking an MSc in Translational Neuroscience at Imperial College London. She graduated with a first-class BSc in Neuroscience and Psychology from Keele University in 2023. During this time, her studies included extensive wet-lab experience with techniques such as polymerase chain reaction, insect dissections, EEG, brain tissue cultures, in-vivo rodent observations, and human nervous system examinations. Alongside her studies, Ms Watford served as a Student Voice Representative and Peer Supporter, providing academic support and mental health advice to fellow students. She has also worked as an online science tutor, significantly improving the exam scores of GCSE and A-level biology students, and since 2023, as a secondary school science cover teacher.



### FURTHER READING

T Watford, Naqash Masood, [Psilocybin, an Effective Treatment for Major Depressive Disorder in Adults – A Systematic Review](https://doi.org/10.9758/cpn.23.1120), *Clinical Psychopharmacology and Neuroscience*, 2024, 22(1), 2–12. DOI: <https://doi.org/10.9758/cpn.23.1120>



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**Web of Science ID:** KIG-0396-2024



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