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Psilocybin combined with psychotherapy shows significant efficacy in treatment-resistant depression

The results of the EPIsoDE study show that psilocybin can have a significant antidepressant effect. It is important that its use be integrated into psychotherapeutic pre- and post-treatment care.

For more than 30 percent of people with depression, currently available medications are not effective. In up to 80 percent of those affected, the condition recurs within twelve months of treatment. New approaches to treating depression are therefore urgently needed.

Various studies in recent years have already suggested that the psychedelic psilocybin, when combined with psychotherapy, can have positive effects on depression. Following this, the Central Institute of Mental Health (CIMH), in collaboration with Charité – Universitätsmedizin Berlin and the MIND Foundation, conducted the EPIsoDE study (Efficacy and Safety of Psilocybin in Treatment-Resistant Major Depression). This large clinical trial investigated the efficacy and safety of psilocybin in combination with psychotherapy.

Between 2021 and 2024, a total of 144 people with treatment-resistant depression were treated as part of the study. The results have now been published in the journal JAMA Psychiatry.

Psilocybin at different doses compared to a placebo

The study used two different doses of psilocybin: 25 milligrams (mg) as a dose presumed to have antidepressant effects, and 5 mg as a control dose that was unlikely to have therapeutic effects. In addition, a placebo was administered for comparison. To ensure that all participants received a high dose of psilocybin at least once, they were randomly assigned to four groups: These groups received high-dose psilocybin, low-dose psilocybin, or a placebo in varying sequences at two predetermined time points. Psychotherapeutic sessions for preparation and therapeutic processing took place both before and after the administration of psilocybin.

A wide range of outcome measurements were taken one week before and after each psilocybin session, as well as six weeks afterward. The researchers focused on the efficacy and safety of the therapy, as well as on potential psychological and biological mechanisms of action. In addition, brain activity and structure were examined in 97 participants using brain imaging (magnetic resonance imaging). The long-term effects of the therapy were assessed through follow-up examinations six and twelve months after the first psilocybin session.

Key factors: Context and environment

In psychedelic therapy, patients' internal state, including their current emotions and perceptions (*set*) as well as the therapeutic environment (*setting*) play an important role. To create the best possible conditions for both, psychotherapeutic preparatory sessions were held prior to each session involving psilocybin (or placebo—hereinafter referred to as "dosing sessions"). The dosing sessions were followed by further psychotherapeutic sessions in which the experiences were processed and connections to everyday life were established.

The dosing sessions took place in a pleasant, quiet atmosphere accompanied by music. Special therapy rooms were set up for this purpose at both the CIMH in Mannheim and the Charité in Berlin. Two therapists were present in the therapy room during each of the six- to eight-hour dosing sessions. "With the help of a therapy manual, specific training, and regular supervision, we have succeeded in achieving a high and as consistent as possible quality of psychotherapeutic support," emphasizes Dr. Michael Koslowski, a specialist in psychiatry and psychotherapy at the Department of Psychiatry and Psychotherapy at Charité – Universitätsmedizin Berlin, as well as coordinator and study therapist at the Berlin site.

Response to treatment and reduction of symptoms

Prior to the start of the study, the response to treatment six weeks after the first dose was defined as the primary efficacy endpoint. A response is defined as a reduction of at least half in the total score on the HAMD-17 depression scale (Hamilton Depression Rating Scale with 17 symptom categories), as measured prior to the first treatment session. Treatment response is recorded as a yes-or-no criterion: a person either responds to treatment or does not.

One week after application of 25 mg psilocybin, the response rate was significantly higher than after application of placebo. Six weeks after the administration, however, there was no longer a statistically significant difference between psilocybin and the placebo. Thus, the study's primary endpoint was not met.

Additional outcomes (secondary endpoints) included reductions in depressive symptoms after six and twelve weeks, as measured using the standard HAMD-17 questionnaire. After six weeks, a significant difference was observed between 25 mg of psilocybin and placebo: Among participants who had taken 25 mg of psilocybin, depressive symptoms were reduced by an average of 4.6 points on the HAMD17 scale more than in the placebo group. After twelve weeks, when all participants had received 25 mg of psilocybin at least once, depressive symptoms were significantly reduced by an average of 7.5 points across all treatment groups. There were no longer any differences between the groups.

These results suggest that administration of 25 mg of psilocybin in combination with psychotherapy has a significant antidepressant effect. However, further studies are needed to confirm these findings.

Safety: Adverse events

In clinical trials, so-called adverse events are recorded systematically and in a standardized manner. An adverse event is defined as "any adverse medical occurrence in a subject who has been administered an investigational drug and that is not necessarily causally related to that treatment." It has not yet been conclusively determined which adverse events may also be beneficial to the therapeutic effect of psilocybin.

Administration of 25 mg psilocybin led to adverse events on dosing days that primarily affected perception and emotions, such as affective lability (rapid and intense mood swings—in 62% of all 25 mg sessions), vivid inner imagery (56%), and dissociation (fragmentation of consciousness—22%). Physical symptoms such as headaches (55%), high blood pressure (51%), nausea (34%), and dizziness (19%) also occurred. In most cases, these symptoms subsided within the following days, with headaches (20%) and fatigue (8%) being the most commonly reported.

Following the administration of 25 mg of psilocybin, serious adverse reactions occurred in two cases: a strong rise in blood pressure in one participant and a prolonged perceptual disturbance in another participant. Appropriate care was provided, and the course of these adverse events was carefully monitored. "Overall, we assess the safety of the treatment as good. Most adverse events were transient and consistent with expectations in terms of type and intensity. However, serious adverse reactions occurred in two cases. This underscores how crucial careful psychotherapeutic support is for the safe application," summarizes Lea Mertens, a psychological psychotherapist at the Central Institute of Mental Health and coordinator and study therapist at the Mannheim site.

In Search of the Mechanisms

The analysis of patients' reports of so-called "emotional breakthroughs" provided initial insights into how psilocybin may exert its antidepressant effects. These refer to states of heightened emotional openness and profound insights that occur while a psychedelic substance is taking effect. The analysis revealed that there may be a link between the psilocybin dose, emotional breakthroughs, and the antidepressant effects of psilocybin. For instance, emotional breakthrough experiences were reported more frequently in the high-dose group. The higher the measured value of the breakthrough experiences, the stronger the antidepressant effect. "We are currently analyzing additional data that may also provide insights into biomarkers as well as psychological and psychotherapeutic mechanisms of action. We will publish the results as soon as possible," Mertens announced.

Significant antidepressant effect with a good safety profile

Although the results did not show a significant effect on the primary endpoint (response), the administration of 25 mg of psilocybin in combination with adjunctive psychotherapy was associated with a significant antidepressant effect. The treatment was well tolerated by most participants. "Our study results expand on previous findings regarding the potential of psilocybin treatment for depression," says study lead Prof. Dr. Gerhard Gründer.

Publication

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Further information

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