Awakened Soul Journey

MAJOR DEPRESSION, KETAMINE & PSILOCYBIN

What Current Research Is Showing

For many people, standard antidepressants are helpful. For others, depression persists despite trying one medication after another.

One of the largest real-world studies of antidepressant treatment, the **STAR*D trial**, followed people with major depressive disorder through as many as four successive treatment steps. Remission rates declined substantially with each additional step: approximately **37% after the first treatment, 31% after the second, 14% after the third, and 13% after the fourth**.

That decline is one reason researchers have become increasingly interested in treatments that work through different biological pathways, including **ketamine, esketamine and psilocybin-assisted treatment**.

KETAMINE

Ketamine is a dissociative anesthetic that has been used medically for decades. At lower doses, it has demonstrated rapid antidepressant effects, particularly in people whose depression has not responded adequately to conventional medications.

Unlike traditional antidepressants, which generally work through serotonin, norepinephrine or related monoamine systems, ketamine primarily affects **glutamate signaling through the NMDA receptor system**. Research suggests that downstream effects may promote synaptic remodeling and neuroplasticity.

One of the striking features of ketamine research is **speed**. Early randomized trials found measurable antidepressant improvement within hours rather than weeks.

In the large **ELEKT-D trial**, published in *The New England Journal of Medicine* in 2023, adults with nonpsychotic treatment-resistant major depression were randomized to either intravenous ketamine or electroconvulsive therapy, or ECT. After the initial three-week treatment period, approximately **55% of the ketamine group experienced at least a 50% reduction in depressive symptoms**, compared with approximately **41% receiving ECT**. Ketamine met the study's criterion for noninferiority to ECT.

This does not mean ketamine is universally more effective than ECT. ECT remains one of the strongest treatments available for severe depression, particularly depression with psychotic features, and the ELEKT-D study specifically excluded psychotic depression.

Esketamine

Esketamine is closely related chemically to ketamine and is administered as a nasal spray under medical supervision.

In the **ESCAPE-TRD trial**, people with treatment-resistant depression receiving esketamine nasal spray plus an SSRI or SNRI were more likely to achieve remission than people receiving extended-release quetiapine augmentation plus an SSRI or SNRI.

Ketamine itself is widely used off-label for depression, while esketamine has an FDA-approved depression indication.

PSILOCYBIN

Psilocybin works very differently from ketamine. It is a classic psychedelic that primarily activates **serotonin 5-HT2A receptors**.

Researchers are investigating whether psilocybin temporarily increases flexibility within brain networks involved in habitual thinking, emotional processing and self-referential thought.

Brain-imaging studies suggest psilocybin can temporarily alter connectivity within and between large-scale brain networks and may increase communication between regions that normally operate more independently. Some changes have persisted for weeks after a single administration.

This has led researchers to explore the idea that psychedelic treatment may create a temporary period of increased psychological and neurological flexibility during which deeply entrenched patterns of thinking may become easier to examine and change.

That mechanism remains an active area of research rather than an established explanation.

JOHNS HOPKINS — MAJOR DEPRESSIVE DISORDER

A randomized clinical trial from Johns Hopkins published in *JAMA Psychiatry* examined psilocybin-assisted therapy in adults with major depressive disorder.

Participants received two psilocybin sessions accompanied by preparation and psychological support.

The study found **large, rapid reductions in depressive symptoms**, with improvement persisting through the four-week follow-up period.

Because the study was small, these response percentages should be interpreted as promising early findings rather than expected success rates for every person with depression.

PSILOCYBIN VERSUS ESCITALOPRAM

One particularly interesting trial directly compared psilocybin-assisted treatment with the commonly prescribed SSRI **escitalopram — Lexapro**.

The study included 59 adults with moderate-to-severe major depression.

On the study's primary depression measure, **psilocybin was not statistically superior to escitalopram at six weeks**.

Several secondary measures favored psilocybin, however. Approximately **70% of the psilocybin group met criteria for treatment response compared with 48% in the escitalopram group**, while remission occurred in approximately **57% versus 28%**, respectively.

Those secondary comparisons were exploratory and were not corrected for multiple statistical comparisons, so they cannot be interpreted as definitive proof that psilocybin is more effective than antidepressant medication.

SINGLE-DOSE PSILOCYBIN — JAMA 2023

A larger multicenter randomized clinical trial published in *JAMA* in 2023 examined a **single 25-mg dose of psilocybin** in adults with major depressive disorder.

Participants receiving psilocybin showed significantly greater reductions in depression severity than those receiving an active placebo.

Improvement occurred rapidly and remained measurable through the study's six-week follow-up period.

TREATMENT-RESISTANT DEPRESSION — NEJM 2022

A major Phase 2 study published in *The New England Journal of Medicine* evaluated psilocybin in people with treatment-resistant depression.

Participants received either **25 mg, 10 mg or 1 mg of psilocybin**, along with psychological support.

At three weeks, the 25-mg group had significantly greater improvement in depression scores than the 1-mg control group.

This study also reinforces an important point: psychedelic treatments can produce adverse psychological and physiological effects and require careful screening and supervision.

AN IMPORTANT 2026 STUDY

New research also reminds us that psilocybin is not producing dramatic results in every clinical trial.

A 2026 randomized trial involving **144 adults with treatment-resistant depression** compared 25-mg psilocybin with lower-dose psilocybin and an active placebo, all accompanied by psychotherapy.

The study **did not demonstrate a statistically significant advantage on its primary outcome at six weeks**, although several secondary depression measures suggested clinically meaningful improvement.

The investigators also identified safety signals, including transient increases in suicidal ideation on dosing days and rare serious adverse reactions.

Another 2026 randomized trial involving adults with recurrent major depressive disorder reported that a single 25-mg dose produced significantly greater improvement than niacin placebo at day 8, with benefits lasting beyond three months.

Taken together, these findings illustrate where the science currently stands: **promising and increasingly sophisticated, while still evolving.**

HOW DOES THIS COMPARE WITH ANTIDEPRESSANTS?

It is tempting to compare the percentages directly:

Conventional antidepressant treatment — STAR*D
First treatment step: approximately **37% remission**
Second treatment step: approximately **31% remission**
Third treatment step: approximately **14% remission**
Fourth treatment step: approximately **13% remission**

Psilocybin studies
Some controlled studies have reported response rates around **60–70%** and remission rates above **50%** following one or two supported psychedelic sessions.

Ketamine
Controlled studies of treatment-resistant depression commonly demonstrate clinically meaningful improvement within hours or days, with response rates in some major trials around **50% or higher**.

There is an important limitation: **These numbers are not directly comparable.**

STAR*D included thousands of patients treated in real-world psychiatric and primary-care settings.

Psychedelic trials generally involve much smaller and more carefully selected populations, intensive screening, hours of preparation and monitoring, psychological support, and substantial follow-up.

Participants with certain psychiatric or medical conditions are frequently excluded.

Because psychedelic effects are obvious to many participants, maintaining true blinding in clinical trials is also unusually difficult.

So the research does **not** currently justify saying that psilocybin is "70% effective while antidepressants are 37% effective."

What it does suggest is that these treatments may help some people who have not responded adequately to traditional approaches.

WHY MIGHT THEY WORK DIFFERENTLY?

Traditional antidepressants generally involve taking medication every day and gradually altering neurotransmitter signaling.

Ketamine and psilocybin appear to produce a very different pattern.

Ketamine can trigger rapid changes in glutamate signaling and synaptic plasticity.

Psilocybin temporarily produces large-scale changes in communication among brain networks. Imaging research has shown decreased segregation between normally distinct networks and increased global integration following treatment, changes that have correlated with improvement in depression in some studies.

Researchers sometimes refer to this as a temporary **window of neuroplasticity**.

The idea is that during this period, rigid emotional and cognitive patterns may become more flexible.

The medicine itself may therefore represent only one part of the treatment. Preparation, the therapeutic environment, the experience itself and subsequent integration may influence how that period of flexibility is used.

IMPORTANT SAFETY CONSIDERATIONS

Neither ketamine nor psilocybin is appropriate for every person.

Screening should include psychiatric history, medical history, current medications and family history.

Particular caution is warranted with a personal or family history of **bipolar disorder, mania, psychotic disorders or schizophrenia-spectrum illness**.

Ketamine may temporarily increase blood pressure and heart rate and can cause dissociation, dizziness, nausea and perceptual changes.

Repeated or heavy ketamine exposure can also carry risks of misuse, dependence and urinary/bladder complications.

Psilocybin can produce temporary anxiety, fear, disorientation, nausea, increases in blood pressure and emotionally intense experiences.

People taking psychiatric medications should discuss medication interactions and any potential tapering only with the clinician who prescribes them. Abruptly stopping antidepressants can produce withdrawal symptoms and recurrence or worsening of depression.

Neither medication should be viewed simply as a substance to take.

The strongest clinical research involves **screening, preparation, monitored administration and follow-up care**.

THE BIG PICTURE

For someone who has experienced repeated major depression or who has tried several antidepressants without achieving lasting remission, the research surrounding ketamine and psilocybin gives legitimate reason for interest.

Ketamine currently has the more extensive clinical evidence base for rapid treatment of treatment-resistant depression.

Psilocybin research is newer and remains investigational, but several high-quality controlled studies have demonstrated rapid and sometimes sustained improvement following only one or two treatment sessions.

At the same time, newer studies remind us that results vary and that these treatments carry genuine risks.

The most useful question therefore may be less:

“Which treatment has the biggest percentage?”

and more:

“Given my history, biology, previous treatments, risks and goals, which approach offers the most reasonable balance of potential benefit and safety?”

That is a question worth exploring collaboratively with a psychiatrist, physician or other qualified clinician who understands both conventional depression treatment and emerging psychedelic therapies.

Selected Research

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