# For Major Depression Treatment Short-Duration Psychedelic Therapy Shows Promise

Researchers evaluated the safety and efficacy of a short-acting psychedelic, dimethyltryptamine (DMT), in adults with major depressive disorder (MDD).

MDD is a leading global cause of disability, impacting quality of life and creating a significant public health burden. Many patients experience insufficient responses or unacceptable side effects with commonly used first-line treatments such as selective serotonin reuptake inhibitors, underscoring the need for more effective therapies.

Psychedelics have recently shown promise for treating mood disorders. DMT is a naturally occurring tryptamine that acts as a serotonin 5-hydroxytryptamine receptor 2A agonist. Unlike other psychedelics, DMT has a short half-life and brief psychoactive duration, allowing shorter treatment sessions, a feature that may improve feasibility and scalability rather than demonstrating direct cost savings.

## Study

In this study, researchers evaluated the safety and effectiveness of an intravenous DMT infusion in individuals with MDD. This was a two-stage, randomized, placebo-controlled phase IIa trial, with stage 1 conducted double-blind and stage 2 conducted open-label. Participants were aged 18 years or older with a diagnosis of moderate-to-severe MDD and had a history of at least two previous unsuccessful treatment attempts.

Individuals with a positive pregnancy test, history of serious suicide attempts, use of serotonergic psychedelics, preexisting psychiatric conditions, or personal or family history of psychosis were excluded. Participants received up to two intravenous doses of DMT or placebo along with psychotherapeutic support that included structured preparatory sessions, therapist-monitored dosing sessions, and post-session psychological integration visits.

In stage 1, participants were assigned to blinded treatments, placebo or DMT. Because DMT produces pronounced subjective effects, investigators noted that functional unblinding may have occurred. Two weeks later, in stage 2, DMT was administered either as a first dose to those who had received a placebo in stage 1, the placebo-active (PA) group, or as a second dose to those who had received DMT in stage 1, the active-active (AA) group. The dose, 21.5 mg DMT

fumarate, was infused intravenously over 10 minutes in two phases, consisting of an initial lower infusion followed by the remaining dose.

The primary outcome was the change in the Montgomery–Åsberg Depression Rating Scale (MADRS) score from baseline at two weeks after the first dose. Secondary efficacy measures included MADRS scores at week 1 after the first dose and at weeks 1, 2, 4, and 12 after the second dose. Adverse events were recorded and classified by severity. Safety monitoring included heart rate, blood pressure, electrocardiograms (ECGs), and laboratory tests. Depression severity assessments were conducted by independent raters not present during dosing sessions to reduce bias.

Tolerability was assessed post-dose by asking participants whether they regretted the experience. The primary endpoint was analyzed using t-tests. Secondary endpoints were evaluated using mixed models for repeated measures. Logistic regression was used to analyze response rates (defined as a greater than 50% decrease in MADRS score) and remission rates (defined as a MADRS score less than or equal to 10).

## Findings

The study randomized 34 participants to the PA or AA group. Four participants in the AA group did not receive their second dose but remained in the trial. Participants had a mean age of 32.8 years, and most identified as White (88%), which may limit generalizability to more diverse populations. Depression severity was comparable across groups at baseline.

The mean change in MADRS score from baseline to two weeks after the first dose was significantly greater in DMT recipients than in placebo recipients. Reductions were also significant at one week after dosing. MADRS scores did not differ significantly between individuals who received a single DMT dose and those who received two doses at any follow-up time point, although this comparison was exploratory because stage 2 lacked blinding and a placebo control.

Most clinical improvements among those receiving two DMT doses occurred within two weeks of the first dose. At one week, MADRS response was observed in 6% of the PA group and 44% of the AA group, while remission occurred in 13% and 44%, respectively. At two weeks, response rates were 12% in PA and 35% in AA, and remission rates were 12% and 29%, respectively. These estimates should be interpreted cautiously, given the small sample size and exploratory nature of later-stage analyses.

Exploratory analyses suggested that antidepressant effects were partly associated with the intensity of the acute psychedelic experience, indicating possible psychological mediation rather than a purely pharmacological effect.

The treatment was generally well tolerated. Treatment-emergent adverse events (TEAEs) occurred in most participants, with approximately three-fourths reporting events possibly related to treatment. TEAEs were mild in 15 participants and moderate in 10. Injection site pain, anxiety, insomnia, headache, and restlessness were most frequently reported.

No serious adverse events or deaths occurred. Clinical evaluations, including ECGs and laboratory tests, revealed no significant abnormalities during the trial. Transient increases in

heart rate and blood pressure were noted immediately after DMT infusion. No meaningful changes in suicidal ideation were observed.

## Conclusion

A single 21.5 mg dose of DMT, administered with psychological support, resulted in rapid and significant reductions in depressive symptoms that persisted for up to three months in adults with MDD within the constraints of a small, carefully screened phase IIa study population. The treatment was safe and well-tolerated during the short follow-up period. Larger, longer studies, including comparisons with current therapies, are needed to further evaluate the safety, efficacy, durability of response, and cost-effectiveness of DMT for the treatment of MDD.

## Source:

https://www.news-medical.net/news/20260217/Short-duration-psychedelic-therapy-shows-promise-for-major-depression-treatment.aspx