Moe Halawani, MD | O-Two Clinical Specialist

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Insights on Nitrous Oxide in Depression Treatment

Introduction

Major depressive disorder (MDD) and treatment-resistant depression (TRD) are among the most challenging mental health conditions to manage, particularly when patients do not respond to standard antidepressant medications. Traditional treatments often take weeks to show effect, and for a significant portion of patients, they may not work at all.

A recent meta-analysis led by the University of Birmingham, in collaboration with the University of Oxford and Birmingham and Solihull Mental Health NHS Foundation Trust, examined the potential of nitrous oxide (N_2O), commonly used for anesthesia and pain relief, as a fast-acting treatment for depression.

The review included seven clinical trials and four protocol papers, evaluating the effects of nitrous oxide in adults diagnosed with MDD, including those with TRD. The findings suggest that clinically administered nitrous oxide, delivered in controlled settings, may offer rapid symptom relief, with greater benefit observed when administered repeatedly over time.

1 Rapid Reduction in Depressive Symptoms After a Single Dose

The analysis showed that a single session of inhaled nitrous oxide at 50% concentration led to clinically significant reductions in depressive symptoms within 24 hours. These effects were reported in trials involving patients with MDD and TRD, defined as depression that remains inadequately controlled after at least two different antidepressant medications. While the antidepressant response was clear, it was typically short-lived, with symptoms often returning to baseline within one week. This suggests that nitrous oxide may offer short-term relief, especially valuable in acute depressive episodes or during the waiting period for conventional treatments to take effect.

www.otwo.com
45A Armthorpe Road, Brampton, ON, Canada, L6T 5M4
Telephone: +1 905 792-OTWO (6896) N.A. Toll Free: +1 800 387 3405
Facsimile: +1 905 799 1339 Email: resuscitation@otwo.com

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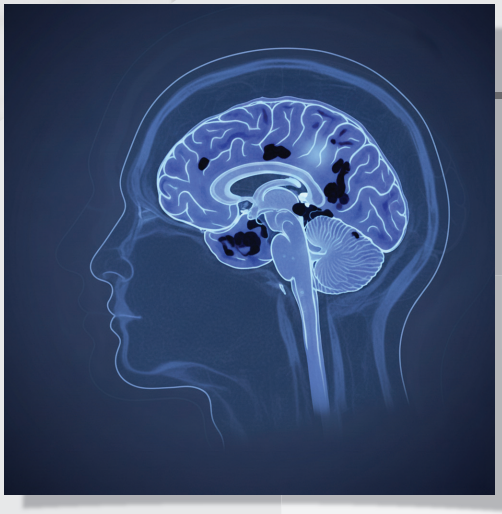
2 Sustained Benefits with Repeated Dosing

Repeated administration of nitrous oxide over several weeks was associated with more durable antidepressant effects. Compared to a single session, multiple treatments resulted in longer-lasting symptom relief, as demonstrated across several clinical trials.

These findings support the view that a structured course of nitrous oxide sessions may be required to sustain clinical improvement. This is consistent with how other fast-acting treatments, such as ketamine, are used in current practice. However, further research is needed to determine the optimal frequency and duration of dosing.



3 Mechanism of Action Involving Glutamatergic Modulation

Nitrous oxide appears to work differently from most standard antidepressants. Rather than targeting serotonin, norepinephrine, or other monoamines, it is believed to act primarily on the glutamatergic system, specifically by blocking N-Methyl-D-aspartate (NMDA) receptors. This mechanism is similar to that of ketamine, another rapid-acting antidepressant. By modulating glutamate signaling, nitrous oxide may

influence neural circuits involved in mood regulation more directly and rapidly than traditional medications. This could help explain the fast antidepressant effects observed in clinical trials, and why some patients who do not respond to monoaminergic drugs may still benefit from nitrous oxide.

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4 Comparison with Conventional Antidepressants and Ketamine

Conventional antidepressants often take several weeks to achieve clinical effect and are insufficient for many patients. In contrast, nitrous oxide has demonstrated a rapid antidepressant effect, often within 24 hours of administration. Like ketamine, nitrous oxide targets the glutamatergic system via NMDA receptor antagonism. While ketamine is already used in specialist clinics for TRD, nitrous oxide may offer practical advantages, such as shorter duration of action, easier administration, and existing familiarity in medical environments.

5 Clinical Safety Profile and Side Effects

Across the reviewed trials, nitrous oxide was associated with a favorable short-term safety profile. Reported side effects included nausea, dizziness, and headache, all of which were mild, transient, and resolved without medical intervention.

While higher concentrations were more likely to cause side effects, no immediate safety concerns were identified in any of the studies. The authors of the meta-analysis emphasize the need for future studies to assess long-term safety, particularly with repeated exposure and extended treatment courses.

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Conclusion

This meta-analysis offers strong early evidence that clinically administered nitrous oxide may provide rapid, short-term relief from depressive symptoms in adults with major depressive disorder, including those with treatment-resistant depression. Its mechanism of action sets it apart from traditional treatments and aligns it with other fast-acting antidepressants like ketamine. The reviewed studies also suggest that nitrous oxide is well tolerated in the short term, with only mild and temporary side effects. These findings highlight nitrous oxide's potential as part of a new generation of rapid-acting treatments for depression. Further clinical trials, including the first NHS-based study, are planned to evaluate its safety, dosing strategies, and integration into existing mental health care pathways. If confirmed, nitrous oxide could expand treatment options for patients who have not responded to current approaches.

Reference

Gill, K., de Cates, A. N., Wiseman, C., Murphy, S. E., Williams, E., Harmer, C. J., Morales-Muñoz, I., & Marwaha, S. (2025). Nitrous oxide for the treatment of depression: A systematic review and meta-analysis. eBioMedicine, Article 106023. https://doi.org/10.1016/j.ebiom.2025.106023

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