A Phase 2 Trial of Inhaled Nitrous Oxide for Treatment-Resistant Major Depression

Short Title: Nitrous Oxide and Treatment-Resistant Depression

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Abstract

Background: In a prior proof-of-concept study, a single inhalation of 50% nitrous oxide rapidly improved depressive symptoms in patients with treatment-resistant major depression. It is unknown, however, whether a lower concentration of 25% nitrous oxide provides similar efficacy while reducing the risk of adverse side effects and how long antidepressant effects last.

Methods: In this phase 2 clinical trial, 20 patients with severe treatment-resistant major depression were randomly assigned in a crossover fashion to receive a single 1-hour inhalation with (1) 50% nitrous oxide, (2) 25% nitrous oxide, or (3) placebo (air). Inhalation treatments were at least 4 weeks apart. Primary outcome was the change on the Hamilton Depression Rating Scale 21-item (HDRS-21).

Results: Nitrous oxide inhalation (25% and 50% combined) led to a significant improvement in depressive symptoms versus placebo (p=0.002), but we did not observe a statistically significant difference between 25% and 50% nitrous oxide (p=0.55). The estimated HDRS-21 differences between 25% and placebo were -1.01 points at 2 hours (p=.66), -1.82 points at 24 hours (p=.42), -5.05 points at 1 week (p=0.03), and -6.58 points at 2 weeks (p=0.004). The estimated differences between 50% and placebo were -0.88 points at 2 hours (p=.70), -1.88 points at 24 hours (p=.40), -2.81 points at 1 week (p=0.21), and -8.06 points at 2 weeks (p=0.003). Adverse events declined with dose: 43 (50% nitrous oxide), 11 (25% nitrous oxide), and 4 (placebo) (p=0.0003). None of the adverse events were serious and nearly all occurred during or immediately after inhalation and resolved within several hours.