Priority Communication

Biological Psychiatry

Nitrous Oxide for Treatment-Resistant Major Depression: A Proof-of-Concept Trial

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ABSTRACT

BACKGROUND: *N*-methyl-D-aspartate receptor antagonists, such as ketamine, have rapid antidepressant effects in patients with treatment-resistant depression (TRD). We hypothesized that nitrous oxide, an inhalational general anesthetic and *N*-methyl-D-aspartate receptor antagonist, may also be a rapidly acting treatment for TRD.

METHODS: In this blinded, placebo-controlled crossover trial, 20 patients with TRD were randomly assigned to 1-hour inhalation of 50% nitrous oxide/50% oxygen or 50% nitrogen/50% oxygen (placebo control). The primary endpoint was the change on the 21-item Hamilton Depression Rating Scale (HDRS-21) 24 hours after treatment.

RESULTS: Mean duration of nitrous oxide treatment was 55.6 ± 2.5 (SD) min at a median inspiratory concentration of 44% (interquartile range, 37%–45%). In two patients, nitrous oxide treatment was briefly interrupted, and the treatment was discontinued in three patients. Depressive symptoms improved significantly at 2 hours and 24 hours after receiving nitrous oxide compared with placebo (mean HDRS-21 difference at 2 hours, −4.8 points, 95% confidence interval [CI], −1.8 to −7.8 points, $p = .002$; at 24 hours, −5.5 points, 95% CI, −2.5 to −8.5 points, $p < .001$; comparison between nitrous oxide and placebo, $p < .001$). Four patients (20%) had treatment response (reduction ≥50% on HDRS-21) and three patients (15%) had a full remission (HDRS-21 ≤ 7 points) after nitrous oxide compared with one patient (5%) and none after placebo (odds ratio for response, 4.0, 95% CI, .45–35.79; OR for remission, 3.0, 95% CI, .31–28.8). No serious adverse events occurred; all adverse events were brief and of mild to moderate severity.

CONCLUSIONS: This proof-of-concept trial demonstrated that nitrous oxide has rapid and marked antidepressant effects in patients with TRD.

Keywords: Major depression, Nitrous oxide, Treatment-resistant depression

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Treatment-resistant depression (TRD) is a severe form of major depressive disorder (1). Patients with TRD often fail multiple treatments with standard antidepressants and have an unfavorable long-term prognosis; one in three patients with major depression (estimated prevalence in the United States is 10 million adults) is affected (2). Therapeutic options for TRD are very limited.

There is a strong biological rationale supporting the potential therapeutic use of nitrous oxide in TRD. Although nitrous oxide is known to modulate several central nervous system targets (3–14), like ketamine, the primary target of nitrous oxide appears to be the *N*-methyl-D-aspartate (NMDA) receptor, where nitrous oxide acts as a noncompetitive inhibitor (15–17). NMDA receptor signaling has been implicated in the neurobiology of depression and is a key component of central nervous system information processing (18–20). Consistent with the relevance of NMDA receptor signaling in the pathophysiology of major depression, NMDA receptor antagonists, such as ketamine (a general, dissociative anesthetic), have been shown to provide rapid and sustained antidepressant effects at subanesthetic doses in TRD (21–27). Given the similar mechanisms of action, we hypothesized that nitrous oxide may also have rapid antidepressant effects in TRD. This proof-of-concept trial assessed the immediate (2 hours) and sustained (24 hours) antidepressant effects of nitrous oxide in a population of well-characterized patients with TRD.

METHODS AND MATERIALS

Study Design and Oversight

This study was designed as a randomized, placebo-controlled crossover pilot clinical trial testing the antidepressant effects of nitrous oxide in 20 patients with TRD. In this study, patients had two treatment sessions that were 1 week apart (nitrous oxide or placebo). The sequential order of the sessions was assigned by a random number generator. Other than the gas mixture administered, the sessions were indistinguishable in setting, setup, and monitoring.

We undertook several measures to ensure treatment blinding. First, we completely separated personnel and location of

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the team providing nitrous oxide treatment from the team performing psychiatric evaluations. The two locations were physically separated from each other, and no team member was allowed to enter the other space while a study patient was present. Second, records for the nitrous oxide and placebo treatment administration were kept separate from the psychiatric assessment case report forms until completion of the study. Third, all equipment used to provide treatments was identical between nitrous oxide and placebo sessions. Lastly, patients were blinded as to the nature of the inhaled gas at each inhalation session; all patients were informed that they would receive either nitrous oxide or an air mixture with a high nitrogen component (placebo).

A data and safety monitoring board monitored the trial. The study was approved by the Washington University in St. Louis Institutional Review Board, and all patients provided written, informed consent. The trial was registered at clinicaltrials.gov (NCT02139540).

Patients

Patients were recruited from an existing database of patients with TRD administered by the Washington University Department of Psychiatry and from the "Volunteers for Health" patient pool (individuals with various medical or psychiatric conditions who volunteer to participate in clinical research) within Washington University School of Medicine. Inclusion criteria were 1) age 18–65 years; 2) meeting DSM-IV-TR criteria for major depressive disorder without psychosis, as determined using a structured clinical interview [Mini International Neuropsychiatric Interview (28)]; 3) a pretreatment score >18 on the 21-item Hamilton Depression Rating Scale (HDRS-21); and 4) meeting criteria for TRD, defined as having had at least two adequate dose-duration, antidepressant medication failures in the current depressive episode and a lifetime failure of at least three antidepressant medication trials. Exclusion criteria were 1) a history of bipolar disorder, schizophrenia, schizoaffective disorder, obsessive-compulsive disorder, panic disorder, or documented Axis II diagnoses; 2) active or recent substance abuse or dependence ("recent" defined as within the past 12 months; exception was made for nicotine use disorder); 3) the presence of acute medical illness that could interfere with study participation, including, but not limited to, significant pulmonary disease; 4) active suicidal intention; 5) active psychosis; 6) previous administration of NMDA receptor antagonists (e.g., ketamine); 7) ongoing treatment with electroconvulsive therapy; 8) pregnancy or breast-feeding in female patients; and 9) contraindications against the use of nitrous oxide (e.g., pneumothorax, middle ear occlusion, elevated intracranial pressure, chronic cobalamin or folate deficiency treated with folic acid or vitamin B_{12}). Patients were instructed to continue their current standard of care treatment for major depression and were required to maintain a stable medication or psychotherapy regimen without changes for 4 weeks before initiation of the study and to continue on the same dosage throughout the study.

Treatment

Patients received either an admixture of up to a maximum of 50% nitrous oxide and 50% oxygen ("active treatment") or 50% nitrogen/50% oxygen ("placebo") for 1 hour. The inspiratory nitrous oxide concentration was titrated during the first 10 min until 50% was achieved. The 50% nitrous oxide concentration was selected in this pilot trial based on clinical experience for sedation in dentistry and obstetric analgesia, where 50% nitrous oxide has been used for decades with an excellent safety and effectiveness record. We decided to maintain an equal oxygen concentration (50%) in the placebo treatment to limit the variability between treatment and placebo. The gas mix was administered via a standard anesthesia facemask through tubing connected to an anesthesia machine. A small sample connector line was inserted into the facemask allowing the measurement of inhaled and exhaled gas concentrations. Total gas flow was 4–8 L/min. Patients were monitored during and after the treatment according to the American Society of Anesthesiologists standard, which includes continuous three-lead electrocardiogram, pulse oximetry, noninvasive blood pressure, and end-tidal carbon dioxide under the supervision of an attending-level anesthesiologist. After the 1-hour treatment session, patients were transferred to a recovery area and monitored for 2 hours. A study team physician determined if the patients met criteria for discharge before patients were allowed to leave the treatment facility.

Outcomes

Outcomes were assessed at six time points for each patient (three per session; two sessions): at baseline (pretreatment), 2 hours after treatment for each session, and 24 hours after treatment for each session. A 1-week outcome assessment was not formally planned but was available as part of the baseline assessment for the second treatment session. The primary study endpoint was the change in the HDRS-21 at 24 hours after treatment. Secondary endpoints included change on the Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) scale. The primary mood assessment was selected to be administered at 24 hours to ensure that any acute euphoric effects of nitrous oxide had dissipated by this time (nitrous oxide euphoric effects typically cease shortly after discontinuation of nitrous oxide administration). Psychiatric safety endpoints were assessed via careful clinical observations and questioning for dangerousness to self (suicidality) as well as for emergence of psychosis (hallucinations, delusions, disorganized thinking). Other safety endpoints included cardiovascular, respiratory, and central nervous system adverse events determined by hemodynamic and respiratory monitoring. The extent of nitrous oxide–induced inactivation of vitamin B_{12} was determined by measurement of plasma total homocysteine before and after treatment.

Statistical Analysis

The primary outcome (HDRS-21) was analyzed with a repeated-measures mixed effects linear model using restricted maximum likelihood estimation. To adjust for the observed carryover effect, the model included a randomization group term and a three-way interaction (treatment × time × randomization group). Also, we performed a similar repeated-measures mixed model for only the first treatment session (with a two-way interaction). These analyses were repeated for the QIDS-SR scale.