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Nitrous Oxide Reduced Suicidal Ideation in Treatment-Resistant Major Depression in Exploratory Analysis

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Nitrous oxide (N_2O) is a colorless, odorless gas commonly used as an anesthetic in dental and obstetric settings.[1] Previously, our group demonstrated that N_2O has rapid antidepressant effects.[2,3] N_2O has *N*-methyl-d-aspartate receptor antagonist properties

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shared with ketamine; esketamine, an enantiomer, has received FDA approval for rapid reduction in suicidal ideation in major depressive disorder (MDD). In the present analysis, we examined N_2O's ability to reduce suicidal ideation in a pooled secondary analysis of data from 3 crossover trials investigating N_2O in subjects with treatment-resistant major depression (TRMD).

Methods

Data were pooled from 3 completed N_2O trials at Washington University School of Medicine (ClinicalTrials.gov identifiers: NCT02139540, NCT03283670, and NCT02994433). All studies were double-blind, randomized, placebo-controlled, outpatient crossover trials assessing depression reduction as the primary outcome. Subjects were adults with MDD as determined by the Mini-International Neuropsychiatric Interview.[4] All trials enrolled TRMD subjects (at least 3 lifetime adequate dose-duration antidepressant failures, with 1 or more in the current episode). All subjects received separate, 60-minute inhalations of 50% N_2O (50% N_2O in 50% oxygen) and placebo (air/oxygen mixture). Washout period between conditions was variable across the studies, with inhalations delivered 1–6 weeks apart.

Suicidal ideation (SI) was measured using the standard Hamilton Depression Rating Scale (HDRS)[5] suicide item (item 3) at 2 and 24 hours post-inhalation. A clinically meaningful reduction in SI was defined as at least a 2-point score reduction on item 3. Hence, subjects had to start with a score of at least a 2 ("wish he/she were dead or any thoughts of possible death to self") or a 3 ("suicidal ideas or gestures") on item 3; ie, those rating a 1 ("feels life is not worth living") were excluded from the SI reduction analysis. Of note, there were no subjects with a score of 4 ("attempts at suicide") or any active suicidal intention or planning, as more severe forms of suicidality were excluded from these outpatient trials. A 2-sided Fisher exact test was used to compare the proportion of subjects with clinically meaningful reduction in suicidality across N_2O and placebo conditions.

Results

Twenty-four subjects were pooled from the 3 N_2O TRMD trials (12/6/6 as per the 3 clinical trials, respectively). A total of 13 subjects in the N_2O arm and 17 subjects in the placebo arm scored at least 2 and were included in the analysis.

Using a 2-point decrease in the HDRS suicide item score to define reduction in SI, no trend in SI reduction was observed at the earlier time point (2 hours; $P = 1$). However, at 24 hours post-inhalation, there was a significant change in SI (N_2O vs placebo; $P = .019$). Figure 1 is a "heat map" showing SI reduction effects of N_2O compared to placebo. Of note, 7/13 (54%) of the subjects who received N_2O had a meaningful reduction in SI, whereas only 2/17 (12%) in the placebo group showed a similar change. There was a strong relationship between reduction in SI and reduction in total depressive scores for the treatment arm at the 24 hour time mark (Spearman $\rho = 0.763$).

Discussion

While preliminary, this post hoc analysis of 3 crossover trials demonstrated that N_2O, as compared to placebo, reduced SI in a TRMD sample. Similar to ketamine, this SI reduction occurred within 24 hours of exposure.[6,7] These findings suggest that N_2O may have rapid antisuicidal effects in depressed subjects. Further post hoc analyses demonstrated that the reduction in SI was strongly linked to reduction in depression; further study is needed to elucidate the persistence of the SI and MDD symptom reduction association.

There are several limitations to this secondary analysis: (1) a small sample size; (2) stability of SI prior to study inclusion and randomization is not known; (3) possible carryover effects, as existing N_2O studies suggest that antidepressant effects persist at least 2 weeks; and (4) all subjects had TRMD, limiting generalizations to non-resistant depressed populations. Despite the limitations, these findings are promising, and additional study of the potential antisuicidal ideation effects of N_2O is warranted.

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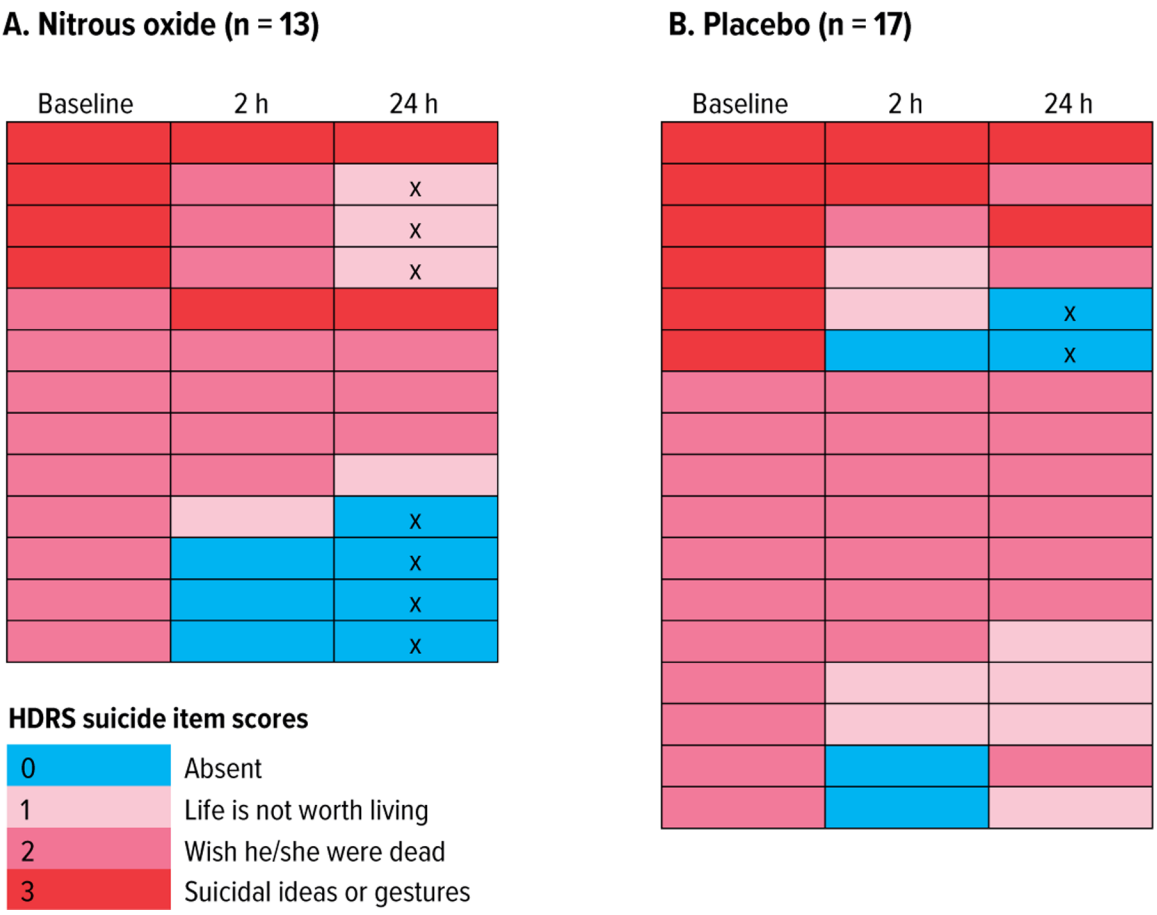

Figure 1. Cell Plot (Heat Map) of Individual Responses to (A) Nitrous Oxide vs (B) Placebo as Measured on the Hamilton Depression Rating Scale (HDRS) Suicide Item (Item 3)[a]

[a]Color indicates severity of suicidal thinking (see figure key). Time points used were prior to inhalation, to establish a baseline, and 2 hours and 24 hours following inhalation. Each row represents a subject. An "x" indicates subjects that had a meaningful reduction in suicidal thinking.