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 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.

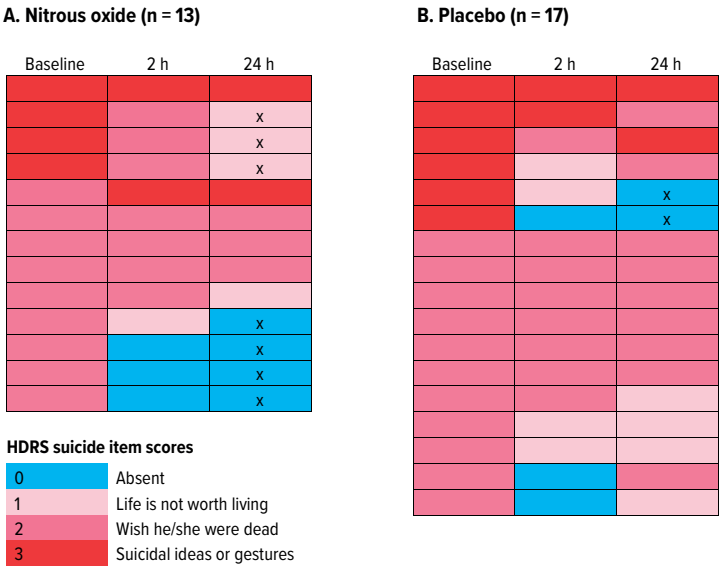
Using a 2-point decrease in the HDRS suicide item score to define reduction in SI, no trend in SI reduction was observed at the earlier time point (2 hours; $P = 1$). However, at 24 hours post-inhalation, there was a significant change in SI (N_2O vs placebo; $P = .019$). Figure 1 is a "heat map" showing 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.

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.

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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