Does Nitrous Oxide Help Veterans With Posttraumatic Stress Disorder?

A Case Series

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Posttraumatic stress disorder (PTSD) is a serious problem for many Veterans. Innovative and fast-acting therapeutic interventions are needed for those not helped by first-line treatments.[1–4] Nitrous oxide, an inhaled anesthetic and noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, may be a promising new approach for rapid reduction in PTSD symptoms.[5] Nitrous oxide is reported to speed the reduction of distressing intrusive memories in an experimental model of psychological trauma[6] and has shown promise as a rapidly acting antidepressant.[7] To our knowledge, this is the first study testing the effects of nitrous oxide in individuals with PTSD.

Method

Three veteran outpatients (ages 31, 43, and 46 years) who met PTSD criteria of at least moderate symptom severity (Clinician-Administered PTSD Scale for *DSM-5* [CAPS-5] score ≥ 40)[8] were recruited from the Veterans Affairs Palo Alto Health Care System between April 2018 and July 2019. Individuals were excluded if they had comorbid psychiatric or medical conditions that increased the risk of participation.

All participants completed a single 1-hour subanesthetic inhalation of 50% nitrous oxide and 50% oxygen administered by an anesthesiologist via face mask and standard semiclosed anesthetic circuit with a total gas flow rate of 4–8 L/min. A trained independent evaluator rated PTSD symptoms using CAPS-5 at baseline and 1 week after drug administration. Response was defined a priori as a CAPS-5 score reduction of 12 points at 7 days.[9] We additionally explored immediate (1 hour post-inhalation [120 minutes]) and interim (1, 2, 3, and 7 days) effects of nitrous oxide inhalation on self-reported PTSD symptoms using the Impact of Events Scale—Revised (IES-R).[10] To evaluate safety, participants were assessed for symptoms of dissociation, psychosis, mania, suicidality, and other side effects at the same time points.

Results

Participant clinical characteristics and effects of nitrous oxide are shown in Table 1. At baseline, all participants exceeded the criteria for clinically significant PTSD (CAPS-5 score ≥ 40); the mean CAPS-5 was 45 (SD = 6). At 1 week post-inhalation, 2 out of 3 participants met treatment response criteria by CAPS-5 with a 17-point (40 to 23) and 16-point change (41 to 25). Both responders showed near complete cessation of symptoms by IES-R by day 1; one showed sustained improvement, while the other showed gradual return of symptoms to near baseline by day 7. In contrast, the nonresponder reported early reduction in PTSD by IES-R by 120 minutes and quickly returned to baseline by day 1. There were no reports of new-onset dissociation, psychosis, mania, or suicidal ideation at any time point. Two of 3 participants reported side effects including nausea and poor concentration (see Table 1 for full list). The first participant vomited once during the inhalation yet nevertheless wished to continue with study procedures. Because of this, nitrous oxide concentration was increased slowly over 10 minutes to target dose for the 2 subsequent participants; neither vomited.

There are several limitations of this small, open-label case series, including inability to control for placebo effects and nonspecific effects of nitrous oxide. This case series suggests that adjunctive nitrous oxide can reduce self-reported PTSD symptoms within 1 day, lasting up to 1 week without causing new onset psychiatric symptoms. Future research is warranted to determine whether nitrous oxide effects are replicated in a larger sample under randomized, controlled conditions and whether the effects benefit specific PTSD domains. If our hypotheses are replicated in independent samples, it may be feasible that nitrous oxide

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Table 1. Participant Clinical Characteristics and Effects of Nitrous Oxide in a Case Series (N = 3)

Patient No.	Age (y)/ Sex	Race	Comorbid Disorders	No. of Prior SRI/CBT Trials[a]	Current Psychotropic Medications[b]	Adverse Effects 120 Min Post-Inhalation	CAPS-5			IES-R					
							Baseline	1 Week	Responder?	Baseline	120 Min Post-Inhalation	Day 1	Day 2	Day 3	Day 7
1	31/M	C	None	1/1	Mixed amphetamine salts	Nausea, vomiting, poor concentration, decreased energy, general malaise, fingers tingling, body warmth, increased perspiration, blurry vision	40	23	Yes	16	16	3	4	7	18
2	43/M	C	Excoriation disorder	2/0	None	None	41	25	Yes	26	17	1	2	2	8
3	46/M	C	SAD, GAD	0/0	Nortriptyline	Nausea, poor concentration, dry mouth, dizziness, headache, restlessness, anxiety, fatigue	54	55	No	68	29	61	73	81	67

[a]Of the 3 participants, 2 had failed at least 2 prior trials of standard first-line posttraumatic stress disorder treatment per American Psychiatric Association Practice Guidelines[11]; 1 participant had refused these treatments due to concerns about intolerable side effects.
[b]Of the 3 participants, 2 were on psychotropic medications, but these medications were stable for at least 4 weeks before study entry.
Abbreviations: C = Caucasian, CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, CBT = cognitive behavioral therapy, GAD = general anxiety disorder, IES-R = Impact of Events Scale—Revised, M = male, SAD = social anxiety disorder, SRI = serotonin reuptake inhibitor.

can be safely and effectively implemented to achieve rapid symptom reduction while longer-term PTSD treatments like psychotherapy or pharmacology are allowed to take effect over a longer time course.

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