

## Combination of Nitrous Oxide with Isoflurane or Scopolamine for Treatment-resistant Major Depression

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### TO THE EDITOR

The *N*-methyl-D-aspartate (NMDA) receptor antagonists, including ketamine, are receiving increasing attention because ketamine rapidly causes a long-lasting reduction in depressive symptoms in patients whose major depression resists conventional treatment.<sup>1-4)</sup> We read with great interest the recent article by Nagele *et al.*<sup>5)</sup> about the efficacy of nitrous oxide (N<sub>2</sub>O), an inhaled general anesthetic and NMDA receptor antagonist, in patients with treatment-resistant major depression. The article describes a randomized, double-blind, placebo-controlled, cross-over study in which patients (n=20) were treated in two sessions 1 week apart with either nitrous oxide (50% nitrous oxide/50% oxygen or placebo [100% oxygen]) for 1 h. As measured by the 21-item Hamilton Depression Rating Scale (HDRS-21), depression symptoms improved significantly more at 2 h and 24 h after receiving nitrous oxide than after placebo (mean difference of HDRS-21: -4.8 points at 2 h, *p*=0.002, and -5.5 points at 24 h, *p*<0.001). Furthermore, patients (n=10) treated with nitrous oxide first reported a significant improvement of depressive symptoms at 2 h, 24 h, and 1 week (mean difference of HDRS-21: -7.1 points at 2 h, -8.6 points at 24 h, -12.8 points at 1 week). Four patients' (20%) improvement qualified as a treatment response (reduction ≥50% on HDRS-21), and three patients (15%) reported a full remission (≤7 points on the HDRS-21) after nitrous oxide inhalation.

The results indicate a sustained antidepressant effect of nitrous oxide. No serious adverse events occurred; all adverse events were brief and mild. Importantly, nitrous oxide did not cause psychotomimetic effects, such as hallucinations and delusions, which commonly occur after the administration of ketamine, the other NMDA receptor antagonist in clinical use. This study suggests that nitrous oxide has a rapid and sustained antidepressant effect in patients with treatment-resistant major depression, although further studies using a larger sample size are needed.

Nitrous oxide is a colorless, non-flammable gas with a slightly sweet odor and taste and is also known as "laughing gas" because it can cause euphoric effects, including laughter, in humans. Nitrous oxide is also a drug of abuse, and its abuse potential represents a possible limitation for its utility in clinical psychiatry.<sup>5)</sup> Although nitrous oxide had been used in surgery and dentistry for its anesthetic and analgesic effects, this was gradually eliminated due to its neurotoxic side effects. More recently, nitrous oxide-induced neurotoxicity has been implicated in the development of long-lasting cognitive deficits when administered in very young or very old patients.<sup>6)</sup> Exposure to nitrous oxide during surgery is also widely known to elevate homocysteine levels in many patients.<sup>6)</sup> This likely results from nitrous oxide's inactivation of methionine synthase, which generates methyl groups (via the active intermediary, *S*-adenosylmethionine) for the synthesis of DNA, RNA, myelin, and catecholamines, among other products. Elevated homocysteine after nitrous oxide inhalation is likely associated with neuronal death and subsequent cognitive decline.

The precise mechanisms by which nitrous oxide exerts its antidepressant effect have not been fully elucidated. The predominant pharmacological effect of nitrous oxide is non-competitive inhibition of the NMDA receptor.<sup>6,7)</sup> Both 50% nitrous oxide and 0.5 mg/kg ketamine are sub-anesthetic doses that can produce a rapid antidepressant effect in patients with treatment-resistant major depression.<sup>5)</sup> A recent study showed that the anesthetic midazolam (active placebo control: benzodiazepine, 0.045 mg/kg), also had an antidepressant effect (a 28% response rate at 24 h post-infusion), although its effect was significantly

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less potent than that of ketamine (0.5 mg/kg).<sup>8)</sup> Isoflurane, another gaseous anesthetic, is also known to moderately inhibit the NMDA receptor,<sup>7)</sup> and has antidepressant effects (administered in 10 treatments over 3 weeks) in patients with treatment-resistant depression.<sup>9)</sup>

In contrast, a study in rats by Olney *et al.*<sup>10)</sup> found that NMDA receptor antagonists, including phencyclidine and ketamine, cause acute neuropathological changes in the posterior cingulate cortex and retrosplenial cortex, known to be involved in cognitive functioning. Subsequently, the same group<sup>11)</sup> reported that neuropathological changes in these regions following NMDA receptor antagonist administration could be prevented by diazepam. Furthermore, short-term exposure to nitrous oxide is also reported to cause neuropathological changes in the posterior cingulate and retrosplenial cortex of rats.<sup>12)</sup> The concentration that induces neuropathological changes in rat brain is roughly equivalent to the maximum concentration of nitrous oxide used in human anesthesia.<sup>12)</sup> Pretreatment with a single dose of diazepam or concurrent administration of isoflurane (which antagonizes the GABA receptor as well as the NMDA receptor) prevents nitrous oxide-induced neuropathological changes in these regions of the rat brain.<sup>12)</sup> In contrast, a recent study using a surface Laplacian derivation shows that nitrous oxide (20-60%, 20 min inhalation) reduced parietal network-level functional connectivity in healthy subjects, suggesting that cortical networks are most affected by nitrous oxide inhalation.<sup>13)</sup> Taken together, preclinical and clinical findings suggest that nitrous oxide may have detrimental effects in the human cerebral cortex, but not serious side effects such as delusions.<sup>5)</sup> Therefore, isoflurane seems likely to potentiate the antidepressant effect of nitrous oxide by decreasing the potential side effects (e.g., reduced cortical network connectivity and euphoria) of nitrous oxide.

In the same study reporting the neuroprotective effects of diazepam in rats, Olney *et al.*<sup>11)</sup> also found that the anticholinergic drug scopolamine prevents pathological changes in the posterior cingulate and retrosplenial cortex. This finding indicates that muscarinic acetylcholine receptors also mediate NMDA antagonist-induced neurotoxicity. Intravenous scopolamine has also been shown to rapidly reduce symptoms in patients with depression.<sup>14)</sup> Therefore, scopolamine may also represent a promising means of reducing the detrimental side effects of nitrous oxide while enhancing its antidepressant benefits in patients with treatment-resistant depression.

In conclusion, adding isoflurane or scopolamine to inhaled nitrous oxide gas would provide a new therapeutic

approach for depression by reducing the detrimental side effects of nitrous oxide.

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