Correspondence

Study of Antidepressant Actions of Subanesthetic Nitrous Oxide: Importance of Adequate Blinding and Opioid Receptors

To the Editor:

I read the recent paper by Palanca *et al.* (1). My interest is prompted by the authors'

(1) statement that their study was double-blind;
(2) not mentioning the opioid antidepressant properties of nitrous oxide (N_2O);
(3) suggesting that the observation of the antidepressant actions of subanesthetic N_2O was recent;
(4) proposing that it is clinically appropriate to expose volunteers to 60 minutes of 50% N_2O via a semiclosed system.

Double-Blind Technique. In a double-blind technique, neither the observer nor the participant can differentiate the experimental and control conditions (2). The authors themselves state, "Participants correctly guessed the condition in 21 of 28 sessions (75%)," showing that their study was not double-blind (1,3). Furthermore, some of the current investigators acknowledged previously that the same blinding technique was not double-blind (4). Nevertheless, they state that this study was double-blind (1). Based on the above, I contend that the study (1) was not double-blind (2), although an appropriate double-blind technique exists (5).

N_2O Exerts Its Antidepressant Action via Opioid Receptors. If N_2O and ketamine are predominately antidepressant via blocking NMDA receptors, then why is the NMDA receptor antagonist memantine, without opioid agonist actions, not antidepressant (2)? Although the authors mention that other receptors may be involved in the antidepressant actions of ketamine and N_2O, they do not discuss the opioid system (1). The latter is important because opioids have antidepressant effects (6,7), and both N_2O and ketamine have opioid properties (8–11). The significance of the antidepressant actions of the opioid system is underlined by its role in the pathogenesis of depression (12). Moreover, ketamine and tricyclic antidepressants lose their antidepressant action when blocked by opioid antagonists (13–15). Interestingly, our initial observation of the antidepressant actions of subanesthetic concentrations of N_2O (16,17) was predicated on the opioid properties of subanesthetic N_2O.

Additionally, opioid receptors exist in mammalian visual areas (18) that seem to be involved in the prolonged actions of subanesthetic N_2O (1).

Using a Semiclosed Circuit With 50% N_2O. In this study, there is little mention of side effects, although "six individuals withdrew after the first inhalation session or the first postinhalation imaging session." (1). The authors are silent on the reasons for these withdrawals. This is a significant omission, particularly because earlier work that also used 50% N_2O with a face mask strapped to the volunteers' faces produced a number of anticipated side effects, including nausea and vomiting (19–21). There is a danger of aspiration when 50% N_2O is given for 30 minutes when breathed through a relatively loose-fitting nasal mask (20,22). Thus, the risk increases when the gases are given via a tightly applied facial mask for 60 minutes (23), and aspiration is potentially lethal (24,25).

Given the above, there are definite risks to using continuous flow 50% N_2O, particularly via a full-face mask strapped to the face (19–21).

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I am a Medical Advisor to Sedatek, which sells equipment for subanesthetic nitrous oxide administration in South Africa. I own no shares in Sedatek.

Article Information

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References

1. Palanca BJA, Conway CR, Zeffiro T, Gott BM, Nguyen T, Janski A, *et al.* (2023): Persistent brain connectivity changes in healthy volunteers following nitrous oxide inhalation. Biol Psychiatry Glob Open Sci 3:698–704.
2. Institute of Medicine (US) Committee on Strategies for Small-Number-Participant Clinical Research Trials, Evans CH Jr, Ildstad ST (2001): Appendix B, Glossary of statistical and clinical trials terms. In: Small Clinical Trials: Issues and Challenges. Washington, DC: National Academies Press. Available at: https://www.ncbi.nlm.nih.gov/books/NBK223325/. Accessed January 22, 2024.
3. Zarate CA Jr, Machado-Vieira R (2015): Potential pathways involved in the rapid antidepressant effects of nitrous oxide. Biol Psychiatry 78:2–4.
4. Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, Walker M, *et al.* (2015): Nitrous oxide for treatment-resistant major depression: A proof-of-concept trial. Biol Psychiatry 78:10–18.
5. Gillman MA, Lichtigfeld FJ (2002): Randomised double-blind trial of psychotropic analgesic nitrous oxide compared with diazepam for alcohol withdrawal state. J Subst Abuse Treat 22:129–134.
6. Matussek N (2003): Opioid system in depression. Int J Neuropsychopharmacol 6:443.
7. Bodkin JA, Zornberg GL, Lukas SE, Cole JO (1995): Buprenorphine treatment of refractory depression. J Clin Psychopharmacol 15:49–57.
8. Matussek N, Hoehe M (1989): Investigations with the specific mu-opiate receptor agonist fentanyl in depressive patients: Growth hormone, prolactin, cortisol, noradrenaline and euphoric responses. Neuropsychobiology 21:1–8.
9. Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG (1999): Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells. Anesthesiology 90:174–182.
10. Sarton E, Teppema LJ, Olievier C, Nieuwenhuijs D, Matthes HW, Kieffer BL, Dahan A (2001): The involvement of the mu-opioid receptor

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in ketamine-induced respiratory depression and antinociception. Anesth Analg 93:1495–1500.
11. Gillman MA, Lichtigfeld FJ (1994): Opioid properties of psychotropic analgesic nitrous oxide (Laughing Gas). Perspect Biol Med 38:125–138.
12. Gross-Isseroff R, Dillon KA, Israeli M, Biegon A (1990): Regionally selective increases in mu opioid receptor density in the brains of suicide victims. Brain Res 530:312–316.
13. Klein ME, Chandra J, Sheriff S, Malinow R (2020): Opioid system is necessary but not sufficient for antidepressive actions of ketamine in rodents. Proc Natl Acad Sci U S A 117:2656–2662.
14. Olianas MC, Dedoni S, Onali P (2012): The atypical antidepressant mianserin exhibits agonist activity at κ-opioid receptors. Br J Pharmacol 167:1329–1341.
15. Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, *et al.* (2018): Attenuation of antidepressant effects of Ketamine by opioid receptor antagonism. Am J Psychiatry 175:1205–1215.
16. Lichtigfeld FJ, Gillman MA (1982): The treatment of alcoholic withdrawal states with oxygen and nitrous oxide. S Afr Med J 61:349–351.
17. Gillman MA, Matussek N, Lichtigfeld FJ (1985): Effect of nitrous oxide on depressive patients and volunteers. In: Pichot P, Berner P, Wolf R, Thau K, editors. Biological Psychiatry, Higher Nervous Activity. New York: Springer Science, 397–403.
18. Walker JM, Bowen WD, Thompson LA, Frascella J, Lehmkuhle S, Hughes HC (1988): Distribution of opiate receptors within visual structures of the cat brain. Exp Brain Res 73:523–532.
19. Malamed SJ (1989): Inhalation Sedation: Complications. In: Sedation: A Guide to Patient Management, 2nd ed.. (247–252). St Louis: Mosby, 247–252.
20. Clark M, Brunick A (2008): Signs and symptoms of N2O/O2 sedation. In: Handbook of Nitrous Oxide and Oxygen Sedation, 3rd ed. St Louis: Mosby, 117–122.
21. Gillman MA (2022): What is better for psychiatry: Titrated or fixed concentrations of nitrous oxide? Front Psychiatry 13:773190.
22. Rubin J, Brock-Utne JG, Greenberg M, Bortz J, Downing JW (1977): Laryngeal incompetence during experimental "relative analgesia" using 50% nitrous oxide in oxygen. A preliminary report. Br J Anaesth 49:1005–1008.
23. Eger EI (1985): Respiratory effects of nitrous oxide. In: Eger EI, editor. Nitrous Oxide/N2O. New York: Elsevier, 109–123.
24. Robinson M, Davidson A (2014): Aspiration under anaesthesia: Risk assessment and decision-making. Contin Educ Anaesth Crit Care Pai 14:171–175.
25. Hayashi R, Maeda S, Hideki T, Higuchi H, Miyawaki T (2020): Pulmonary aspiration during induction of General Anesthesia. Anesth Prog 67:214–218.