

## Nitrous Oxide

### Authors

Kayla Knuf<sup>1</sup>; Christopher V. Maani<sup>2</sup>.

### Affiliations

<sup>1</sup> Brooke Army Medical Center

<sup>2</sup> US Army

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## Continuing Education Activity

Nitrous oxide is an odorless, colorless, non-flammable gas. While nitrous oxide is not flammable, it will support combustion to the same extent as oxygen. It leads to a state of euphoria, explaining its nickname, 'laughing gas.' Nitrous oxide is the least potent inhalational anesthetic. Compared to other anesthetic agents, nitrous oxide causes minimal effects on respiration and hemodynamics. It cannot be a sole anesthetic agent and is often combined with a more potent and volatile anesthetic. The combination of analgesic and anesthetic effects makes nitrous oxide a valuable adjunct. This activity outlines the indications, mechanism of action, methods of administration, significant adverse effects, contraindications, monitoring, and toxicity of nitrous oxide, so providers can direct patient therapy to optimal outcomes in anesthesia and other conditions where nitrous oxide has therapeutic benefits.

### Objectives:

- Summarize the indications for using nitrous oxide.
- Describe the mechanism of action of nitrous oxide.
- Identify the contraindications and adverse events associated with nitrous oxide.
- Review the importance of improving care coordination among the interprofessional team to enhance the delivery of care for patients who can benefit from the administration of nitrous oxide.

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## Indications

Nitrous oxide is an odorless, colorless, non-flammable gas. While nitrous oxide is not flammable, it will support combustion to the same extent as oxygen. It leads to a state of euphoria, explaining its nickname, 'laughing gas.' Nitrous oxide is the least potent inhalational anesthetic. Nitrous oxide requires a concentration of 104% to reach one minimum alveolar concentration (MAC). Thus it cannot be a sole anesthetic agent, and it is often combined with a more potent and volatile anesthetic. The combination of analgesic and anesthetic effects makes nitrous oxide a valuable adjunct. Nitrous oxide has a low blood solubility (blood-gas partition coefficient of 0.47), leading to a quick onset and offset. The low solubility leads to a concentrating effect for administered volatile agents in the lungs and is known as the second gas effect.[1]

Nitrous oxide can be used for general anesthesia, procedural sedation, dental anesthesia, and to treat severe pain. Nitrous oxide's potent analgesic properties can be useful in providing analgesia in settings such as the obstetrical ward or emergency department. Its administration is often a 50% mixture of oxygen in these settings. Compared to other anesthetic agents, nitrous oxide causes minimal effects on respiration and hemodynamics. It leads to decreased tidal

volume and increased respiratory rate but minimizes overall minute ventilation. Nitrous oxide leads to direct myocardial depression, but nitrous oxide's sympathetic stimulation reduces this effect, and the net effect is minimal. Unlike other volatile anesthetics, nitrous oxide has no muscle relaxation properties.[2]

Nitrous oxide is also being investigated as a potential agent for treatment-resistant depression. However, further extensive research is needed.[3]

## Mechanism of Action

Nitrous oxide has multiple supraspinal and spinal targets. The anesthetic effect of nitrous oxide is through non-competitive NMDA inhibition in the central nervous system. The analgesic effects occur by releasing endogenous opioids that act on opioid receptors; its analgesic actions are like morphine. The anxiolytic effects are through GABA-A activation. Nitrous oxide has a central sympathetic stimulating activity that supports blood pressure, systemic vascular resistance, and cardiac output. Nitrous oxide stimulates cerebral blood flow and increases intracranial pressure.[4]

## Pharmacokinetics

Absorption: Inhaled nitrous oxide is rapidly absorbed through alveoli. The onset of action is within 2 to 5 mins.[5][6]

Distribution: Nitrous oxide may produce the second-gas effect because nitrous oxide diffuses more rapidly across alveolar basement membranes than other gases. The rapid exit of nitrous oxide from the alveoli results in remaining alveolar gases being concentrated, thus accelerating nitrous oxide uptake into the blood and speeding the onset of anesthesia. Nitrous oxide has a MAC of 105%. Minimal Alveolar Concentration (MAC) relates to the potency of volatile anesthetic agents. It is defined as the minimum alveolar concentration of inhaled anesthetic at which 50% of people do not move in response to noxious stimuli. Thus N<sub>2</sub>O is a weak anesthetic inhalational agent but has good analgesic effects. The reversal may occur at the end of anesthesia when nitrous oxide enters the alveoli far more rapidly, causing oxygen dilution within the alveoli and may cause diffusion hypoxia.[7]

Metabolism: Nitrous oxide (a trace amount) is metabolized through reduction by anaerobic bacteria in the gut.

Excretion: Nitrous oxide is primarily eliminated via the lungs.

## Administration

Nitrous oxide administration is via inhalation utilizing a simple face mask, laryngeal mask airway, or an endotracheal tube. Administration of nitrous oxide according to the European Society of Anaesthesiology Task Force on Nitrous Oxide is given below.[7]

For surgical procedural sedation and dental procedures, nitrous oxide (30 to 50%) is combined with oxygen.[8]

For general anesthesia, nitrous oxide(50 to 70%) is used. But due to its low potency, it can not be used as a single anesthetic agent; hence it is combined with other agents. Specially designated equipment for administering NO must be employed to ascertain concentrations of 50% NO and 50% oxygen. In contrast with dental apparatus, the device approved for obstetric use does not allow the clinician to modify the proportion of gases.[9]

- Induction: The combination of lower solubilities in blood and different tissues makes N<sub>2</sub>O one of the fastest anesthetic agents. N<sub>2</sub>O uptake in the lungs improves the blood concentrations of concomitantly administered other volatile inhalation agents and oxygen, leading to faster induction and improved arterial oxygenation.
- Maintenance: N<sub>2</sub>O is mixed with different drugs during maintenance because of its insufficient anesthetic potency. As discussed above, nitrous oxide has a MAC of 105%, but the provision of sufficient oxygen delivery precludes the administration of concentrations above 70–75%, thus limiting its use to 0.7 MAC. Combining

propofol with nitrous oxide for dental sedation decreases propofol requirements and reduces the hypotensive effects compared to propofol alone.

- **Emergence:** Nitrous oxide quickens emergence from anesthesia. In addition, nitrous oxide has a short elimination half-time; hence washout from the brain is swift because of its lower lipid solubility, leading to rapid recovery.[8]

### Use in Specific Patient Populations

**Patients with Renal Impairment:** No information is provided in the manufacturer's labeling for dose adjustments in patients with renal impairment.

**Patients with Hepatic Impairment:** No information is provided in the manufacturer's labeling for dose adjustments in patients with hepatic impairment.

**Pregnancy Considerations:** According to ACOG (American College of Obstetricians and Gynecologists), guidelines 50% nitrous oxide with 50% oxygen is used during labor and for postpartum perineal repair. It is important to recognize that nitrous oxide crosses the placenta, and it is rapidly eliminated by neonates upon the commencement of breathing. However, ACOG and the American Society of Anesthesiologists note that due to the increased risk of sedation and maternal hypoxemic episodes, nitrous oxide should not be combined with systemic opioids or sedatives, or hypnotics.[10]

**Breastfeeding Considerations:** The half-life of nitrous oxide in the mother is short, and the nitrous oxide is not anticipated to be absorbed by the infant. Therefore, if used as part of general anesthesia, breastfeeding can be started after the mother has recovered adequately from anesthesia.[11]

### Adverse Effects

Adverse effects of nitrous include:

- **Respiratory Depression:** When used alone, nitrous has limited respiratory effects, but when used in combination with other sedatives, hypnotics, or opioids, it can potentiate the respiratory depressant effects of these agents.
- **Diffusion hypoxia:** Following discontinuation of nitrous oxide, the concentration gradient between the gases in the lung and alveolar circulation rapidly reverses, leading to rapid oxygen dilution in the alveoli and subsequent hypoxia, and 100% oxygen administration should follow nitrous oxide cessation.
- **Postoperative Nausea and Vomiting:** Nitrous has an increased risk of postoperative nausea and vomiting (PONV) compared with other agents, but this is controllable with prophylactic anti-emetics.[12] The ENIGMA I trial showed an increased incidence of PONV with nitrous oxide use. The ENIGMA II trial showed that severe PONV with nitrous oxide use is more common in procedures lasting over 2 hours. This study also showed nitrous oxide is not associated with increased mortality, cardiovascular complications, or wound infections.[13]
- Fever, pulmonary atelectasis, and infectious complications
- **Hyperhomocysteinemia:** Nitrous oxide irreversibly oxidizes the cobalt atom of vitamin b12 and reduces the activity of vitaminb12 dependent enzymes such as methionine synthetases which can also lead to megaloblastic anemia.[14]
- **Subacute myeloneuropathy:** Nitrous oxide use disorder can cause a severe but potentially reversible myeloneuropathy characterized by axonal sensorimotor neuropathy.[15]

### Contraindications

Many contraindications to nitrous use are relative and may vary based on the provider. These include:

- **Critically ill patients:** Nitrous oxide inactivates methionine synthase via oxidation of the cobalt in vitamin B12 and may lead to megaloblastic anemia. This enzyme is essential for vitamin B12 and folate metabolism and plays a role in DNA and RNA synthesis and the synthesis of other substances. In otherwise healthy patients, the impact is subclinical. However, this may lead to neurologic or hematologic consequences in critically ill patients and should be avoided.
- **Severe cardiac disease:** Methionine synthase is also required to convert homocysteine to methionine, and elevated serum homocysteine levels are associated with an increased risk for adverse coronary events. The clinician should avoid using nitrous oxide in severe cardiac disease, but further studies are needed to determine the actual impact.
- **The first trimester of pregnancy:** Due to the above-referenced impact on B12 and folate metabolism, nitrous use is not recommended in the first trimester of pregnancy.
- **Pneumothorax, small bowel obstruction, middle ear surgery, and retinal surgeries create an intraocular gas bubble:** Nitrous oxide is 30 times more soluble than nitrogen. Nitrous oxide diffuses more rapidly into closed spaces than nitrogen can diffuse out, leading to increased gas volume and pressure within closed spaces. Thus nitrous oxide is contraindicated in pneumothorax, small bowel obstruction, middle ear surgery, and retinal surgeries involving the creation of an intraocular gas bubble. In laparoscopic cases, nitrous oxide can accumulate in the pneumoperitoneum, and some avoid its use.
- **Severe psychiatric disorders:** Nitrous oxide can cause dreaming and hallucinations and should be avoided in patients with severe psychiatric disorders.
- **Pulmonary hypertension:** Nitrous oxide can increase pulmonary artery and wedge pressures via sympathetic stimulation, and clinicians often avoid it in patients with pulmonary hypertension.[16]
- **Head and neck procedures with cautery use:** While nitrous oxide is non-flammable, it supports combustion, and its use should be avoided in these procedures.[17]
- **Impaired consciousness** [7]

## Monitoring

No specific monitoring is necessary for nitrous oxide use. An in-line oxygen analyzer with an alarm should be used to prevent the delivery of a hypoxic gas mixture. Modern anesthetic machines have fail-safe mechanisms to prevent this (nitrous oxide-oxygen proportioning systems). Standard ASA monitoring is necessary when administering nitrous oxide for any indication.[18]

The rooms where NO is utilized should be monitored for proper ventilation, waste gas scavenging, and hazard communication. In addition, a pin-index safety system should be monitored to prevent the random attachment of a nonoxygen tank to the oxygen portal.[19]

According to the American Society of Anesthesiology, periodic assessment of airway patency, oxygen saturation, and respiratory rate should be done during emergence and recovery, with particular attention to monitoring oxygenation and ventilation. Hemodynamic parameters should be monitored during emergence and recovery.[20]

## Toxicity

While nitrous oxide inactivates methionine synthase, intraoperative use results in a transient metabolic abnormality that soon reverses upon replacing the degrading enzyme.

When nitrous oxide is used recurrently (during occupational exposure or as a drug of abuse), it may lead to megaloblastic anemia with neurologic dysfunction. This situation also may occur in patients with an unrecognized cobalamin deficiency (vegans, pernicious anemia, hereditary disorders of cobalamin, and folate metabolism). Subacute combined degeneration of the spinal cord (SACD) and death is reported with repeated exposure in a case of a rare congenital 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency.[7]

## Enhancing Healthcare Team Outcomes

Nitrous oxide is a widely used option for labor analgesia and dentistry. One reason for limited use in the United States is the limited availability of anesthesia coverage. The nursing staff has shown that nitrous oxide administration and management are safe, cost-effective labor analgesia options.[21] A meta-analysis of 35 RCTs showed no differences in the in-hospital fatality rates of nitrous oxide-based and nitrous oxide-free anesthesia. Still, clinicians should avoid nitrous oxide in patients with poor pulmonary function and patients at higher risk for postoperative nausea and vomiting.[22] [Level 1] Certified registered nurse anesthetists(CRNAs) administered nitrous oxide has also provided procedural sedation in pediatric radiology, resulting in fewer adverse effects and a quicker return to baseline than oral midazolam.[23][24]

Hospitalists or internists usually check preoperative assessment.[25] Anesthetists and CRNAs administer nitrous oxide. The perioperative pharmacy team should assist in medication procurement, promote safe medication use according to regulations, and review preoperative and postanesthesia care unit (PACU) orders. When used in obstetric settings, the safe and appropriate use of nitrous oxide requires coordination and communication of an interprofessional team of obstetricians, perinatologists, certified registered nurse anesthetists (CRNAs), anesthesiologists, neonatal intensive care units, and biomedical and risk management departments.[9]

Nitrous oxide is also widely used in dental settings. Dental hygienists and assistants are authorized to administer nitrous oxide in certain states. According to CDC, chronic occupational exposure to nitrous oxide may lead to neurological complications and an increased risk of miscarriage. Hence, an interprofessional approach between dentists, dental hygienists, and dental assistants is needed when administering nitrous oxide to prevent occupational hazards.[26] [Level 5]

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## Review Questions

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## References

1. Zafirova Z, Sheehan C, Hosseinian L. Update on nitrous oxide and its use in anesthesia practice. *Best Pract Res Clin Anaesthesiol.* 2018 Jun;32(2):113-123. [PubMed: 30322453]
2. Galinski M, Hoffman L, Bregeaud D, Kamboua M, Ageron FX, Rouanet C, Hubert JC, Istria J, Ruscev M, Tazarourte K, Pevirieri F, Lapostolle F, Adnet F. Procedural Sedation and Analgesia in Trauma Patients in an Out-of-Hospital Emergency Setting: A Prospective Multicenter Observational Study. *Prehosp Emerg Care.* 2018 Jul-Aug;22(4):497-505. [PubMed: 29384419]
3. Quach DF, de Leon VC, Conway CR. Nitrous Oxide: an emerging novel treatment for treatment-resistant depression. *J Neurol Sci.* 2022 Mar 15;434:120092. [PubMed: 34953347]
- 4.

- Emmanouil DE, Quock RM. Advances in understanding the actions of nitrous oxide. *Anesth Prog.* 2007 Spring;54(1):9-18. [PMC free article: [PMC1821130](#)] [PubMed: [17352529](#)]
5. Khinda V, Rao D, Sodhi SP, Brar GS, Marwah N. Physiological Effects, Psychomotor Analysis, Cognition, and Recovery Pattern in Children Undergoing Primary Molar Extractions under Nitrous Oxide Sedation Using Two Different Induction Techniques: A Split-mouth Randomized Controlled Clinical Trial. *Int J Clin Pediatr Dent.* 2021;14(Suppl 2):S131-S137. [PMC free article: [PMC9108797](#)] [PubMed: [35645480](#)]
  6. Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. *Anesth Prog.* 2008 Winter;55(4):124-30; quiz 131-2. [PMC free article: [PMC2614651](#)] [PubMed: [19108597](#)]
  7. Buhre W, Disma N, Hendrickx J, DeHert S, Hollmann MW, Huhn R, Jakobsson J, Nagele P, Peyton P, Vutskits L. European Society of Anaesthesiology Task Force on Nitrous Oxide: a narrative review of its role in clinical practice. *Br J Anaesth.* 2019 May;122(5):587-604. [PubMed: [30916011](#)]
  8. Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. *Anesthesiology.* 2018 Mar;128(3):437-479. [PubMed: [29334501](#)]
  9. Collins M. Use of Nitrous Oxide in Maternity Care: AWHONN Practice Brief Number 6. *J Obstet Gynecol Neonatal Nurs.* 2018 Mar;47(2):239-242. [PubMed: [29449117](#)]
  10. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 209: Obstetric Analgesia and Anesthesia. *Obstet Gynecol.* 2019 Mar;133(3):e208-e225. [PubMed: [30801474](#)]
  11. Drugs and Lactation Database (LactMed) [Internet]. National Library of Medicine (US); Bethesda (MD): Nov 16, 2020. Nitrous Oxide. [PubMed: [30000561](#)]
  12. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E., ENIGMA Trial Group. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology.* 2007 Aug;107(2):221-31. [PubMed: [17667565](#)]
  13. Myles PS, Leslie K, Chan MT, Forbes A, Peyton PJ, Paech MJ, Beattie WS, Sessler DI, Devereaux PJ, Silbert B, Schricker T, Wallace S., ANZCA Trials Group for the ENIGMA-II investigators. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. *Lancet.* 2014 Oct 18;384(9952):1446-54. [PubMed: [25142708](#)]
  14. Rao LK, Francis AM, Wilcox U, Miller JP, Nagele P. Pre-operative vitamin B infusion and prevention of nitrous oxide-induced homocysteine increase. *Anaesthesia.* 2010 Jul;65(7):710-5. [PMC free article: [PMC3732777](#)] [PubMed: [20477781](#)]
  15. Swart G, Blair C, Lu Z, Yogendran S, Offord J, Sutherland E, Barnes S, Palavra N, Cremer P, Bolitho S, Michael Halmagyi G. Nitrous oxide-induced myeloneuropathy. *Eur J Neurol.* 2021 Dec;28(12):3938-3944. [PubMed: [34427020](#)]
  16. Schulte-Sasse U, Hess W, Tarnow J. Pulmonary vascular responses to nitrous oxide in patients with normal and high pulmonary vascular resistance. *Anesthesiology.* 1982 Jul;57(1):9-13. [PubMed: [7091732](#)]
  17. Miller AL, Theodore D, Widrich J. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Sep 6, 2022. Inhalational Anesthetic. [PubMed: [32119427](#)]
  18. Pandya AN, Majid SZ, Desai MS. The Origins, Evolution, and Spread of Anesthesia Monitoring Standards: From Boston to Across the World. *Anesth Analg.* 2021 Mar 01;132(3):890-898. [PubMed: [32665466](#)]
  19. Donaldson M, Donaldson D, Quarnstrom FC. Nitrous oxide-oxygen administration: when safety features no longer are safe. *J Am Dent Assoc.* 2012 Feb;143(2):134-43. [PubMed: [22298554](#)]
  20. Apfelbaum JL, Silverstein JH, Chung FF, Connis RT, Fillmore RB, Hunt SE, Nickinovich DG, Schreiner MS, Silverstein JH, Apfelbaum JL, Barlow JC, Chung FF, Connis RT, Fillmore RB, Hunt SE, Joas TA, Nickinovich DG, Schreiner MS., American Society of Anesthesiologists Task Force on Postanesthetic Care. Practice



- guidelines for postanesthetic care: an updated report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. *Anesthesiology*. 2013 Feb;118(2):291-307. [PubMed: 23364567]
21. Pinyan T, Curlee K, Keever M, Baldwin KM. A Nurse-Directed Model for Nitrous Oxide Use During Labor. *MCN Am J Matern Child Nurs*. 2017 May/Jun;42(3):160-165. [PubMed: 28448331]
  22. Sun R, Jia WQ, Zhang P, Yang K, Tian JH, Ma B, Liu Y, Jia RH, Luo XF, Kuriyama A. Nitrous oxide-based techniques versus nitrous oxide-free techniques for general anaesthesia. *Cochrane Database Syst Rev*. 2015 Nov 06;2015(11):CD008984. [PMC free article: PMC9326975] [PubMed: 26545294]
  23. Farrell MK, Drake GJ, Rucker D, Finkelstein M, Zier JL. Creation of a registered nurse-administered nitrous oxide sedation program for radiology and beyond. *Pediatr Nurs*. 2008 Jan-Feb;34(1):29-35; quiz 35-6. [PubMed: 18361084]
  24. Zier JL, Drake GJ, McCormick PC, Clinch KM, Cornfield DN. Case-series of nurse-administered nitrous oxide for urinary catheterization in children. *Anesth Analg*. 2007 Apr;104(4):876-9. [PubMed: 17377099]
  25. Hudspeth JC, Schwartz M, Fleming P, Ostrander T, Eyllon M. Essential Principles of Preoperative Assessment in Internal Medicine: A Case-Based Teaching Session. *MedEdPORTAL*. 2021;17:11178. [PMC free article: PMC8339074] [PubMed: 34423125]
  26. Hansen J, Schaal N, Juarez T, Woodlee C. Nitrous Oxide Exposure Among Dental Personnel and Comparison of Active and Passive Sampling Techniques. *Ann Work Expo Health*. 2019 Mar 29;63(3):337-348. [PubMed: 30855661]

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