

RESEARCH MONOGRAPH . COMPOUND PROFILE

Nitrous Oxide

The oldest anesthetic gas in continuous clinical use, an NMDA antagonist with low potency that supplements other agents and provides dental and obstetric analgesia.

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ABSTRACT

Nitrous oxide (N₂O; dinitrogen monoxide; CAS 10024-97-2; molecular weight 44.01) is the oldest inhalational anesthetic agent in continuous clinical use, introduced by Horace Wells in 1844 for dental analgesia and by William Morton in operative anesthesia (in combination with ether) in the 1840s. The minimum alveolar concentration (MAC) is 104 percent at one atmosphere, indicating that nitrous oxide cannot produce surgical anesthesia at atmospheric pressure when administered alone (because hypoxia precedes anesthetic depth at concentrations approaching 100 percent inspired) and is used clinically as a co-administered agent with halogenated volatiles or intravenous induction agents to achieve MAC additivity at safe inspired oxygen fractions. Mechanism differs from the halogenated ethers: the principal target is NMDA glutamate receptor antagonism (similar to ketamine and xenon), with secondary effects on opioid receptor function (modest mu-receptor agonism contributing to analgesia), GABA-A modulation, and two-pore domain potassium channel activation. Pharmacokinetics: the blood-gas partition coefficient is 0.47 (rapid uptake and elimination); recovery is fast. The principal clinical risks are pneumothorax expansion (nitrous diffuses into closed gas spaces faster than nitrogen escapes), middle ear pressure increase, hyperhomocysteinemia from oxidation of cobalamin (B12) cofactor in methionine synthase (clinically apparent with prolonged or repeated exposure), and postoperative nausea and vomiting at higher rates than with halogenated agents alone. Recreational and substance-use disorder concerns have grown with availability of food-grade nitrous oxide cartridges; chronic non-medical use produces subacute combined

degeneration of the spinal cord through methionine synthase inhibition. Dental and obstetric analgesic use (Entonox, 50:50 N₂O/O₂ premix) remains widespread.

1. Compound Identification

Nitrous Oxide is described as inorganic gaseous anesthetic and analgesic. The oldest anesthetic gas in continuous clinical use, an NMDA antagonist with low potency that supplements other agents and provides dental and obstetric analgesia.

1.1 Class summary

Inorganic gaseous anesthetic and analgesic

1.2 Subtitle

The oldest anesthetic gas in continuous clinical use, an NMDA antagonist with low potency that supplements other agents and provides dental and obstetric analgesia.

2. Abstract

Nitrous oxide (N₂O; dinitrogen monoxide; CAS 10024-97-2; molecular weight 44.01) is the oldest inhalational anesthetic agent in continuous clinical use, introduced by Horace Wells in 1844 for dental analgesia and by William Morton in operative anesthesia (in combination with ether) in the 1840s. The minimum alveolar concentration (MAC) is 104 percent at one atmosphere, indicating that nitrous oxide cannot produce surgical anesthesia at atmospheric pressure when administered alone (because hypoxia precedes anesthetic depth at concentrations approaching 100 percent inspired) and is used clinically as a co-administered agent with halogenated volatiles or intravenous induction agents to achieve MAC additivity at safe inspired oxygen fractions. Mechanism differs from the halogenated ethers: the principal target is NMDA glutamate receptor antagonism (similar to ketamine and xenon), with secondary effects on opioid receptor function (modest mu-receptor agonism contributing to analgesia), GABA-A modulation, and two-pore domain potassium channel activation. Pharmacokinetics: the blood-gas partition coefficient is 0.47 (rapid uptake and elimination); recovery is fast. The principal clinical risks are pneumothorax expansion (nitrous diffuses into closed gas spaces faster than nitrogen escapes), middle ear pressure increase, hyperhomocysteinemia from oxidation of cobalamin (B12) cofactor in methionine synthase (clinically apparent with prolonged or repeated exposure), and postoperative nausea and vomiting at higher rates than with halogenated agents alone. Recreational and substance-use disorder concerns have grown with availability of food-grade nitrous oxide cartridges; chronic non-medical use produces subacute combined degeneration of the spinal cord through methionine synthase inhibition. Dental and obstetric analgesic use (Entonox, 50:50 N₂O/O₂ premix) remains widespread.

3. Mechanism of Action

Principally NMDA antagonism. Secondary mu-opioid agonism (analgesia), GABA-A modulation, K2P channel activation. Methionine synthase inhibition through cobalamin oxidation drives chronic-use neurotoxicity.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

MAC 104 percent (sub-anesthetic alone); clinically used at 50 to 70 percent inspired with oxygen and a co-administered agent.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Jevtovic-Todorovic V, et al. Nitrous oxide is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 1998.
2. Sanders RD, et al. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology 2008.
3. Myles PS, et al. The safety of addition of nitrous oxide to general anaesthesia (ENIGMA-II). Lancet 2014.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.