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editorial-office@sciformat.ca

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NITROUS OXIDE IN MEDICINE - ENHANCING PATIENT COMFORT AND HEALTH: A NARRATIVE REVIEW

Natalia Borek *(Corresponding Author, Email: nataliaborek50@gmail.com)*
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0005-7653-7386

Emilia Miśkiewicz
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0003-7756-1981

Julia Gałązka
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0007-8675-6181

Ewa Stopa
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0002-8337-6064

Hanna Krupa
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0004-4366-8999

Magdalena Kędrak
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0008-8954-8633

Zofia Wieczorek
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0001-9850-8464

Dominik Stanisławski
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0009-8583-9895

Wiktoria Jabłońska-Trzosek
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0004-1466-928X

Jakub Pochwalski
Independent Researcher, Warsaw, Poland
ORCID ID: 0009-0007-6387-5997

ABSTRACT

Introduction: Nitrous oxide (N2O) is a colorless inhalational agent widely used in medicine due to its analgesic, anxiolytic, and sedative properties. Owing to its effectiveness and safety, it has become an important tool for improving patient comfort during various medical and dental procedures.
Aim: The aim of this narrative review was to summarize current evidence regarding the pharmacological properties, clinical applications and safety profile of nitrous oxide.
Material and methods: A narrative review of the literature was conducted using peer-reviewed publications indexed in major medical databases, including PubMed, Scopus, and Google Scholar. Articles published in English from 2016 to 2025 were analyzed. The reviewed studies included original research, systematic reviews, meta-analyses, and clinical reports related to the use of nitrous oxide in medicine.
Results: Nitrous oxide is widely used in dentistry, pediatrics, obstetrics, emergency medicine, and during minor surgical procedures. It effectively reduces anxiety and increases patient tolerance of procedures. The most common adverse effects include nausea, vomiting, and dizziness. Prolonged or repeated exposure may lead to significantly more serious. However, when administered under appropriate supervision, nitrous oxide remains a highly safe agent with a low risk of severe adverse effects.
Conclusions: Nitrous oxide remains a safe, effective, and versatile medical agent, provided that patients are properly qualified for the procedure and that it is correctly administered under supervision by trained personnel. Its broad clinical applications, positive impact on patient comfort, and low risk of serious adverse effects when used appropriately support its continued use across many medical specialties. In the future, there is potential for a significant expansion of the indications for its use. However, further research is necessary to achieve this.

KEYWORDS

Nitrous Oxide, Laughing Gas, Conscious Sedation, Analgesia in Pediatrics, Analgesia in Dentistry, Labor Analgesia

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1. Introduction

Nitrous oxide is a colorless gas with the chemical formula N2O, widely used in medicine due to its analgesic and sedative properties. It is commonly referred to as “laughing gas” because it induces a state of euphoria in patients. It is the weakest inhalational anesthetic, exerting only minimal effects on respiration and hemodynamics. [14] Currently, studies are also being conducted on the antidepressant effects of nitrous oxide. The results obtained so far are promising; however, they require confirmation in larger, randomized clinical trials. [1]

Nitrous oxide is characterized by rapid absorption, which results in a quick onset of action. After the end of exposure, however, its effects subside rapidly. [1] These pharmacokinetic characteristics make nitrous oxide particularly valuable in ambulatory medicine and in procedures requiring rapid recovery and early discharge. In comparison with deeper forms of sedation or general anesthesia, the short duration of action allows patients to regain full psychomotor function relatively quickly, which may improve workflow efficiency in healthcare facilities.

For many years, this gas has been used in dentistry, obstetrics, emergency medicine, and in short-term surgical procedures. Its popularity has also been influenced by the relatively simple method of administration and the possibility of titrating the concentration according to the patient’s needs and clinical response. It is considered highly safe, provided that it is administered in appropriate doses and under the supervision of trained medical personnel. The growing emphasis on minimally invasive medicine and improvement of patient experience has further increased interest in nitrous oxide. In many clinical situations, reduction of fear and

procedural stress is nearly as important as the technical success of the medical intervention itself. Therefore, agents that combine anxiolysis, analgesia, and high safety have become particularly valuable in everyday medical practice.

However, like any pharmacological agent, nitrous oxide also has side effects, which are discussed later in this review. There are concerns about the potential adverse neurological, hematological, and immunological effects of this agent. Nevertheless, studies show that if nitrous oxide is used under proper supervision and the patient is appropriately qualified for a procedure performed under sedation, the risks associated with its use are low. [2]

There are also concerns about the impact of nitrous oxide on the natural environment. This compound is one of the main greenhouse gases - alongside carbon dioxide and methane - contributing to the greenhouse effect. However, nitrous oxide used in medicine constitutes only a very small fraction of the total emissions of this gas into the atmosphere. [1, 2]

The aim of this narrative review is to summarize current knowledge on the use of nitrous oxide in medicine and its safety, with particular emphasis on its role in enhancing patient comfort and clinical outcomes.

2. Materials and methods

This narrative review was conducted to summarize the current evidence regarding the medical use of nitrous oxide, with particular emphasis on its clinical applications, role in improving patient comfort and safety profile. A literature search was performed using peer-reviewed publications available in major medical databases, including PubMed, Scopus, and Google Scholar. The search included articles published in English from 2016 to 2025. Search terms included: “nitrous oxide”, “laughing gas”, “conscious sedation”, “analgesia in pediatrics”, “analgesia in dentistry”, “labor analgesia”. Original studies, systematic reviews, meta-analyses, clinical guidelines, and relevant narrative reviews were considered eligible. Articles focusing on recreational misuse without relevance to medical practice, duplicate publications, and studies lacking sufficient methodological quality were excluded. The selected literature was analyzed descriptively, and the findings were organized into thematic categories including pharmacological mechanisms, clinical applications, adverse effects and safety. Special attention was given to publications discussing patient comfort, reduction of procedural anxiety, and comparisons between nitrous oxide and alternative sedation methods. Preference was given to recent studies with clear methodology and clinically relevant outcomes.

3. Results

Pharmacological properties of nitrous oxide

At room temperature and pressure, nitrous oxide is a colorless and odorless gas. The exact mechanism of action of this compound is not fully understood. It is believed to interact with NMDA, alpha-2, dopaminergic, and gamma-aminobutyric acid (GABA) receptors. [2] The antidepressant effect of nitrous oxide is associated with its antagonistic action on the N-methyl-D-aspartate (NMDA) receptor. [3] In turn, its anxiolytic effect is likely mainly due to agonism at the benzodiazepine binding site on the $GABA_A$ receptor. [4] Nitrous oxide also acts on opioid receptors. [1] The nitrous oxide molecule is highly soluble in lipids, which allows it to readily cross the blood–brain barrier. There, it binds to mu, delta, and kappa opiate receptors. [13] It does not cause skeletal muscle relaxation. [2] This gas is rapidly absorbed from the alveoli into the bloodstream and exhibits low solubility in blood. It quickly diffuses from the blood into the central nervous system. [1, 4] These properties result in a very rapid onset of action, occurring within approximately one minute. [5] The possibility of gradual titration allows clinicians to adjust the depth of sedation according to individual patient needs and age. This improves predictability of response and contributes to the favorable safety profile of nitrous oxide compared with other sedative techniques. It is eliminated via the lungs in unchanged form immediately after discontinuation of administration. [2, 4] As a result, recovery after sedation with nitrous oxide is usually rapid and predictable. This is particularly important in outpatient settings, as it helps shorten the patient observation period, allowing the patient to return home earlier. N2O causes irreversible oxidation of cobalamin (vitamin B12). Since cobalamin is a cofactor for two important enzymes involved in metabolic pathways - methylmalonyl-CoA mutase and methionine synthase - this property underlies one of the main adverse effects associated with nitrous oxide use, which will be discussed in more detail later in this review. [1]

Clinical applications of nitrous oxide

The use of a mixture of nitrous oxide and oxygen for labor pain relief was first introduced in 1881 by the Russian physician Stanislav Klikovich. [6] Since then, there has been significant progress in knowledge regarding the use of nitrous oxide during childbirth.

Currently, obstetric wards use ready-made mixtures of nitrous oxide and oxygen in a 50% O2 and 50% N2O ratio, which is considered safe for both the mother and the newborn. [4, 6] Nitrous oxide is easy to administer. A woman in labor can independently put on and remove the mask, allowing her to control the level of pain relief during childbirth.

N2O is a less invasive anesthetic method than epidural anesthesia and opioid medications. It does not cause the side effects in the newborn that are observed with opioid administration. [5] This compound does not negatively affect the course of labor or interfere with uterine contractions.

One of the main disadvantages of using nitrous oxide during labor is its lower effectiveness compared to other pain management methods. To maintain its effectiveness, the woman in labor must remain under continuous sedation. Nitrous oxide is approved for use in all stages of labor, as well as during postpartum procedures. It can also be used in combination with epidural anesthesia.

Nitrous oxide is widely used in pediatrics. Study results show that sedation with nitrous oxide makes it possible to perform a greater number of procedures in children without the need for general anesthesia. [7] This gas can be used in children without the involvement of anesthesiology staff. The administration of nitrous oxide to patients by non-anesthesiologist medical personnel is common worldwide. It may be administered not only by physicians and nurses, but also by other appropriately trained healthcare professionals under a physician's order. [9] Nitrous oxide can be safely used even in children during the first months of life. [7] Owing to its anxiolytic effects, it not only facilitates medical procedures in anxious children, but may also help reduce long-term negative psychological consequences. Although N2O also has analgesic properties, these are often insufficient. During painful procedures, the effects of nitrous oxide should be supplemented with local anesthesia. [7, 8] Nitrous oxide has also been successfully used during diagnostic procedures in children, such as venipuncture, imaging examinations, wound management, or lumbar puncture. In such settings, reducing fear and movement may significantly improve procedural success and decrease emotional distress for both children and caregivers. N2O also has the ability to increase the patient's pain threshold. In this way, it enhances the effect of the administered local anesthesia. [11] Nitrous oxide is widely used not only in pediatric hospital wards, but also in pediatric dentistry. Nitrous oxide is often used in dentistry to achieve conscious sedation in the patient. This is classified as a method of minimal sedation. N2O is the most commonly used inhalation anesthetic agent in dentistry. [21] During this type of sedation, a reduction in the patient's physiological and psychological responses to the procedure is obtained. However, there is no loss of consciousness or protective reflexes. Cooperation with the patient can be maintained. [16] Fear of dental treatment is a global problem. Although it also affects adults, it is often much more pronounced in children. In adult dental patients, nitrous oxide may be especially beneficial in individuals with severe dental anxiety, exaggerated gag reflex, or fear related to previous traumatic dental experiences. Its use may therefore improve adherence to dental treatment and encourage regular preventive care. Sedation with nitrous oxide facilitates dental procedures in children and reduces the patient's level of anxiety. [10] In addition to anxiety reduction, conscious sedation may improve operator conditions by limiting sudden movements and enhancing patient cooperation. This may increase procedural precision and shorten treatment time, particularly during more complex dental interventions. In anxious children, the importance of pharmacological methods such as sedation with nitrous oxide increases particularly when behavioral techniques fail. Due to its rapid elimination and the possibility of titration, the risk of nitrous oxide overdose in children is low, making it a relatively safe and effective anxiolytic method. [10] The use of nitrous oxide will not be effective in completely uncooperative children. Although the use of nitrous oxide is permitted in anesthesiology for the youngest children, in the case of outpatient dental procedures it is recommended for children aged 4 years and older. [21] Nitrous oxide is also increasingly used during minor dermatological, surgical, and emergency procedures such as wound suturing, abscess drainage, burn dressing changes, or fracture reduction. In these situations, rapid anxiolysis and analgesia may improve procedural tolerance while avoiding deeper sedation techniques.

There are preclinical studies showing that, through its antagonistic action on the NMDA receptor, nitrous oxide may have therapeutic and neuroprotective potential in patients after stroke. [15] Although these findings are preliminary, they indicate that nitrous oxide may have future applications beyond procedural sedation.

Safety and side effects of nitrous oxide

The most commonly reported adverse effects associated with the use of nitrous oxide include excessive drowsiness, nausea, vomiting, and transient headaches and dizziness. [3, 5] These symptoms are usually mild and resolve shortly after discontinuation of inhalation. Slow titration of gas concentration may further reduce their incidence. Serious adverse effects related to nitrous oxide use occur rarely. They are usually observed in patients who additionally received benzodiazepines or opioids, as well as in cases where the duration of sedation exceeded 30 minutes. [9] Most complications reported in clinical practice are reversible and related either to inadequate patient selection or improper technique of administration.

N_2O causes irreversible oxidation of cobalamin, therefore, its chronic and intensive use may lead to significant cobalamin deficiency. [1] Oxidized vitamin B12 cannot function as a cofactor for methionine synthase and methylmalonyl-coenzyme A mutase. [12] Vitamin B12 deficiency leads to neurological disorders and may cause paresthesia, myelopathy, and subacute combined degeneration of the spinal cord. [12] Other possible complications associated with vitamin B12 deficiency, including agranulocytosis, bone marrow suppression, and psychosis, have also been reported in individuals using nitrous oxide. [12] In patients suffering from nitrous oxide-induced myeloneuropathy, elevated serum levels of homocysteine and methylmalonic acid are observed. Treatment includes high doses of vitamin B12, folic acid, and methionine. [13] There are suggestions that the neurotoxicity of nitrous oxide may also be caused by mechanisms independent of vitamin B12, such as NMDA receptor antagonism and interference with the cytokine system. This may explain why, despite supplementation with high doses of vitamin B12 in patients with myeloneuropathy, not all neurological symptoms resolve. [13] Another potential side effect of nitrous oxide use is respiratory depression. However, when used alone, nitrous oxide has a limited effect on the respiratory system. [14]

Nitrous oxide may also lead to diffusion hypoxia. This occurs because, after the end of sedation, the concentration gradient between the gases in the lungs and the alveolar circulation reverses. As a result, oxygen in the alveoli becomes diluted, which may lead to hypoxia in the patient. To prevent this, the patient should receive 100% oxygen after the completion of nitrous oxide sedation. [14]

Nitrous oxide may also lead to inhibition of leukocyte production, reduced leukocyte motility, and impaired chemotaxis, which can affect cellular immunity. [18] Therefore, chronic exposure to nitrous oxide may result in adverse immunological effects.

Nitrous oxide exerts minimal effects on the cardiovascular system. It causes a slight decrease in cardiac blood flow, with a small increase in peripheral vascular resistance. As a result, blood pressure remains unchanged. [16] The reduction of protective reflexes caused by nitrous oxide, such as coughing or swallowing, is minimal, which also does not increase the risk to the patient during the procedure. [16]

A very rare adverse effect reported in the literature following nitrous oxide use is epistaxis. [19]

When used properly, nitrous oxide is characterized by a wide safety margin and a low incidence of side effects. Continuous monitoring of patient consciousness and respiratory status is recommended during administration. Even though severe complications are rare, adherence to standardized protocols and staff training is essential for maintaining the high safety profile of nitrous oxide sedation. The feeling of euphoria that appears immediately after inhalation has contributed to an increase in the recreational use of nitrous oxide in society. [17] Uncontrolled use of nitrous oxide may lead to adverse effects that can be dangerous for the patient. However, the use of this gas in medical facilities under the supervision of trained personnel is highly safe. Studies have shown that the use of nitrous oxide as an adjunct to general anesthesia does not increase postoperative mortality and does not significantly worsen patients' health status. It may, however, increase the incidence of postoperative nausea and vomiting. On the other hand, it reduces the need for opioid medications during surgical procedures. [20]

To ensure maximum patient safety, proper qualification for nitrous oxide sedation is essential. Contraindications to the use of this agent include, among others: complete lack of patient cooperation, children who breathe through the mouth, chronic obstructive pulmonary disease, respiratory tract infections, middle ear infections, the first trimester of pregnancy and vitamin B12 deficiency. [21] Careful pre-procedural assessment should also include evaluation of airway patency, current medications, neurological history, and previous reactions to sedation. Such screening improves safety and helps identify patients who should benefit from alternative approaches.

Exposure of medical personnel

There are also concerns regarding the impact of chronic exposure on personnel working in clinics and hospitals where nitrous oxide is used. Long-term exposure among medical staff is associated with more pronounced adverse health effects, which are related to the duration and intensity of exposure to nitrous oxide. [18] Healthcare workers may experience neurological symptoms that gradually worsen over time but subside after cessation of exposure to N2O. [18] The main symptoms reported in individuals working with this compound include headaches, dizziness, nausea, vomiting, euphoria, and tachycardia. These symptoms occur significantly more often in people working with nitrous oxide compared with groups not exposed to this compound. [18] However, studies show that when a properly fitted mask is used, leakage of nitrous oxide into the environment is limited. No increase in the miscarriage rate or infertility risk has been found among medical personnel working with nitrous oxide. Likewise, no increased incidence of congenital abnormalities has been demonstrated in the children of healthcare workers exposed to this gas. [7] To ensure safe levels of nitrous oxide exposure for healthcare workers, it is necessary to implement appropriate measures, including reducing working time with the gas and rotating staff, as well as providing adequate ventilation and gas scavenging systems. [18] Regular technical inspection of equipment, monitoring of ambient gas concentrations and staff education may further reduce occupational exposure. These preventive measures are now considered standard elements of safe workplace organization in facilities using inhalational sedation.

4. Discussion

Nitrous oxide remains an important agent in modern medicine due to its combination of analgesic effects, good anxiolytic properties, and favorable safety profile. Unlike many other pharmacological agents with similar properties, nitrous oxide is characterized by a minimally invasive route of administration, rapid onset of action, and effects that wear off almost immediately after discontinuation of sedation. This makes the compound particularly useful for short procedures and those performed in outpatient settings. From a healthcare systems perspective, the use of nitrous oxide may contribute to reducing anesthesiology support in selected low-risk procedures, which may help hospitals improve accessibility and decrease waiting times for general anesthesia. An additional advantage is that administration of nitrous oxide does not require the presence of an anesthesiology team.

One of the most common indications for the use of nitrous oxide is procedural sedation in dentistry and pediatrics. In children, nitrous oxide reduces anxiety and improves cooperation. In many cases, this makes it possible to avoid general anesthesia, which would not be feasible without sedation using nitrous oxide. This is clinically significant, as avoiding general anesthesia lowers costs, shortens recovery time, and reduces anesthesia-related risks. Similar benefits are observed in dental practice, where conscious sedation enables effective treatment of anxious patients while preserving protective reflexes, as well as the ability to cooperate and communicate with the patient. This may have long-term benefits extending beyond a single procedure.

In obstetrics, nitrous oxide offers a patient-controlled and less invasive alternative to epidural anesthesia or opioid-based pain relief. Although its analgesic effectiveness is lower than that of epidural anesthesia, many women value its anxiolytic and calming effects, rapid reversibility, and the ability to independently apply and remove the mask. For this reason, nitrous oxide may be considered an important component of labor pain management strategies. Its role may be especially relevant in settings where epidural analgesia is unavailable, contraindicated, or declined by the patient.

Recent studies have also increased interest in psychiatric applications. The antidepressant potential of nitrous oxide, probably related to its antagonistic action on NMDA receptors, represents an innovative therapeutic direction. Preliminary results are promising, but current evidence is limited, and larger randomized controlled trials are necessary before routine implementation.

Despite its generally favorable safety profile, nitrous oxide is not without risk. The most serious concerns involve disruption of vitamin B12 metabolism, which may lead to neurological and hematological complications after prolonged or repeated exposure. For this reason, patient selection remains crucial, particularly in individuals with diagnosed vitamin B12 deficiency, malnutrition, or a history of chronic exposure.

Another important aspect is occupational exposure among medical personnel. Although modern scavenging systems and appropriate ventilation significantly reduce environmental contamination, chronic exposure without proper safety measures may still pose a health risk. This highlights the importance of institutional protocols and workplace monitoring. Environmental considerations should also be acknowledged. Although medical use accounts for only a small proportion of global nitrous oxide emissions, implementation

of efficient scavenging systems and responsible use policies may further minimize unnecessary release into the atmosphere.

This review has several limitations. As a narrative review, it does not follow the strict methodology of a systematic review and may be subject to selection bias. Furthermore, the available literature varies in quality and includes heterogeneous study populations and clinical settings.

Nevertheless, the collected evidence suggests that nitrous oxide, when properly administered by trained personnel under physician supervision and following appropriate patient qualification, remains a valuable and versatile medical agent that can significantly improve patient comfort while maintaining a high margin of safety.

5. Conclusions

Nitrous oxide continues to play an important role in modern medicine as a safe, effective, and versatile agent for anesthesia and conscious sedation. Its rapid onset of action, short post-procedure recovery time, ease of administration, and effective anxiolytic properties make it particularly useful in dentistry, pediatrics, obstetrics, and minor medical procedures. Additionally, it can be effectively used not only in adult patients but also in children - following appropriate qualification and under supervision - from the first months of life. It is especially valuable in the youngest patients, not only because of its high effectiveness, but also due to its favorable safety profile compared with other pharmacological agents used for similar purposes. Emerging evidence regarding psychiatric and neuroprotective applications may further increase the clinical importance of nitrous oxide in the future. Its ability to reduce fear and improve cooperation makes nitrous oxide especially valuable in patient-centered care models focused on comfort and minimally invasive management.

Like any pharmacological agent, nitrous oxide may also cause adverse effects, especially in cases of prolonged exposure or improper use. However, most adverse effects associated with nitrous oxide are not harmful to patients' health or life-threatening. Furthermore, proper patient qualification for sedation procedures, appropriate dosing of nitrous oxide, and supervision by trained medical personnel make it a truly safe agent for use in analgesia.

Overall, nitrous oxide remains a valuable tool for improving patient comfort and supporting positive clinical outcomes across many medical specialties. Considering both clinical effectiveness, safety and patient satisfaction, nitrous oxide remains one of the most practical pharmacological options for short procedural sedation in contemporary medicine.

Author's Contribution:
Conceptualization: N.B.
Methodology: E.M. and J.G.
Validation: Z.W., E.S. and D.S
Formal analysis: H.K. and E.S.
Investigation: M.K. and N.B.
Data curation: E.S and J.G.
Writing-original draft preparation: N.B. and W.J
Writing-review and editing: H.K., M.K. and J.P.
Supervision: E.M. and Z.W.
Project administration: N.B.

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