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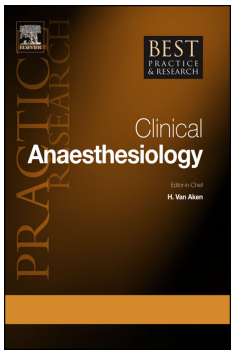

Update on Nitrous Oxide and Its Use in Anesthesia Practice

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Update on Nitrous Oxide and Its Use in Anesthesia Practice

Abstract.

Nitrous oxide is an anesthetic and analgesic gas with long history of medical applications. It acts on multiple supraspinal and spinal targets, and has utility in a wide range of clinical situations. The relative safety, low incidence and acuity of adverse effects of nitrous oxide, along with the ability to be administered by trained medical providers with varying clinical backgrounds, as well as self-administered by patients, assure its persistent and expanding role in clinical practice.

Key words: nitrous oxide; general anesthesia; labor analgesia; adverse effects

Introduction.

Nitrous oxide (N_2O) was first used in anesthesia in 1772 by the English chemist Joseph Priestly, under the term phlogisticated nitrous air [1], and has asserted itself as a mainstay of the anesthetic world, due to its rapid uptake and elimination, as well as its analgesic effects.

Pharmacology of nitric oxide.

Nitrous oxide is the least potent of currently available inhalation agents, requiring a concentration of 104% to achieve 1 MAC. However, its analgesic and anesthetic properties render it an effective adjuvants to a balanced anesthetic technique. Multiple targets have been identified and investigated to contribute to the clinical effects of nitrous oxide, including non-competitive inhibition of N-Methyl-D-Aspartate (NMDA) and non-NMDA glutamate receptors, nicotinic acetylcholine (nACh) receptors, gamma-aminobutyric acid receptors (GABA), as well

as activity on low voltage-activated (T-type) calcium channels and two pore domain potassium channels (TREK-1). [2,3] The analgesic effects of N_2O involve supraspinal NMDA receptor antagonism, that mediates release of corticotrophin-releasing factor from the hypothalamus, stimulating opioidergic and noradrenergic supraspinal receptors, which in turn inhibit GABAergic supraspinal interneurons, leading to disinhibition of spinal adrenergic and GABAergic neurons, thus effecting the antinociceptive action of N_2O.[4, 5]. Along with providing anesthesia and analgesia, the N_2O gas properties assist in the induction of anesthesia through both an additive effect on the total MAC and the second gas effect. The rapid uptake of N_2O due to low solubility in blood (blood:gas ratio of 0.412) and tissue (blood:brain 0.437) along with an inability to bind to hemoglobin leads to a concentrating effect of additional agents in the lung, causing a more rapid rise in the FA/FI ratio of other halogenated agents (ie: the second gas effect)[4,6,7] This effect is often underestimated due to inability to monitor arterial partial pressure of volatile agents which more closely reflects the partial pressure in central nervous tissue than alveolar pressures[2]. In portions of the lung that have a somewhat low V/Q ratio the impact of the second gas effect is more prominent[2].

Pharmacological effects of N_2O rise concerns regarding potential adverse clinical consequences. The oxidation of cobalt $^{+}$ to cobalt $^{3+}$ cation by N_2O attenuates the function of cobalamin as a coenzyme of the methionine synthase, thus reducing the enzyme activity, and impacting multiple biochemical processes, including DNA and RNA synthesis and homocysteine metabolism, with potential for clinically significant outcomes. [8,9,10]

Adverse effects of N_2O.

Cardiovascular impact.

There has been debate regarding the proposed increased risk of perioperative vascular risk including stroke and myocardial infarction when using N_2O. It interferes with vitamin B12 and folate metabolism. It inhibits methionine synthase, preventing the conversion of homocysteine to methionine and resulting in increase of homocysteine levels. Hyperhomocyestinemia can cause endothelial dysfunction and hypercoagulability. The Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia (ENIGMA-I) trial randomized 2,050 patients who underwent non cardiac surgery with N_2O based or N_2O free anesthesia.[11] The study showed increased occurrence of myocardial infarction, venous thromboembolism, stroke and death within 2 days of surgery. However the ENGIMA-II trial [12,13] which randomized 7112 patients with known or suspected coronary artery disease having major non-cardiac surgery to have a general anesthetic with our without N_2O did not show an increase risk of death and cardiovascular complications. Other support for the safety of N_2O include the General Anesthesia Compared with Local Anesthesia for Carotid Surgery trial (GALA) and the Perioperative Ischemic Evaluation (POISE) trial which did not show increased risk of myocardial infarction or stroke post op in patients who received an anesthetic with N_2O.[14] N_2O has been also shown to increase pulmonary artery pressure and should be avoided in pulmonary hypertension.

Pulmonary effects.

N_2O has a low blood: gas partition coefficient and it displaces nitrogen and oxygen from hollow compartments in the body including the lungs. Elimination of N_2O leads to diffusion hypoxia during emergence from anesthesia. Lampe et al performed a large randomized controlled trial to study postoperative hypoxia and its relationship to N_2O.[15] They observed that patients in the N_2O group had lower intraoperative O_2 saturation but this did not affect their postoperative O_2

saturation, incidence of postoperative hypoxia, cough or sputum production.[15] ENIGMA-I showed an increase in pneumonia, pneumothorax, and pulmonary embolism[11] but there was not a statistically significant increase in respiratory events in patients' receiving N_2O in the ENIGMA-II trial.[13]

Surgical Wound Infections.

Several studies have demonstrated effects of N_2O on the immune cell structure and function, in part through DNA alterations, rising concern for increase in wound infections and impaired wound healing.[16,17] The ENIGMA-I trial demonstrated an increased risk of wound infections in the N_2O based group[11], however the follow up study ENIGMA-II, as well as other trials, have not demonstrated an increased risk of surgical site infections or sepsis [13, 17,18]

Neuropsychological effects.

N_2O does not appear to have a strong association with long-term adverse neurologic outcomes even in patients having neurosurgical procedures who are at risk for developing neurologic complications post operatively. [14] Neurological side effects are a result of vitamin B12 deficiency and include myelinopathies, neurotoxicity/hypoxic-ischemic injury, neurodevelopment disturbances, postoperative cognitive dysfunction and alterations in intracranial dynamics. Subacute combined degeneration of the cord is a rare myelinopathy. [17] Patients with acquired vitamin B12 or folate deficiency are at increased risk, including those with nutritional deficits, gastrointestinal diseases, infections and surgical resections, as well as those with genetic metabolic abnormalities. Patients who have abused N_2O have described neurological complaints

such as peripheral neuropathy, myeloneuropathy, polyneuropathy and myelopathy. Numbness, paresthesia and weakness are the most common complains.[19,20] In head injured neurosurgical patient, nitrous oxide may convert a pneumocephalus into a tension pneumocephalus. There is also a risk that nitrous oxide might expand a venous air embolism.[21]

Mutagenicity and teratotoxicity.

N_2O can affect DNA production via its inhibition of the production of the essential amino acid methionine. Studies on occupational exposure have identified evidence of genomic alterations and instability, as well as cytotoxicity and proliferative changes.[22-26] The clinical significance of these changes in regards to risk for development of clinical disease remain in debate, particularly, as investigations have indicated that such risk is ameliorated by appropriate occupational exposure control.

Many animal studies have demonstrated teratogenic effects of N_2O [27,28]. However, the heterogeneity of the data, including the much higher exposure dose in animal studies, do not render these conclusions applicable to human subjects. There is little evidence to show any teratogenic complications in pregnant patients. [29]

Earlier studies have shown increased risk of spontaneous abortions in female dental professionals with N_2O exposure[30]; however, other studies that could not find a link between exposure to N_2O and miscarriage or congenital malformations and the increased risk appears to have been relevant in the pre-scavenging era. [31,32] An American Society of Anesthesiologists Task Force concluded

that there is no data suggesting that waste anesthetic gases are a danger to those women who are contemplating pregnancy or who are already pregnant.

Hematologic effects.

N_2O can cause bone marrow suppression, cobalamin deficiency and folate deficiency resulting in megaloblastic anemia. It irreversibly binds, oxidizes, inactivates and eventually depletes Vitamin B12. But there is little evidence of clinical significance. [14]

Postoperative Nausea and Vomiting.

The most common side effect of N_2O is nausea and vomiting. N_2O tends to cause bowel extension and may act on dopamine and opioid receptors in the brain which is a possible mechanism by which N_2O causes post operative nausea and vomiting. In the Evaluation of Nitrous oxide in the gas mixture for Anesthesia II trial, 7,112 noncardiac patients were randomly assigned to nitrous oxide or nitrous oxide-free anesthetic. The results showed that avoiding nitrous oxide reduced the risk of severe post op nausea and vomiting but that risk was near eliminated by antiemetic prophylaxis [33]. Other studies have also indicated that omitting N_2O has either modest or no significant impact on the incidence of PONV, except in cases of high risk of PONV, and that use of prophylaxis can ameliorate this concern.[34,35,36] A meta-analysis looked at whether duration of exposure increased risk of PONV with nitrous oxide use. Patients that received nitrous oxide for less than an hour did not have an increased risk of postoperative nausea and vomiting. [37]

Gas Filled Spaces.

N_2O will enter gas filled spaces over 30 times faster than nitrogen can exit, thus, producing increased pressure in the compartment to potentially dangerously high. This can result in bowel distension, penumothorax, rupture of tympanic membrane, and serous otitis or eye damage due to expanding gas bubbles.

Clinical use of Nitrous Oxide.

Use in obstetric anesthesia.

The popular use of inhaled anesthetics for labor analgesia can be traced back to Queen Victoria accepting chloroform sedation in 1853 for the birth of her eighth child[38]. The growing concerns regarding chloroform's cardiac side effects lead to increase in the use of N_2O for labor pain in 1881 with a roughly 20% success rate, along with use of 80% nitrous oxide and 20% oxygen mixtures for treatment of hyperemesis gravidarum[39]. The application of nitrous oxide remained a difficult and equipment-intensive task until 1963 with the development of a self-contained canister with 50% nitrous oxide and 50% oxygen pre-mixed, later named Entonox[40]. Since its introduction, as a labor analgesic, nitrous oxide has remained as an alternative to neuraxial analgesia [41,42]. The analgesic and anxiolytic properties of N_2O, along with the ability for self-administration by the patient and the avoidance of an invasive procedure render it an attractive agent in the peripartum period; however, its effectiveness as an analgesic agent remains debated. A review by Klomp and associates comparing nitrous oxide against placebo, different concentrations of nitrous oxide, and a combination of nitrous oxide with a fluorane agent, has demonstrated improved analgesic effect compared to placebo.[43] Additionally, increasing the concentration of nitrous oxide to 70% did not improve the analgesic effect. However, the

analysis was affected by significant heterogeneity in study design, leading to low quality evidence. Side effects identified were increased rates of nausea, vomiting, and dizziness. [43] Likis and colleagues have analyzed 58 studies looking at the effects of nitrous oxide on pain control and satisfaction with the birthing experience. [42] A pattern of better analgesia with an epidural appears common; N_2O in some studies was better or comparable to intravenous pain medications. [44] Some results showed a greater level of satisfaction with the birthing experience when using nitrous oxide.[45] Researchers have raised the idea that perhaps pain control is not the sole appropriate determinant of success for labor analgesic modalities, including N_2O, considering that the analgesic effects are typically dissociative in nature, and some women are willing to accept less analgesic effect in order to avoid more invasive procedures. Furthermore, the results vary depending on the postpartum timing of the study evaluation. [46] This concept was investigated by Richardson and colleagues, who conducted a review of the literature with a focus on overall patient satisfaction with the birthing experience rather than on pain control[47]. While the analgesia effectiveness of nitrous oxide was found to be more variable than neuraxial analgesia, the satisfaction rates of the roughly 60% of patients who used nitrous oxide alone were equivalent to the neuraxial group. The risks of peripartum N_2O use in the general population are relatively low, provided that it is avoided in patient populations at increased risk of significant side effects; those are addressed in the aforementioned section on adverse effects. Systematic reviews have indicated no difference in negative neonatal effects[43] as well as no difference in Apgar scores or negative neonatal effects were reported.[42] A study from 1996 demonstrated that the maternal and fetal central vascular resistance were decreased by N2O, raising concern for potential increase in the risk of fetal cerebral hemorrhage, particularly in preterm infants; however, no evidence in the literature can be found regarding the clinical relevance of this alteration. [48.] Therefore, N_2O remains a viable option for attenuation of labor discomfort and pain for a subset of patients, determined by the balance between the

desired level of pain control and the avoidance of invasive procedures; with the option of conversion to neuraxial analgesia during labor remaining an option. [49] A study has demonstrated a significant but still lower conversion rate to neuraxial analgesia during labor with N_2O compared to no-N_2O group - 63.2% vs. 85.1%; the factors contributing to the conversion were labor induction and labor augmentation. [50]

General anesthesia (GA).

N_2O continues to offer multiple benefits as an adjunct to other anesthetics for GA. The lack of pungent odor and airway irritation makes it a useful agent in inhalation induction, particularly in children. Due to low solubility in blood and tissue, N_2O accelerates induction and recovery from anesthesia; the second gas effect remains relevant, even if less so with the modern low-solubility volatile agents. [51-53] Furthermore, in some studies N_2O has attenuated emergence agitation, although this effect is not consistent in other data. [54,55] The use of N_2O reduces the required amount of other anesthetic agents for adequate anesthesia [56]; thus it aids in hemodynamic stabilization due to reduction of the vasodilatory and cardiodepressant impact of other anesthetics, as well as the inherent increase in SVR and sympathetic activation of N_2O itself. [57-59] Association between addition of N_2O and decrease in intraoperative awareness is indicated by some studies [35], although Cochrane review that analyzed accidental awareness as a secondary outcome did not reach a definite conclusion due to insufficient data [60] and further investigations are needed. The effects of N_2O on EEG and bispectral index (BIS) further compound our understanding of the impact on awareness and neuromonitoring. Under N_2O, EEG and somatosensory evoked potentials (SSEP) responses differ from those due to other anesthetic and sedative agents [61,62], with EEG waves demonstrating evidence of paradoxical arousal. While Hans et al found reduction of BIS during spine surgery under sevoflurane and epidural morphine with addition of N_2O[63], Mishra et al demonstrated that during spine surgery with sevoflurane or

deslfurane at equi-MAC levels, N_2O raised the BIS index for both volatile agents, more pronounced for the sevoflurane[64].

The benefits of the use of N_2O as adjunct to GA must be balanced against the associated risks. An analysis of the studies from the Cochrane group[65], as well as the ENIGMA-II trial[13], have concluded that risks of cardiovascular morbidity, in-hospital mortality and hospital length of stay are not significantly impacted by the use of the gas. Similar findings were demonstrated regarding PONV[33-37]. The concern for PONV should not contraindicate the use of the agent, expect in patients with significantly elevated risk, particularly as it can be ameliorated by preventative measures. Pulmonary complications such as pneumonia and atelectasis remain a potential concern with use of N_2O. In the Cochrane review[65], while a trend for increase in the incidence of pneumonia with N_2O was suggested, the lower quality of evidence rendered lack of statistical significance; however, association with perioperative atelectasis was significant. Therefore, it may be prudent to avoid N_2O in patients at high risk for perioperative pulmonary complications.

Analgesia.

The analgesic properties of N_2O have been demonstrated in several studies, including acute and chronic pain reduction, and amelioration of opioid-induced hyperalgesia[66-69]. A randomized trial of patients with long bone fracture or main joint dislocation in the emergency department, who had moderate to severe pain, found N_2O to be comparable to analgesic dose of fentanyl in relieving pain [70]. Evidence in animal and human studies indicates that the analgesic effect is attenuated by interaction between N_2O and GABAergic agents, such as benzodiazepines and volatile anesthetics[71,72]; however, as subanesthetic doses of agents were used in some studies,

clear understanding of the impact remains to be elucidated. The analgesic benefits may not be realized in multi-agent GA regimen, and may be more clinically relevant in sedation settings with use of N_2O without other agents. Naloxone in a study of healthy volunteers did not appear to attenuate the analgesic effects of N_2O, or its effects on mood or psychomotor performance [73]. Investigations into the role of N_2O in chronic pain point to reduction in chronic postsurgical pain, as well as cancer. A study of patients with chronic pain, who underwent N_2O sedation for one or several dental procedures, demonstrated improvement of the chronic pain after the sedation[74]; however, the duration of the relief was not assessed. The ENIGMA investigators found improvement in chronic surgical pain in the nitrous-based group of patients (7%) vs. the nitrous-free group (14.8%), however, no impact on early postoperative pain (within 3 days) was seen[75]. A double-blind placebo-controlled randomized trial of cancer patients with breakthrough pain demonstrated a significant reduction in the pain score in the group treated with morphine and N_2O/oxygen mixture (2.0±1.1) compared with the morphine/oxygen group (5.6±1.3), $p < 0.01$ [76]. A recent Cochrane review on prevention of chronic postsurgical pain[77], as well as study of the utility of N_2O for therapy of chronic low back pain[78], have failed to demonstrate benefits. The analgesic properties of N_2O are evident in many clinical situations; further investigation into its role for chronic surgical pain is needed.

Sedation and analgesia outside of the operating room.

N_2O is suitable for sedation in variety of procedures outside of the operating room, due to its analgesic and anxiolytic properties, as well as its safety profile, rapid reversal and unique ability to be self-administered by patients. The agent continues to be widely used, particularly in the pediatric population and in adults.

Prehospital use.

An investigation of use of 50:50 N_2O:oxygen in 1243 patients over a period of 18 months for self-administered patient analgesia in prehospital setting demonstrated no major adverse events[79]. The side effects ranged included numbness 0.3%, nausea/vomiting 5.7%, drowsiness 7.6%; no impairment of cough or airway protection was noted. Another randomized double-blind trial[80] compared 50/50 50:50 N_2O:oxygen with medical air for in-ambulance treatment of moderate acute trauma-related pain in 60 adults found that at 15 minutes median pain scores were lower in the N_2O group - 2 (interquartile range, IQR, 1 to 4), versus 5 (IQR 3-6). The only adverse effect was nausea 3% in the N_2O group vs 10% in the control group.

Hospital and clinic utilization.

The use of N_2O has been extensively studied, predominantly in pediatric populations for various procedures and settings. A survey[81] of 1019 patients aged 0–18 found that N_2O/oxygen was used in lumbar punctures, bone marrow aspirations, laceration repairs, minor procedures (surgical dressing, burn dressing, gauze removal of open wounds, venous cannulation, clip removal, cast remodeling, pin removal or section, bladder catheterization, and nasal packing), minor surgery (nail surgery, foreign body exploration and extraction, laceration exploration, and abscess drainage), punctures (lymph nodes, renal biopsy, and hematoma), fractures, dental care, and pulmonary endoscopy. The investigators demonstrated the safety and efficacy of N_2O: no significant adverse events were noted; the side effects (absent in 62.8%) resolved in 5 minutes after discontinuation, and included euphoria (20.1%), visual/auditory perception change (7%), dreams (5.7%), nausea/vomiting (3.7%), deep sedation (2.1%), paresthesia (1.7%), dizziness (1.6%), restlessness (1.5%), and miscellaneous (1.9%). 9% of the administrations were done by non-physicians. A randomized double-blind study[82] investigated 50:50 N_2O:oxygen vs placebo

(50:50 nitrogen:oxygen) in patients aged 1-18 for cutaneous, muscle, or bone/joint procedures: the study group had significantly lower pain scores and required less rescue with propofol and sevoflurane; rare minor side effects were noted. A retrospective analysis of 1634 N_2O administrations outside the operating room by wide range of practitioners (only 1.3% anesthesiologists), including higher N_2O concentrations, revealed absence of side effects in 93.5% and very low incidence of serious adverse events 0.2% (airway obstruction, oxygen desaturation)[83]; similar results were confirmed in other studies[84,85].

An investigation of self-administration of 50:50 N_2O:oxygen in 210 children aged 2.7-16.5, for minor procedures, found that 80.5% of all patients were pain free, and 81.9% were relaxed and calm[86]. The incidence of mild side effects was <2%, and only one case of lack of compliance with administration was noted.

Investigation into the use of N_2O:oxygen in colonoscopy have suggested that it provides similar patient comfort scores, cecal intubation rates and polyp detection rates, compared to intravenous sedation with midazolam and opioid[87]. A Cochrane review was not unable to perform a meaningful meta-analysis of the studies in regards to comparison of to placebo or other sedation for colonoscopy, due to study variability[88]. However they identified several studies, indicating equal effectiveness and faster recovery time for the nitrous oxide groups.

Randomized, double-blinded trial compared N_2O:oxygen inhalation through a self-administration valve with control group of oxygen inhalation for transrectal ultrasound-guided prostate biopsy; both groups received topical anesthesia in the anal canal[89]. The mean pain scores of the study group were 2.52 vs. 5.95 in the control group (two-tailed p value of 0.0001.); the satisfaction indexes in the N_2O:oxygen group were mean of 8.14 vs. 4.69 in the control.

A systematic review of minor dermatologic procedures has suggested that N_2O, alone or as adjunct anesthesia, provides pain reduction[90].

Overall, N_2O is safe and effective sedative analgesic for wide range of procedures, it can be administered by diverse group of trained practitioners, as well as self-administered by adult and pediatric patients. It has low rate of side effects; the significant adverse events are very rare and frequently associated with prolonged exposure, inadequate monitoring or administration of additional sedatives and opiate analgesics.

Nonprocedural use of N_2O.

The NMDA receptor antagonism of N_2O has directed investigations into its potential therapeutic role for treatment-resistant depression[91,92]. Further studies are needed to establish the benefits in psychiatric disorders.

Additional considerations.

Abuse:

Recreational use of N_2O for its euphoric properties is not a recent phenomenon. Laughing gas parties were popular since the Victorian times. The possession of N_2O is not illegal and it is readily available. It is typically inhaled commonly from bulbs or balloons. Bulbs or whippits are commercially available and used in whipped cream charging bottles. The most common method of inhalation is from a balloon followed by a whipped cream dispenser. The effect includes euphoria, heightened consciousness, disassociation and excitement all of which have a

quick onset and offset. Young adult clubbers comprise the largest population to recreationally use N_2O. In some countries (UK, Netherlands and Australia) recreational use of N_2O seems to be an increasing trend[93].Dental professionals have an increased incidence of abusing N_2O. There are occasional reports of people being asphyxiated by improper use, but on a whole it is relatively safe. Heavy usage generally results in neurological and hematologic effects due to N_2O induced Vitamin B12 deficiency[93].

Occupational exposure to Nitrous Oxide.

The occupational exposure to N_2O is a concern, given its adverse effects. [22-25] The recommended exposure limit (REL) from the National Institute of Occupational Safety and Health (NIOSH) is N_2O is 25 ppm as a time-weighted average (TWA) during the period of anesthetic administration, based on prevention of decrease in mental performance, audiovisual ability, and manual dexterity. [94] A REL to prevent adverse reproductive effects has not established. The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for N_2O is 50 ppm as an 8-hour TWA.[95] In Europe, the occupational exposure limit (OEL) or maximum workplace concentration (MAK) is 180 mg/m^3. A study comparing various ventilation models with and without gas scavenging system indicates that natural ventilation with supplementary pressure ventilation with or without gas scavenging unit is inadequate in maintaining the N_2O concentrations bellow the OEL value, as are pressure and exhaust ventilation or air-conditioning systems without gas scavenging ability. [96] The study concludes that maintenance of N_2O below the OEL limit requires an active scavenging system along with efficient ventilation such as air conditioning or pressure/exhaust ventilation. Various organizations publish guidelines on the appropriate ventilation design criteria, addressing

scavenging systems and their effectiveness. The Facility Guidelines Institute publishes guidelines for design and construction of health care facilities stipulates minimum ventilation requirement of 6 air changes per hour (ACH) of total ventilation (outdoor air plus recirculated air) for treatment rooms, 15 ACH for operating/surgical cystoscopic rooms with a minimum of 3 ACH of outdoor air.

Conclusion.

Nitrous oxide is one of the earliest anesthetics in use. It has retained its role as a versatile agent with anesthetic, analgesic and sedative role, due to its efficacy and relative safety. Advances in the understanding of its effects and administration logistics assure its safe use and potential for novel and expanding clinical applications.

Practice points.

- Nitrous oxide is an effective anesthetic that can be used in versatile settings in and out of the operating room to provide sedation, analgesia and adjunct anesthesia for wide range of procedures.
- Nitrous oxide is a viable alternative to more invasive procedures for labor analgesia.
- The agent can be safely administered by trained non-anesthesiologists as well as self-administered by patients with very few side effects with low severity.
- The potential adverse impact with occupational exposure can be mitigated by proper scavenging systems.

Research agenda.

- Further research is needed to more precisely identify the mutagenic effects of nitrous oxide and their implications for the clinical practice.
- Biochemical and pharmacological mechanisms of the actions of nitrous oxide have been identified, however, investigations will to further elucidate discrete processes on molecular level.
- The interactions between nitrous oxide and other anesthetic and analgesic agents should be further defined to clarify their impact on the clinical applications of the agents.
- The effects of the agent on neurophysiologic monitoring and implications for anesthesia and awareness warrant further study

Conflicts of interest.

All the authors declare that they have no conflicts of interest related to this manuscript.

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