Published in final edited form as:

J Clin Psychopharmacol. 2018 April ; 38(2): 144–148. doi:10.1097/JCP.0000000000000837.

Exploring Nitrous Oxide as Treatment for Mood Disorders: Basic Concepts

Peter Nagele, M.D., M.Sc., Charles F. Zorumski, M.D., and Charles Conway, M.D.

Division of Clinical and Translational Research, Department of Anesthesiology (PN), Department of Psychiatry (CFZ, CC), Taylor Family Institute for Innovative Psychiatric Research (PN, CFZ, CC), Washington University in St. Louis

Abstract

Nitrous oxide (laughing gas) has shown early promise as a rapidly acting antidepressant in patients with treatment-resistant major depression and is currently investigated in several clinical trials. Because nitrous oxide is rarely administered outside operating rooms or dental practices, most psychiatrists are not familiar with how nitrous oxide is administered in a medical setting and what regulations guide its use. The goal of this brief review was to educate psychiatrists about the basic concepts of nitrous oxide administration and pharmacology. Furthermore, common misconceptions about nitrous oxide will be discussed.

Psychiatry is currently seeing a renewed effort in developing novel drug treatments for mood disorders,^{1,2} with a strong emphasis directed towards drugs that inhibit NMDA-(N-methyl-D-aspartate)-receptors.^{3,4} Several lines of evidence support the importance of glutamatergic signaling, of which NMDA-receptors are a critical component, in the pathogenesis of mood disorders and their potential treatment.^{5–7} Ketamine, among other targets, inhibits NMDA-receptors, and has shown great promise as a rapid antidepressant, even in patients with treatment-resistant depression.^{8–11} The exciting finding of ketamine's rapid antidepressant efficacy has initiated the search for alternative drugs that act via similar mechanism but may be devoid of some of the serious side effects of ketamine, including memory impairment and psychosis.^{12,13} Nitrous oxide, also an NMDA-receptor antagonist, has shown early promise as a rapidly acting antidepressant in patients with treatment-resistant major depression.^{3, 14}

Corresponding Author: Peter Nagele, MD, MSc, Division of Clinical and Translational Research, Dept. of Anesthesiology, Washington University School of Medicine, 660 S. Euclid Ave, Box 8054, St. Louis, MO 63110, nagelep@wustl.edu; phone: 314-362-5129; fax: 314-362-1185.

Conflicts of Interest:

- Nagele: Dr. Nagele has filed for intellectual property protection related to the use of nitrous oxide in major depression. No other conflicts of interest related to this work. He has received research support from Roche Diagnostics, Abbot, and Express Scripts unrelated to this work.
- Zorumski: Dr. Zorumski serves on the Scientific Advisory Board of Sage Therapeutics. Sage Therapeutics was not involved in this study.
- Conway: Dr. Conway was previously on the speaker's bureau for Bristol-Myers Squibb and Otsuka Pharmaceuticals. He has received research funding from Bristol-Myers Squibb, Cyberonics, the Stanley Baer Foundation and the Brain and Behavior Research Foundation

Role of the funding sources:

The sponsoring departments had no role in the collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript.

However, the precise mechanism of the antidepressant effects of ketamine and nitrous oxide are unclear and may involve other molecular targets and receptor systems. A detailed discussion of these aspects is beyond the scope of this article.

While psychiatrists may have been exposed to nitrous oxide as a patient, e.g. during dental procedures, most psychiatrists are less familiar with how nitrous oxide is administered in a medical setting and what regulations guide its use. This brief review will provide psychiatrists and related health professionals with the basic concepts of nitrous oxide pharmacology and clinical administration. Furthermore, common misconceptions about nitrous oxide will be discussed.

Basic facts about nitrous oxide

Nitrous oxide is a gas. This trivial fact accounts for the unfamiliarity most physicians have with nitrous oxide as a drug. Inhalational administration of gaseous drugs is the near exclusive domain of anesthesiology. Thus, it is important to outline some basic considerations of nitrous oxide pharmacology and administration for psychiatrists.¹⁵

Nitrous oxide is a colorless and nearly odorless gas. It is one of the weakest anesthetic drugs available and cannot achieve surgical anesthesia when given as sole agent. The human EC50 equivalent (called minimal alveolar concentration or MAC) is 105% inspiratory concentration, a concentration that can only be achieved in a hyperbaric environment. Safety concerns limit the inspiratory nitrous oxide concentration to 70% - the balance of 30% must be oxygen to avoid dangerous hypoxia. Nitrous oxide has a very low blood-gas solubility, which means a rapid on- and offset of action, on the order of a few minutes. Patient recovery is very quick and most patients have fully recovered within 10–15 minutes. Nitrous oxide is not metabolized and thus its uptake and elimination are entirely via the lungs, which could potentially make it ideal for patients with comorbid renal/hepatic disease.

On a molecular level, strong evidence exists that the dominant mechanism of action of nitrous oxide as anesthetic agent involves non-competitive NMDA-receptor antagonism.^{16–18} However, nitrous oxide also has inhibitory effects on non-NMDA-glutamate receptors (e.g., AMPA and kainate), low voltage activated (LVA, T-type) calcium channels, and certain nicotinic acetylcholine receptors, and has been shown to activate the 2-pore-domain potassium channel, TREK-1.^{19–23} Nitrous oxide has also potent analgesic effects, which are likely mediated via α -adrenoceptors in brain stem and spinal cord.^{24–28}

Nitrous oxide is N₂O and should not be confused with nitric oxide (NO, formerly known as endothelium-derived relaxing factor), or NO₂ (nitrogen dioxide, an air pollutant without known health benefits but substantial human toxicity). Nitrous oxide is also a potent greenhouse gas, and accounts for approximately 7% of all greenhouse gas emissions, although the vast majority comes from soil bacteria and agriculture with only 1% stemming from healthcare use (i.e. 0.07% of total greenhouse gas emission).

Where and how is nitrous oxide currently used clinically?

Indications for the medical use of nitrous oxide are inhalational general anesthesia, the relief of severe pain (e.g. labor and delivery),²⁹ or for analgesia and sedation during short painful procedures (e.g. in dentistry or emergency medicine).^{30,31} Nitrous oxide is inexpensive and on the WHO-list of essential drugs. It is not a controlled substance and can legally be purchased. Outside of medicine, nitrous oxide is used in racecar engines and space rockets, and as an approved food supplement. Nitrous oxide is the gas used in whipped cream (please see nitrous oxide abuse section for “whippits”) and in certain beers from Ireland known for their smooth foam.

In operating rooms, nitrous oxide for general anesthesia is normally supplied via piped-in wall outlets that link central gas supply to individual anesthesia machines, similar to oxygen. The anesthesia provider then selects a nitrous oxide flow rate (in L/min) that corresponds to an inspiratory concentration between 0 – 75%. A “fail-safe” valve prohibits hypoxic gas mixtures with oxygen concentrations below 25%. Standard anesthesia machines are complicated and expensive, and have features (e.g., ventilation), which are not required for the administration of nitrous oxide. Only licensed anesthesia providers (anesthesiologists, nurse anesthetists) are allowed to use anesthesia machines.

In office-based environments, such as in a dental office, or in remote locations, nitrous oxide is typically not available via wall outlets. Providers use small portable nitrous oxide delivery systems to administer nitrous oxide (Fig. 1 shows an example). These devices have a simpler construction than a standard anesthesia machine and function like a SCUBA-device. They contain a cylinder of nitrous oxide and a cylinder of oxygen, with a valve that mixes the two gases (again up to an inspiratory nitrous oxide concentration of 70%) and regulates the flow of the gas mix (between 0 – 12 L/min total flow). Some devices have demand-valves that only administer the gas mix on demand when the patient triggers a breath, but most devices provide a constant flow. An important feature of all nitrous oxide delivery devices is the requirement for a scavenging system. This is due to the potential toxicity of chronic nitrous oxide exposure (see below under known side effects), for which the National Institute for Occupational Safety and Health has set strict exposure limits (25 ppm as a time-weighted average; as a comparison, 50% inspiratory nitrous oxide equals 50,000 ppm). Thus, nitrous oxide must be scavenged away from the patient, which is typically accomplished by connecting the system to a wall suction (vacuum) system. The gas is then vented outside the building.

Regulatory Aspects of nitrous oxide administration

The administration of nitrous oxide outside of FDA-approved indications, such as treatment of mood disorders, is considered “off-label” but legal. Any licensed physician can prescribe drugs outside their FDA-approved indication when deemed appropriate and of benefit for a patient. Thus far, nitrous oxide has only been studied in research settings in a relatively small group of patients with treatment-resistant major depression; hence, clinicians should follow existing treatment guidelines before considering the experimental use of nitrous oxide.

Regulatory aspects differ whether nitrous oxide is administered in a hospital or a private practice/office setting. In hospitals, nitrous oxide administration typically falls under the purview of the anesthesia department and the hospital sedation committee. In such settings, providers must have privileges to administer general anesthesia or deep sedation (e.g., anesthesiologists, nurse anesthetists). Often these privileges extend to emergency physicians and intensivists, who have been trained in conscious and moderate sedation. In some, but not all, hospitals that provide nitrous oxide for labor analgesia, midwives may be credentialed to administer nitrous oxide after receiving formal training and passing an exam.

In office settings, such as a dental office, responsibility as to who can administer nitrous oxide falls to individual providers (dentists, physicians). To mitigate safety concerns, individual states, for instance, require that dentists or related professionals must take a certification course before being allowed to administer nitrous oxide to patients. Training includes a basic understanding of nitrous oxide pharmacology, safe administration, the recognition and management of common and serious side effects related to nitrous oxide. Providers must also have current basic life support training.

Known side effects of nitrous oxide

Nitrous oxide is widely regarded as very safe.¹⁵ Side effects that may be experienced by patients during and after nitrous oxide administration must be distinguished from side effects that can occur to practitioners, who routinely administer nitrous oxide and get repeated, continued occupational exposure.

Nitrous oxide, when given at inspiratory concentrations of 50–70%, does not cause respiratory or cardiovascular depression and typically results in mild sedation. Nitrous oxide increases the risk for nausea and vomiting, and it may cause headaches, dizziness, and euphoria. Unlike ketamine, nitrous oxide does not cause hallucinations, delusions, or other psychotomimetic side effects. Dysphoria, excitement, and restlessness related to its administration are primarily observed in pediatric patients.^{32,33} In our small proof-of-principle trial in patients with treatment-resistant depression, we also observed anxiety and a panic attack-like reaction after nitrous oxide.¹⁴ It is possible that the tight fit of the facemasks may have increased anxiety level in patients.

In a large survey of 35,828 hospitalized adult and pediatric patients, side effects were observed in 4.4% (one in 23 patients); 0.08% were serious (one in 1,250 patients) and 0.01% (one in 10,000 patients) resulted from oxygen desaturation.³⁴ Most, if not all, side effects are of brief duration and dissipate after discontinuation of nitrous oxide. Nitrous oxide has the tendency to expand gas-filled spaces and is thus contraindicated in conditions such as pneumothorax, middle ear occlusion, or bowel obstruction.

Nitrous oxide also has a rather unusual side effect – it inactivates vitamin B₁₂ – this effect, however, is of little concern after a single administration or exposure, but may cause long-term sequelae in individuals who are exposed chronically to nitrous oxide.³⁵ This risk pertains primarily to individuals abusing nitrous oxide (“whippits”)³⁶ and healthcare providers who administer nitrous oxide on a regular basis.³⁷ It is highly unlikely that

patients receiving a small number (e.g., three) of nitrous oxide administrations would experience any serious sequelae. The main reasons why nitrous oxide's inactivation of vitamin B₁₂ may cause untoward side effects are i) because the inactivation occurs fairly rapidly (within 30 minutes), ii) it is chemically irreversible, and iii) the sustained inactivation can last up to three days. Hence, there can be an accumulation of effect with repeated exposures within a short time frame.^{35,38,39} The clinical consequences – mostly seen among daily nitrous oxide abusers – are similar to chronic vitamin B₁₂ or folate deficiency and may include megaloblastic anemia, and damage to the peripheral and central nervous system (e.g., neuropathy, myelopathy).⁴⁰ Despite the potential seriousness, the incidence of this side effect is very low, and probably also mitigated by the fact that in the United States flour is enriched with folic acid and vitamin B₁₂.

Nitrous oxide as drug of abuse

Because nitrous oxide can be legally and easily obtained, it is a common drug of abuse, primarily by teenagers and young adults.⁴¹ Approximately 9.0% of 12- to 17-year-olds in the United States have used inhalants and about 21% of these reported a lifetime nitrous oxide use. This makes nitrous oxide the fourth most prevalent inhalant used nationally among adolescents.⁴² However, nitrous oxide has minimal addiction potential. Its abused form is often referred to as “whippits”, as nitrous oxide is the gas within whipped cream canisters. The main difference between nitrous oxide abuse and its medical use is, when abused, nitrous oxide is inhaled at a 100% concentration without oxygen. Inhaling any pure gas other than oxygen may cause asphyxiation, particularly when taken with other CNS depressants. There is speculation that the brief period of anoxia may contribute to the high experienced by nitrous oxide abusers. As mentioned above, frequent nitrous oxide abusers are at risk of developing long-term sequelae of chronic functional vitamin B₁₂ deficiency.

Evidence of nitrous oxide as potential treatment for mood disorders

Only limited evidence exists about the potential utility of nitrous oxide in the treatment of mood disorders. The first proof-of-principle trial, published in 2015, investigated the efficacy of nitrous oxide in patients with severe treatment-resistant major depression (TRMD).¹⁴ Twenty patients with severe TRMD with a median eight failed antidepressant trials were randomized in a crossover design to either 50% nitrous oxide/50% oxygen or 50% oxygen, both administered over 1 hour. After nitrous oxide treatment, patients experienced a significantly greater reduction in depressive symptoms compared to placebo 24 hours post-inhalation. Four of the TRMD patients (20%) experienced a 50% reduction in the Hamilton Depression Rating Scale-21 item (HDRS-21) score at 24 hours (“response”) and three patients achieved remission. In contrast, only one patient receiving placebo had a treatment response, and none achieved remission.

Studies have begun to explore nitrous oxide in post-traumatic stress disorder (PTSD). Das et al. studied the effects of inhaled nitrous oxide (50% N₂O versus air for 30 minutes) in reducing the intrusive effects of viewing “trauma films” (films with emotionally disturbing scenes).⁴³ Fifty healthy controls (no history of mental illness) were shown two trauma films and were subsequently provided a 30-minute inhalation session of either 50% N₂O or air for

30 minutes. Nitrous oxide was associated with a more rapid reduction in intrusive thought frequency compared to placebo.

Walsh et al. showed recently that healthy individuals with a family history of alcohol disorder (n = 23) were distinguishable from those without such familial risk (n = 37) by an enhanced stimulation-to-sedation ratio during 50% nitrous oxide inhalation.⁴⁴

Common misconceptions

There are several misconceptions about nitrous oxide administration in a medical setting. First, very few, if any, patients get euphoric or “high” after a standard 1-hour inhalation of 50% nitrous oxide. The typical response is sleepiness and mild sedation. Most patients are easily arousable and able to communicate with the treatment team. Second, while nitrous oxide does inactivate vitamin B₁₂, this is of very little clinical relevance after a single nitrous oxide administration. Third, recovery time is very short. Typically, patients are completely recovered within 10 minutes and are able to operate a motor vehicle. While in clinical trial settings, more extensive vital sign monitors are used to increase the sensitivity of detecting adverse events, in dental practice, nitrous oxide is administered without any mandatory vital sign monitors.

Clinical administration of nitrous oxide

Table 1 provides practical tips for the administration of nitrous oxide. Presently, nitrous oxide should preferably be used to treat mood disorders in a research setting. As outlined in the section on regulatory aspects, if nitrous oxide treatments are conducted in a hospital setting, they should be coordinated with, and administered by, the anesthesiology service/department. In an office-based setting, it seems reasonable to use the approach dentistry has taken when implementing nitrous oxide sedation for dental patients. This would include following building code for installation of scavenging systems to vent nitrous oxide outside the building, ensuring adequate oxygen supply, obtaining standard nitrous oxide administration devices such as used in dentistry (no need to use nasal hoods), and obtaining adequate training, and perhaps certification, in administering nitrous oxide safely. However, the experimental and preliminary nature of nitrous oxide’s potential efficacy in the treatment of mood disorders strongly suggests that its use should be restricted at present to research settings.

Acknowledgments

We thank the Taylor Family Institute for Innovative Psychiatric Research at Washington University School of Medicine in St. Louis for their support.

Funding/Support:

This study did not receive any extramural support and was solely funded by the departments of anesthesiology and psychiatry as well as the Taylor Family Institute for Innovative Psychiatric Research at Washington University School of Medicine. Drs. Conway and Nagele are supported by a grant from the National Institute of Mental Health (5R21MH108901); the

References

1. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008; 358(1):55–68. [PubMed: 18172175]
2. Zarate C, Duman RS, Liu G, Sartori S, Quiroz J, Murck H. New paradigms for treatment-resistant depression. *Ann N Y Acad Sci*. 2013; 1292(1):21–31. [PubMed: 23876043]
3. Zorumski CF, Nagele P, Mennerick S, Conway CR. Treatment-Resistant Major Depression: Rationale for NMDA Receptors as Targets and Nitrous Oxide as Therapy. *Front Psychiatry*. 2015; 6:172. [PubMed: 26696909]
4. Ghasemi M, Phillips C, Trillo L, De Miguel Z, Das D, Salehi A. The role of NMDA receptors in the pathophysiology and treatment of mood disorders. *Neurosci Biobehav Rev*. 2014; 47:336–358. [PubMed: 25218759]
5. Autry AE, Adachi M, Nosyreva E, et al. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011; 475(7354):91–95. [PubMed: 21677641]
6. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; 47(4):351–354. [PubMed: 10686270]
7. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994; 51(3):199–214. [PubMed: 8122957]
8. Gideons ES, Kavalali ET, Monteggia LM. Mechanisms underlying differential effectiveness of memantine and ketamine in rapid antidepressant responses. *Proc Natl Acad Sci U S A*. 2014; 111(23):8649–8654. [PubMed: 24912158]
9. Zarate CA Jr, Mathews D, Ibrahim L, et al. A randomized trial of a low-trapping nonselective N-methyl-D-aspartate channel blocker in major depression. *Biol Psychiatry*. 2013; 74(4):257–264. [PubMed: 23206319]
10. Driesen NR, McCarthy G, Bhagwagar Z, et al. The impact of NMDA receptor blockade on human working memory-related prefrontal function and connectivity. *Neuropsychopharmacology*. 2013; 38(13):2613–2622. [PubMed: 23856634]
11. Zorumski CF, Izumi Y. NMDA receptors and metaplasticity: mechanisms and possible roles in neuropsychiatric disorders. *Neurosci Biobehav Rev*. 2012; 36(3):989–1000. [PubMed: 22230702]
12. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry*. 2017
13. Sanacora G, Frye MA, McDonald W, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry*. 2017; 74(4):399–405. [PubMed: 28249076]
14. Nagele P, Duma A, Kopec M, et al. Nitrous Oxide for Treatment-Resistant Major Depression: A Proof-of-Concept Trial. *Biol Psychiatry*. 2015; 78(1):10–18. [PubMed: 25577164]
15. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology*. 2008; 109(4):707–722. [PubMed: 18813051]
16. Nagele P, Metz LB, Crowder CM. Nitrous oxide (N₂O) requires the N-methyl-D-aspartate receptor for its action in *Caenorhabditis elegans*. *Proc Natl Acad Sci U S A*. 2004; 101(23):8791–8796. [PubMed: 15159532]
17. Mennerick S, Jevtovic-Todorovic V, Todorovic SM, Shen W, Olney JW, Zorumski CF. Effect of nitrous oxide on excitatory and inhibitory synaptic transmission in hippocampal cultures. *J Neurosci*. 1998; 18(23):9716–9726. [PubMed: 9822732]
18. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nat Med*. 1998; 4(4):460–463. [PubMed: 9546794]
19. Petrenko AB, Yamakura T, Kohno T, Sakimura K, Baba H. Reduced immobilizing properties of isoflurane and nitrous oxide in mutant mice lacking the N-methyl-D-aspartate receptor GluR(epsilon)1 subunit are caused by the secondary effects of gene knockout. *Anesth Analg*. 2010; 110(2):461–465. [PubMed: 19933527]
20. Richardson KJ, Shelton KL. N-methyl-D-aspartate receptor channel blocker-like discriminative stimulus effects of nitrous oxide gas. *J Pharmacol Exp Ther*. 2015; 352(1):156–165. [PubMed: 25368340]

21. Sato Y, Kobayashi E, Murayama T, Mishina M, Seo N. Effect of N-methyl-D-aspartate receptor epsilon1 subunit gene disruption of the action of general anesthetic drugs in mice. *Anesthesiology*. 2005; 102(3):557–561. [PubMed: 15731593]
22. Todorovic SM, Jevtovic-Todorovic V, Mennerick S, Perez-Reyes E, Zorumski CF. Ca(v)3.2 channel is a molecular substrate for inhibition of T-type calcium currents in rat sensory neurons by nitrous oxide. *Mol Pharmacol*. 2001; 60(3):603–610. [PubMed: 11502893]
23. Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP. Two-pore-domain K⁺ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. *Mol Pharmacol*. 2004; 65(2):443–452. [PubMed: 14742687]
24. Fujinaga M, Maze M. Neurobiology of nitrous oxide-induced antinociceptive effects. *Mol Neurobiol*. 2002; 25(2):167–189. [PubMed: 11936558]
25. Guo TZ, Davies MF, Kingery WS, Patterson AJ, Limbird LE, Maze M. Nitrous oxide produces antinociceptive response via alpha2B and/or alpha2C adrenoceptor subtypes in mice. *Anesthesiology*. 1999; 90(2):470–476. [PubMed: 9952154]
26. Guo TZ, Poree L, Golden W, Stein J, Fujinaga M, Maze M. Antinociceptive response to nitrous oxide is mediated by supraspinal opiate and spinal alpha 2 adrenergic receptors in the rat. *Anesthesiology*. 1996; 85(4):846–852. [PubMed: 8873555]
27. Sawamura S, Kingery WS, Davies MF, et al. Antinociceptive action of nitrous oxide is mediated by stimulation of noradrenergic neurons in the brainstem and activation of [alpha]2B adrenoceptors. *J Neurosci*. 2000; 20(24):9242–9251. [PubMed: 11125002]
28. Zhang C, Davies MF, Guo TZ, Maze M. The analgesic action of nitrous oxide is dependent on the release of norepinephrine in the dorsal horn of the spinal cord. *Anesthesiology*. 1999; 91(5):1401–1407. [PubMed: 10551592]
29. Likis FE, Andrews JC, Collins MR, et al. Nitrous oxide for the management of labor pain: a systematic review. *Anesth Analg*. 2014; 118(1):153–167. [PubMed: 24356165]
30. Huang C, Johnson N. Nitrous Oxide, From the Operating Room to the Emergency Department. *Curr Emerg Hosp Med Rep*. 2016; 4:11–18. [PubMed: 27073749]
31. Tobias JD. Applications of nitrous oxide for procedural sedation in the pediatric population. *Pediatr Emerg Care*. 2013; 29(2):245–265. [PubMed: 23546436]
32. Kanagasundaram SA, Lane LJ, Cavalletto BP, Keneally JP, Cooper MG. Efficacy and safety of nitrous oxide in alleviating pain and anxiety during painful procedures. *Arch Dis Child*. 2001; 84(6):492–495. [PubMed: 11369566]
33. Henderson JM, Spence DG, Komocar LM, Bonn GE, Stenstrom RJ. Administration of nitrous oxide to pediatric patients provides analgesia for venous cannulation. *Anesthesiology*. 1990; 72(2):269–271. [PubMed: 2405740]
34. Onody P, Gil P, Hennequin M. Safety of inhalation of a 50% nitrous oxide/oxygen premix: a prospective survey of 35 828 administrations. *Drug Saf*. 2006; 29(7):633–640. [PubMed: 16808555]
35. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. *Br J Anaesth*. 1987; 59(1):3–13. [PubMed: 3548788]
36. Sethi NK, Mullin P, Torgovnick J, Capasso G. Nitrous oxide “whippit” abuse presenting with cobalamin responsive psychosis. *J Med Toxicol*. 2006; 2(2):71–74. [PubMed: 18072118]
37. Krajewski W, Kucharska M, Pilacik B, et al. Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide. *Br J Anaesth*. 2007; 99(6):812–818. [PubMed: 17951609]
38. Koblin DD, Tomerson BW, Waldman FM. Disruption of folate and vitamin B12 metabolism in aged rats following exposure to nitrous oxide. *Anesthesiology*. 1990; 73(3):506–512. [PubMed: 2393136]
39. Koblin DD, Tomerson BW, Waldman FM, Lampe GH, Wauk LZ, Eger EI 2nd. Effect of nitrous oxide on folate and vitamin B12 metabolism in patients. *Anesth Analg*. 1990; 71(6):610–617. [PubMed: 2240633]
40. Garakani A, Jaffe RJ, Savla D, et al. Neurologic, psychiatric, and other medical manifestations of nitrous oxide abuse: A systematic review of the case literature. *Am J Addict*. 2016; 25(5):358–369. [PubMed: 27037733]

41. Kaar SJ, Ferris J, Waldron J, Devaney M, Ramsey J, Winstock AR. Up: The rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. *J Psychopharmacol.* 2016; 30(4):395–401. [PubMed: 26912510]
42. Wu LT, Pilowsky DJ, Schlenger WE. Inhalant abuse and dependence among adolescents in the United States. *J Am Acad Child Adolesc Psychiatry.* 2004; 43(10):1206–1214. [PubMed: 15381887]
43. Das RK, Tamman A, Nikolova V, et al. Nitrous oxide speeds the reduction of distressing intrusive memories in an experimental model of psychological trauma. *Psychol Med.* 2016; 46(8):1749–1759. [PubMed: 26937942]
44. Walsh K, Das RK, Kamboj SK. The Subjective Response to Nitrous Oxide is a Potential Pharmac-Endophenotype for Alcohol Use Disorder: A Preliminary Study with Heavy Drinkers. *Int J Neuropsychopharmacol.* 2017; 20(4):346–350. [PubMed: 27401180]

Figure 1.
Example of a Nitrous Oxide Delivery System

Table 1**Nitrous Oxide Administration – Practical Tips**

NITROUS OXIDE ADMINISTRATION - PRACTICAL TIPS	
Make sure patient does not have contraindication for nitrous oxide: pneumothorax, middle-ear occlusion, bowel obstruction, chronic severe vitamin B ₁₂ or folate deficiency	
Make sure oxygen supply is available (wall outlet or tank)	
Use standard anesthesia face mask (not oxygen mask) and mask straps – need to be somewhat tight to prevent escape of nitrous oxide into room	
Consider applying standard vital sign monitoring (pulse oximetry, 3-lead ECG, non-invasive blood pressure, capnography)	
Always administer nitrous oxide with oxygen	
Target inspiratory concentration of 50%	
Consider titrating the nitrous oxide concentration up during first 5 min. (start low, then go higher)	
Typical total gas flow rates are between 4–8 L/min	
Typical nitrous oxide treatment may last from 40–60 min.	
At the end of the inhalation treatment, slowly lower the nitrous oxide concentration and finish with 2 min. of 100% oxygen	
Consider monitoring the patient after the treatment for 30 min. in a supervised environment	