Should Nitrous Oxide Be Used for Laboring Patients?

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INTRODUCTION

Despite decades of widespread acceptance as a labor analgesic modality in numerous European countries, self-administered nitrous oxide (N\textsubscript{2}O) has only

The authors have nothing to disclose.

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INTRODUCTION

Despite decades of widespread acceptance as a labor analgesic modality in numerous European countries, self-administered nitrous oxide (N\textsubscript{2}O) has only

- Nitrous oxide
- Labor analgesia
- Maternal satisfaction
- Analgesic effectiveness
- Drug safety

KEY POINTS

- Unlike neuraxial labor analgesia, N\textsubscript{2}O provides highly variable labor analgesia, ranging from very poor to very good.
- Despite this variability, parturients who choose to use N\textsubscript{2}O where neuraxial analgesia is an option (including after trying N\textsubscript{2}O) report satisfaction similar to that reported by women who use neuraxial analgesia. Parturients using N\textsubscript{2}O report higher satisfaction than subsets of parturients who experience inadequate neuraxial labor analgesia.
- Regarding safety, parturient and neonatal adverse effects occur at rates similar to other techniques and may be no more frequent than in patients who undergo labor and delivery without analgesia. Environmental exposure and health risk to health care providers are minimal when proper scavenging of exhaled gas and adequate ventilation are used.
- Costs of administering N\textsubscript{2}O appear similar to other alternatives for labor pain relief. Costs may be lower than for neuraxial techniques because non-anesthesia trained nursing staff can monitor nitrous oxide analgesia safely.
- N\textsubscript{2}O analgesia provides a useful alternative for pain relief in parturients who decline neuraxial labor analgesia or who have contraindications to neuraxial blocks, and may offer advantages over patient-controlled systemic opioid administration and non-pharmacological techniques.
recently captured great interest in the United States. The rare US medical center offering N<sub>2</sub>O for labor in 2007 grew to an estimated 150 hospital labor and delivery units and 50 birthing centers in just a few years. In contrast, roughly half of parturients in Finland, Norway, New South Wales Australia, Canada, and New Zealand and two-thirds of parturients in the United Kingdom and Sweden were estimated to have used N<sub>2</sub>O when birthing centers were surveyed 10 years ago. The availability of N<sub>2</sub>O in institutions where neuraxial block is routine has been debated. Despite a surprising paucity of evidence regarding its analgesic effectiveness, the long history and popularity of its use is compelling; the beneficial attributes of this modality are many, and the drawback are few (Box 1). The evidence as well as adverse effects, environmental exposure risks, and barriers and costs are reviewed, concluding that N<sub>2</sub>O should be added to the modalities available to laboring parturients.

**HISTORICAL CONSIDERATIONS**

Several excellent reviews of the early history of N<sub>2</sub>O use for anesthesia during surgery have been published, and Table 1 depicts a brief historical chronology. The discovery of N<sub>2</sub>O is attributed to Joseph Priestly, who demonstrated its use in 1772. In 1800, Humphry Davy reported that N<sub>2</sub>O was useful at relieving toothache and associated it with pleasurable sensations during self-administration. Dentist Horace Wells first suggested the use of N<sub>2</sub>O as an anesthetic and self-administered it for a tooth removal; however, his public demonstration in Boston for surgery in 1845 was a failure. William Morton, a year later in 1846, demonstrated the successful use of ether as an anesthetic at Massachusetts General Hospital, considered by some as the beginning of anesthesia as a medical practice.

Other inhalational anesthetics preceded N<sub>2</sub>O use in obstetrics. The year after ether for surgical anesthesia was successfully demonstrated in Boston, James Simpson successfully used it for a vaginal delivery in 1847; however, wider acceptance of inhaled anesthesia for labor did not occur until John Snow administered chloroform to Queen Victoria during the birth of 2 children in 1853 and 1857. The first use of N<sub>2</sub>O in obstetrics is credited to Stanislav Klikovich, who developed a machine to deliver an 80/20 mixture of N<sub>2</sub>O and oxygen. Although he wrote of its safety and efficacy during labor in 1881, barriers, including cost, unfamiliarity of equipment, and access to equipment, prevented its widespread acceptance in laboring women.

During the early twentieth century, other devices for N<sub>2</sub>O administration were developed. The Minnitt apparatus (A. Charles King, Ltd, London, England), introduced in 1933, delivered 50% N<sub>2</sub>O in air. In 1936, the Royal College of Obstetricians and Gynecologists certified it as safe for use in obstetric patients attended by nurse midwives. In 1961, Tunstall described Entonox (BOC Healthcare, Manchester, England), a 50%/50% mix of N<sub>2</sub>O and oxygen in a single cylinder, which was introduced into practice in the United Kingdom in 1965. This combination was thought to be safer than mixing N<sub>2</sub>O with air, and the device is currently in widespread use. Although N<sub>2</sub>O was used in the United States during the 1970s, its use declined the following decade, likely eclipsed by the growing popularity of neuraxial analgesia for labor during that time.

Although use of N<sub>2</sub>O for surgical anesthesia has declined in the United States in the twenty-first century, the past 5 years have seen renewed interest in N<sub>2</sub>O for labor. In 2013, a barrier to N<sub>2</sub>O use for labor in the United States was overcome with the
commercial reintroduction of an N₂O apparatus (Porter Nitronox, Porter Instrument, Parker Hannifin, Hatfield, PA, USA). This small, easy-to-use, self-contained device (Fig. 1) is marketed to hospitals, academic medical institutions, and birthing centers as an alternative to natural or neuraxial analgesia for laboring parturients. Advantages of the Nitronox apparatus over the Entonox system include use of readily available N₂O and oxygen E-cylinders (not a proprietary N₂O-oxygen cylinder) and the capability of gas scavenging.

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<table>
<thead>
<tr>
<th>Box 1</th>
<th>Advantages and disadvantages for nitrous oxide analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages of N₂O</strong></td>
<td></td>
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<tr>
<td>- Simplicity</td>
<td></td>
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<tr>
<td>o Simple technique and equipment</td>
<td></td>
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<tr>
<td>o Noninvasive technique</td>
<td></td>
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<tr>
<td>o Self-administration method rapidly mastered by parturient</td>
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<tr>
<td>- Preservation of neurologic function</td>
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<tr>
<td>o Sensory: able to experience the physical sensations of the childbirth process</td>
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<tr>
<td>o Motor: strength and movement preserved</td>
<td></td>
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<tr>
<td>o Autonomic: little hemodynamic effect; no respiratory depression</td>
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</tr>
<tr>
<td>- Pharmacokinetics: rapid onset and offset of effects facilitated by low solubility</td>
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</tr>
<tr>
<td>- Maternal control: able to titrate analgesia and balance desirable and undesirable effects according to her preferences</td>
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<tr>
<td>- Maternal distraction: distracting attention away from labor pain by focusing on breathing</td>
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<tr>
<td>- Easily discontinued in favor of switch to neuraxial analgesia, for the following reasons:</td>
<td></td>
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<tr>
<td>o Ineffective N₂O analgesia as labor progresses and/or pain intensifies</td>
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<tr>
<td>o Parturient fatigued/exhausted during long labor</td>
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<tr>
<td>o Undesirable effects (sense of claustrophobia, physical and mental energy required to hold mask on face during each contraction)</td>
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<tr>
<td>o Side effects (dysphoria, sedation, nausea)</td>
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<tr>
<td>- Allows for a low-risk trial, with option to switch to neuraxial modality</td>
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<tr>
<td>- Versatility</td>
<td></td>
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<tr>
<td>o Supplement to inadequate or incomplete neuraxial analgesia</td>
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<tr>
<td>o Quick option when delivery is imminent, too late for neuraxial</td>
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<tr>
<td>o Supplement to local infiltration and/or pudendal block for repair of perineal lacerations/birth trauma</td>
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<tr>
<td>- Often effective for milder pain: relative lesser analgesic effectiveness may be adequate for</td>
<td></td>
</tr>
<tr>
<td>o Early labor, milder labor pain</td>
<td></td>
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<tr>
<td>o Parturient using effective coping skills</td>
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<tr>
<td>- Additional option: for women who desire neuraxial analgesia but who have contraindications to it</td>
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</tr>
</tbody>
</table>

| Disadvantages of N₂O |
| - Incomplete analgesia: significantly less effective in treating labor pain than neuraxial techniques |
| - Side effects |
|   o Nausea |
|   o Dizziness/dysphoria/sedation |
|   o Sense of claustrophobia |
| - Requires active participation |
NITROUS OXIDE PHARMACOKINETICS AND PHARMACODYNAMICS

N₂O is a vapor anesthetic that is tasteless and odorless. It is a weak anesthetic agent with a minimum alveolar concentration more than 100% at 1 atm, which confers safety during administration of the 50% concentration. N₂O has very low blood/gas solubility,

Table 1
History of nitrous oxide and other inhalational anesthetic administration

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1772</td>
<td>Joseph Priestly synthesized N₂O.</td>
</tr>
<tr>
<td>1800</td>
<td>Humphry Davy described N₂O use to relieve pain.</td>
</tr>
<tr>
<td>1845</td>
<td>Horace Wells demonstrated use of N₂O for surgery.</td>
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<tr>
<td>1847</td>
<td>James Simpson used ether for vaginal delivery.</td>
</tr>
<tr>
<td>1853</td>
<td>John Snow used chloroform for Queen Victoria’s labor.</td>
</tr>
<tr>
<td>1881</td>
<td>Stanislav Klikovich published the first study of N₂O use in laboring women.</td>
</tr>
<tr>
<td>1934</td>
<td>Minnitt apparatus for N₂O self-administration was introduced.</td>
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<tr>
<td>1961</td>
<td>Tunstall introduced the Entonox, combining N₂O with oxygen in one cylinder.</td>
</tr>
<tr>
<td>2013</td>
<td>Nitronox machine becomes widely available in the United States.</td>
</tr>
<tr>
<td>2015</td>
<td>More than 20 hospital systems and 30 birthing centers in the United States report offering N₂O for labor analgesia.</td>
</tr>
</tbody>
</table>

Fig. 1. N₂O apparatus. Photograph shows disposable circuitry and mask, N₂O tank, mixing box allowing delivery of only a 50% N₂O mixture, with wall source oxygen and scavenging tubing. (Courtesy of Porter Instrument, Parker Hannifin, Hatfield, PA; with permission.)
and Waud and Waud\textsuperscript{14} showed that peak brain concentrations occurred 60 seconds after onset of its administration in laboring patients. Its mechanism of action, however, is not well understood. Maze and Fuginaga\textsuperscript{15} hypothesized that N\textsubscript{2}O induces release of endogenous opioid peptides in the periaqueductal gray area of the midbrain. These peptides stimulate descending noradrenergic neuronal pathways, which modulate pain processing by alpha-2 receptors in the dorsal horn of the spinal cord.\textsuperscript{15} Gruss and colleagues\textsuperscript{16} showed that N\textsubscript{2}O has poor action at \(\gamma\)-aminobutyric acid receptors like other volatile anesthetics but noted that N-methyl-D-aspartate (NMDA) receptor inhibition is the mechanism most likely responsible for its anesthetic effects. Richebé and colleagues\textsuperscript{17} demonstrated that the NMDA antagonist properties of N\textsubscript{2}O prevented enhancement of pain sensitivity and reduced postoperative pain. The release of endogenous opioids and the inhibition of NMDA receptors are likely responsible for the analgesic effects of N\textsubscript{2}O.

**Nitrous Oxide: Variable Analgesic Effectiveness**

Despite its introduction as a labor analgesic nearly 6 decades ago, its subsequent routine use throughout Europe, and its growing popularity in the United States, evidence regarding the effectiveness of N\textsubscript{2}O is surprisingly limited. A 2002 systematic review with strict criteria for inclusion (randomization, adequate control group, effectiveness assessments by parturients at the time of or shortly after intervention) identified only 11 trials of adequate quality for review. Data on 340 parturients were analyzed from the studies, which were conducted between 1961 and 1995 (7 before 1985).\textsuperscript{18} Drawing conclusions regarding analgesic effectiveness was difficult as the concentration of N\textsubscript{2}O studied was variable (30\%–70\%), as were methods of administration, methods and timing of effectiveness assessments, and comparator modalities (many now outmoded, such as repeated doses of intramuscular meperidine, inhalational methoxyflurane, anesthesiologist administered enflurane, transcutaneous electrical nerve stimulation, and so forth). A systematic review 12 years later added little.\textsuperscript{19} It identified 12 randomized controlled trials examining effectiveness, including 9 of the same trials as the prior review, excluded 2 low-quality studies from the prior review,\textsuperscript{20,21} and added only a single new study.\textsuperscript{22} Both reviews deemed the strength of evidence for N\textsubscript{2}O labor analgesia effectiveness to be insufficient to make conclusions, owing primarily to unsatisfactory study design.\textsuperscript{18,19} However, N\textsubscript{2}O is an alternative analgesic option for some women.

Although neuraxial techniques are more effective overall in providing labor pain relief than N\textsubscript{2}O, most studies identify subsets of women who report significant analgesic effectiveness from N\textsubscript{2}O, with many stating that they would choose it again for a future delivery.\textsuperscript{21,23–30} Unlike the consistently reliable effectiveness of neuraxial analgesia, N\textsubscript{2}O yields variable analgesic effectiveness. In a postpartum survey study of 1096 nulliparous and 1386 parous Swedish women, most (84\% and 72\%, respectively) rated epidural analgesia as very effective. Despite N\textsubscript{2}O being less effective, 38\% of nulliparous and 49\% of parous women also reported N\textsubscript{2}O to be very effective.\textsuperscript{23} In another study, more than 800 Finnish parturients were assessed before and after various labor analgesic interventions, including N\textsubscript{2}O, epidural alone, and epidural or paracervical block after trying various modalities (N\textsubscript{2}O, meperidine, water blocks).\textsuperscript{24} Although epidural analgesia was superior to all other modalities during the first stage of labor, and a subset of women using N\textsubscript{2}O subsequently switched to regional blocks, many women chose to continue with N\textsubscript{2}O alone for the entirety of their labor, despite the availability of alternatives. After delivery, 94\% of women who used epidural analgesia reported good analgesic effectiveness. In contrast, 28\% of those who delivered with
N₂O alone reported poor and 39% moderate analgesic adequacy, yet 33% rated analgesia as good. Holdcroft and Morgan²⁵ conducted an observational study of 663 parturients who delivered vaginally using N₂O, meperidine, or both. Of the 130 who used N₂O alone, 31% reported no pain relief, 18% slight, yet 47% reported satisfactory and 4% complete analgesia. Most recently, Dammer and colleagues²⁶ reported on 66 laboring women who chose to use N₂O soon after introduction of an inhaled N₂O analgesia program in a German academic center. Reasons for choosing N₂O included refusal to use epidural analgesia (59%), inability to place an epidural (23%), inadequate epidural analgesia (8%), or unspecified reasons (11%). Analgesic effectiveness was variable. Two-thirds of women reported being *quite* or *very likely* to use N₂O again for labor, and one-third reported *absolutely not*, *a little*, or *moderately likely*.

In summary, wide ranges in analgesic effectiveness are consistently reported in published studies. Factors that predict N₂O effectiveness as a sole analgesic agent have yet to be determined. However, it is clear that N₂O serves as an effective analgesic modality for some women who choose to use it.

**WHAT MATTERS: EFFECTIVE PAIN RELIEF VERSUS SATISFACTION?**

Although effectiveness of pain relief is a primary determinant in many parturients’ reported satisfaction with labor analgesic care, especially with neuraxial modalities,²⁴,³¹–³⁶ it is clearly not the only factor.³⁴,³⁷–⁴⁰ Among 28 women with a priori plans to use labor epidural analgesia, effective pain relief (confidence in timely access to it and analgesic effectiveness) was viewed as beneficial in regaining self-control and ability to focus, think, and participate in the birth process.³⁴ Of note, parturients also identified other factors important to birth experience satisfaction, such as preservation of bodily sensations of labor, mobility, and strength. This study highlighted the multidimensional nature of the parturients’ experience of labor analgesia, including measures of cognitive, emotional, and physical domains. Consistent with this, a systematic review of 137 reports investigating factors influencing parturients’ assessments of their childbirth experiences identified factors that strongly affect parturient satisfaction with the childbirth experience, including personal expectations, caregiver support, quality of the relationship with her caregiver, and involvement in decision-making.³⁷ The development and implementation of coping-with-pain algorithms may be an alternative to numerical pain rating scales that quantify only labor pain.³⁸,³⁹ The experience of labor is unique to each individual and comprises the complex interplay between physical, physiologic, psychological, emotional, social, and cultural dimensions.³⁸,³⁹ Unlike traumatic, postoperative, or other pathologic pain, the pain of labor accompanies the unique process of giving birth to new life. The coping algorithm approach does not eliminate but rather de-emphasizes pain as the dominant or sole dimension of the labor experience and allows for a more holistic or global patient-centered assessment. If the parturient is coping well, then continued support is given. If not, then various dimensions can be assessed and appropriate interventions suggested or offered.³⁹ Finally, a qualitative content analysis of 2005 national survey data from 1573 US parturients who delivered a singleton baby revealed the high importance of timely and effective neuraxial analgesia for those who requested it.⁴⁰ However, analgesia was one among many other factors identified by women who were asked open-ended questions about the best and worst aspects of their birth experience.

In summary, although effectiveness of pain relief heavily influences satisfaction with labor analgesia for many women, especially with those who choose neuraxial modalities, it is not the sole determinant. This may explain the consistent popularity of
Nitrous Oxide Use for Laboring Patients

Nitrous oxide (N₂O) labor analgesia use in Europe, and its growing popularity in the United States. Many parturients who deliver with N₂O, in spite of having ready access to neuraxial modalities, report high satisfaction despite incomplete analgesia.

NITROUS OXIDE: 5-YEAR EXPERIENCE AT A HIGH-RISK ACADEMIC CENTER

N₂O has been offered as an option for all laboring women at Vanderbilt Medical Center since June 2011. Soon after admission, anesthesiology personnel assess every woman with a viable pregnancy and counsel them regarding neuraxial and N₂O analgesic options provided by the obstetric anesthesiology service, including benefits, side effects, risks, limitations on mobility, and the relative level of analgesia that may be expected. Consistently, one in 5 laboring women selects N₂O analgesia during some point during labor (Fig. 2). Of those who do and deliver vaginally, 60% use N₂O as the sole analgesic, whereas 40% switch to neuraxial analgesia (see Fig. 2). In contrast, of those who start with N₂O and ultimately deliver by cesarean, the conversion rate during labor is higher, 63%, possibly due to longer and more painful labor associated with those whose labor course culminates in cesarean delivery.⁴¹,⁴² Reasons for converting to neuraxial analgesia after N₂O include the following:

- **Inadequate analgesia**: Some women switch to neuraxial analgesia because they experience little or no analgesic effect soon after trying N₂O. Others are satisfied with N₂O analgesia initially but convert later, as contraction pain intensifies, whether because of progress of labor or oxytocin augmentation.

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**Fig. 2.** Labor analgesia choices among women who deliver vaginally at Vanderbilt University Medical Center. Image shows monthly labor analgesic usage pattern for neuraxial analgesia, N₂O analgesia only, and conversion to neuraxial analgesia after using N₂O over a 34-month period.
• **Undesirable side effects**: These side effects include dizziness, nausea, sedation, and a sense of claustrophobia from the mask.

• **Fatigue/exhaustion**: N₂O use requires being awake and actively holding the mask to the face. As labor pain intensifies or during lengthy labors, some women tire of the effort and coordination required to self-administer the drug. During lengthy labors and/or when parturients are exhausted or sleep deprived, some women opt for the rest and sleep conferred by the complete analgesia produced by neuraxial modalities.

Analysis of routine postpartum assessments of analgesic effectiveness and satisfaction among 6242 parturients who delivered vaginally during a 34-month period (2011–2014) revealed variable levels of effectiveness (21% poor, 27% intermediate, 52% high) among the 678 women who delivered with N₂O alone, yet satisfaction among these women was as high as and not different from those who used neuraxial analgesia (n = 5103) or those who chose neuraxial analgesia after first using N₂O (n = 461). This observation may be due to differences in expected analgesic effects of N₂O versus neuraxial analgesia.

In summary, N₂O seems to serve the analgesic needs of the subset of laboring women who choose to use it, including women whose birth plans include limited medication, unencumbered movement, strong preference to avoid neuraxial techniques, and a high level of control. Some parturients seek to deliver at the authors’ institution specifically because they offer N₂O for labor. Additionally, N₂O serves as an alternative when there are contraindications to neuraxial blocks (eg, coagulation disorders, spine abnormalities, or prior spine surgery).

**NITROUS OXIDE ANALGESIA VERSUS OTHER NON-NEURAXIAL TECHNIQUES**

Unfortunately, there is no useful evidence comparing N₂O with other non-neuraxial analgesic modalities or nonpharmacologic interventions. Most studies of such alternative interventions reveal modest or no analgesic effectiveness, including maternal childbirth preparation, relaxation techniques, water immersion/whirlpool therapy, acupuncture/acupressure, transcutaneous nerve stimulation (TENS), and subcutaneous water injection. A single observational study examined pain relief and satisfaction from use of TENS, N₂O, intramuscular meperidine, and epidural analgesia. Most women reported some pain relief from TENS and N₂O, and half reported no relief from intramuscular opioid.

Similarly, comparisons of N₂O with systemic opioid analgesics are sparse. Analgesia produced by intramuscular opioids is reported to be modest or ineffective (active advanced labor). Intravenous administration seems to improve effectiveness compared with the intramuscular route, especially if patient-controlled modalities are used. Patient-controlled intravenous remifentanil has advantages of rapid onset of action and peak effect compared with other opioids, which may allow timing of administration to coincide with uterine contraction pain. Unfortunately, significant maternal oxygen desaturation, nausea, and pruritus are common. A single study comparing N₂O and patient-controlled intravenous remifentanil demonstrated slightly greater analgesic effectiveness but greater sedation with remifentanil. No hypoxemic episodes were observed in the remifentanil group, although supplemental oxygen was administered to mothers. Without supplemental oxygen, oxygen desaturation was observed in 25% of parturients using remifentanil. The implication for increased monitoring, perhaps requiring one-to-one nursing, is a drawback of remifentanil analgesia.

In summary, evidence comparing N₂O with non-neuraxial pharmacologic or nonpharmacologic alternatives is lacking. Systemic opioid administration is the only other...
modality that has been demonstrated to produce effective analgesia in some women but has more drawbacks compared with N₂O.

**ADVERSE MATERNAL AND NEONATAL EFFECTS**

N₂O is generally well tolerated, without major side effects. Some of the reported adverse reactions and contraindications to N₂O for labor are presented in Box 2. Although N₂O likely has little direct effect on ventilatory drive, its use during labor has been associated with brief self-limited maternal oxygen desaturations between labor contractions.⁵⁷ Self-administration techniques involve focused inhalation of the gas to obtain analgesic effects. Hyperventilation during uterine contractions, and associated hypocapnia, may be the cause of occasional oxygen desaturation.⁵⁸ The alternative hypothesis, diffusion hypoxemia during room air breathing between contractions, is an unlikely cause.⁵⁸ Of note, oxygen desaturation is observed during some unmedicated labors.⁵⁹

A small subset of women experience nausea when using N₂O. In a large systemic review of multiple studies by Likis and colleagues,¹⁹ nausea was reported to occur at rates ranging from 0% to 45%. The possibility of increased nausea with the use of N₂O should be discussed with the parturient, especially if she is already nauseous from labor. Likis and colleagues'¹⁹ review also reported an incidence of dizziness that ranged from 3% to 23%. Dizziness is typically well tolerated if the parturient is informed, but it sometimes requires discontinuation of its use. In another study of 1000 laboring women, 4% of parturients reported drowsiness, 18% experienced reduced awareness, and 5% exhibited mask phobia.⁶⁰ Unconsciousness is most probably rare; 2 studies by Arthurs and Rosen⁶¹ and Westling and colleagues⁶² found a 0% incidence. Adding systemic opioids to N₂O analgesia (and epidural analgesia) may increase the incidence of maternal respiratory depression and intermittent hypoxemia.⁵⁹ The discontinuation of opioids, such as butorphanol, is recommended 2 hours after delivery.

**Box 2**

Maternal side effects of nitrous oxide administration: contraindications to use

<table>
<thead>
<tr>
<th>Maternal side effects</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Absolute</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Relative</td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td></td>
</tr>
<tr>
<td>Unconsciousness</td>
<td></td>
</tr>
</tbody>
</table>

**Contraindications**

- **Absolute**
  - Recent pneumothorax
  - Recent retinal surgery
  - Recent middle ear or sinus infection
  - Known vitamin B12 deficiency

- **Relative**
  - Pernicious anemia
  - Extensive bowel resection due to Crohn disease
  - Vegans who do not consume legumes
  - Methionine synthetase deficiency or reduction
before initiating N2O. In summary, the incidence of various maternal side effects attributable to N2O administration alone is difficult to determine given the lack of adequate comparative studies.

Significant adverse effects on the neonate have not been reported. In an obstetric outcome study conducted in the United Kingdom, the Medical Research Council noted no serious neonatal effects that could be attributed to N2O administration. Likis and colleagues reviewed 29 studies reporting fetal or neonatal adverse outcomes, specifically umbilical cord blood gases and Apgar scores, and reported no significant differences between mothers using N2O compared with other labor pain methods or no analgesia. Leong and colleagues observed no differences in fetal outcomes at 1 and 5 minutes after delivery between groups receiving N2O with meperidine or epidural analgesia, and no newborn had an Apgar score lower than 7 at 5 minutes. Stefani and colleagues conducted validated neurobehavioral assessments on infants at 15 minutes, 2 hours, and 24 hours of age and showed no significant differences between neonates born to mothers receiving 30% to 50% N2O or no inhalational agent during the second stage of labor. Although there is no evidence of adverse effects of N2O for the fetus, the strength of that evidence is far from conclusive; much remains unknown about the effects on the developing brain. Concerns regarding the neurotoxic effects of N2O (and other anesthetic agents) on the developing brain have been raised because of studies showing neuroapoptosis in rodents exposed to anesthetic agents in large doses. Most studies involve concentrations and durations of agent exposure far greater than typically used during general anesthesia.

CONTRAINDICATIONS

Contraindications to N2O use in laboring patients are few (see Box 2). The potential for N2O to expand closed gas spaces is well known; caution is advised in women who have had a recent pneumothorax, pneumocephalus, venous air embolism, bowel obstruction, retinal surgery, middle ear surgery, or sinus infections. N2O should also be avoided in patients with known pulmonary hypertension and certain congenital heart diseases because of its known effects on pulmonary vascular resistance. Risks of N2O use in the presence of reduced methionine synthetase activity have been debated. Although no adverse effects have been reported in laboring parturients, caution is advised in women with B12 deficiency (methylene-tetrahydrofolate reductase; megaloblastic anemia) owing to rare reports of subacute combined degeneration in severely vitamin B12–deficient patients with prolonged exposure to high concentrations of N2O during general anesthesia.

HEALTH CARE WORKER EXPOSURE, ENVIRONMENTAL, EQUIPMENT, AND ADMINISTRATIVE CONCERNS

Although inhaled N2O offers an alternative to neuraxial analgesia and has advantages compared with other non-neuraxial alternatives, several practical issues must be considered before introducing a N2O program (Box 3).

HEALTH CARE WORKER EXPOSURE

The National Institute for Occupational Safety and Health (NIOSH) sets an exposure limit of 25 ppm as a time weighted average (TWA) during periods of anesthetic administration. This recommendation, set in 1977 and not reviewed since 1994, was not intended to prevent long-term health consequences for workers but rather to prevent...
possible effects of exposure on health providers’ sight and audio acuity and mental performance. NIOSH based their 25 ppm recommendation on decreased audiovisual performance noted when test subjects were exposed to 50 ppm N\textsubscript{2}O.\textsuperscript{71} The levels of N\textsubscript{2}O exposure sufficient to pose health risks to obstetric providers are unknown. A meta-analysis of 16 studies published before 2002 failed to establish an association between occupational exposure and risk and concluded that evidence to date could not serve to set occupational health standards for exposure.\textsuperscript{18} This finding is reflected in the wide range of exposure limits in various countries: France, United States, 25 ppm; Italy, Belgium 50 ppm; Sweden, United Kingdom, 100 ppm; Germany, 200 ppm (duration up to 15 minutes, 4 times per day).\textsuperscript{72}

Levels commonly exceed 25 ppm when N\textsubscript{2}O is administered without effective scavenging. Such levels of exposure are also more likely to occur in labor and delivery facilities with minimal room ventilation.\textsuperscript{73-76} Mills and colleagues\textsuperscript{73} measured environmental N\textsubscript{2}O exposure among nurse midwives during N\textsubscript{2}O use in labor and delivery units where it was not scavenged and delivery rooms were not ventilated. Personal N\textsubscript{2}O samplers worn close to the face are used to measure average ambient N\textsubscript{2}O levels in parts per million for each shift. Median N\textsubscript{2}O exposure during 242 sampling periods was 23 ppm, with a range of 0 to 1638 ppm. In 23% of samples, mean levels exceeded 100 ppm during a shift, with 7 (3%) measuring more than 500 ppm. This finding compared with median N\textsubscript{2}O levels of 12 ppm in 111 shifts where midwives had not worked with Entonox.

Routine scavenging and labor room ventilation effectively reduces staff exposure considerably. Munley and colleagues\textsuperscript{74} reported 2.5-fold reductions in measured

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**Box 3**

**Health care worker exposure**

- Government-established exposure limits are measured as time weighted averages and vary by country.
- Exposure limits may be exceeded for staff with prolonged close contact with parturients using N\textsubscript{2}O.
- Correct apparatus use by patients, effective scavenging systems, and room ventilation reduce exposure to acceptable levels.

**Exposure and health safety**

- N\textsubscript{2}O exposure does not seem to increase health care worker risks, except slightly reduced fecundity among women with prolonged exposure to high N\textsubscript{2}O levels.

**Environmental effects**

- The greenhouse gas potency of N\textsubscript{2}O is 300 times greater than carbon dioxide, but the overall contribution of medical N\textsubscript{2}O to atmospheric warming is miniscule.

**Administrative procedures and clinical use**

- Policies that govern N\textsubscript{2}O administration must comply with institutional sedation and analgesia policies as outlined by the institution’s department of anesthesia.
- Effective obstetric and patient instruction is needed for effective use.
- Safe administration can be monitored by nonanesthesia personnel.
- Cost of administration is comparable with neuraxial techniques; personnel costs may be lower if nonanesthesia personnel conduct administration.
N₂O exposure when a rudimentary scavenging system was introduced during N₂O use. Chessor and colleagues⁷⁵ compared conventional scavenging with a novel mask scavenging system similar to that commonly used now in the United States and noted reductions in nurse exposure from 69 ppm to 40 ppm. The greatest reduction in ambient N₂O levels is achieved when effective N₂O scavenging is combined with room ventilation. The use of a scavenging system similar to the system used with Nitronox equipment currently in use in the United States yielded 8-hour TWA levels of 7.5 to 21.0 ppm in ventilated labor and delivery rooms.⁷⁶ Brief periods of high peak exposure were few. N₂O levels, ranging from 50 to 110 ppm, of 15-minute duration, were measured 8 times in 11 of 15 midwives during 88 total hours of sampling. Room air monitoring on the labor and delivery suite at Vanderbilt Medical Center has failed to detect N₂O concentrations in excess of 25 ppm, and obstetric nurse exposure measured by badge dosimeters have not exceeded NIOSH TWA limits.

In summary, equipment that includes N₂O demand valves and effective scavenging systems when used in ventilated delivery rooms seems to limit obstetric health care provider exposure to levels that do not significantly exceed governmental standards.

NITROUS OXIDE EXPOSURE AND HEALTH SAFETY RISK

Survey studies linking N₂O exposure to health care worker reproductive hazards appeared in the 1960s and 1970s. Study subjects were either operating room personnel or dental assistants, and all were exposed to levels of N₂O and other anesthetic gases that far exceeded that found in any current health care environment. Despite such high exposure levels, these studies reported marginal statistical significance for increased risk (relative risk for spontaneous abortion, 1.3; congenital anomalies, 1.2), which may be explained by confounding variables (eg, survey bias, reporting bias, or other uncontrolled variables).⁷⁷,⁷⁸ One study of dental assistants reported statistically significant lower fertility among a small subset of women exposed to very high levels of N₂O (5 or more hours of exposure per week in an unsca- venged environment),⁷⁹ levels not achieved in contemporary operating rooms or labor and delivery environments. The failure to observe increased rates of congenital anomalies among women who have received N₂O during surgery in the first 2 trimesters of pregnancy or during cervical cerclage placement is reassuring.⁷² Two studies examining reproductive outcomes among Swedish midwives exposed to N₂O failed to reveal an increased risk of spontaneous abortion among those exposed to N₂O.⁸⁰,⁸¹ Overall, current epidemiologic data do not support increased reproductive health risks among health care workers exposed to subanesthetic concentrations of N₂O during care of laboring women but slightly reduced fecundity among women with very high levels of exposure may occur.⁸⁰

ENVIRONMENTAL CONCERNS

N₂O is a potent greenhouse gas, approximately 300 times more potent at trapping atmospheric heat than carbon dioxide; most N₂O administered for anesthetic purposes ultimately ends up in the atmosphere.⁸² However, medical use has been estimated to contribute to less than 0.05% of total atmospheric warming and is responsible for less than 1.0% of all N₂O in the atmosphere.⁸² Swedish manufacturers have developed equipment that reclaims and destroys N₂O. Ek and Tjus⁸³ recently reported a near halving of emissions countrywide from 2002 to 2010, thanks to the widespread use of these units in Sweden. The medical use of N₂O has little environmental impact.
ADMINISTRATIVE PROCEDURES AND CLINICAL USE

N\textsubscript{2}O administration should comply with the anesthesia and sedation policies unique to each institution. Within the United States, these policies should follow the Conditions of Participation (42 CFR 482.52) recently updated by the Centers for Medicare and Medicaid Services, which direct that the department of anesthesia at each facility develop and implement all policies for sedation and analgesia. Current American Society of Anesthesiologists’ practice guidelines for sedation and analgesia categorize patient self-administered 50% N\textsubscript{2}O as analgesia or minimal sedation,\textsuperscript{84} so administration and monitoring by an anesthesia provider are not required. The United Kingdom has a long history of safe provision by nonanesthesia personnel of self-administered N\textsubscript{2}O to laboring women. Monitoring parturients with pulse oximetry within 2 hours of having received systemic narcotics is recommended.\textsuperscript{85} Policies for monitoring by nursing staff should be delineated. One-on-one nursing care is not necessary, in contrast to recommendations for one-on-one nursing care when patient-controlled intravenous opioid analgesia is used for labor analgesia.\textsuperscript{53,86} Staff training has been reported to be effective in training such nonanesthesia providers for safe use.\textsuperscript{87}

Effective N\textsubscript{2}O labor analgesia requires proper patient use; this is best achieved by providing the parturient with good instruction, coaching, and initial supervision/monitoring to ensure proper use and confirm clinical effect. The combination of a low blood-gas solubility coefficient and use of a high (50%) inspired concentration, promotes rapid N\textsubscript{2}O uptake. This rapid uptake accelerates onset analgesic effects but also prevents alveolar concentrations from approaching the inspired concentration during the typical intermittent use during uterine contractions. Ideally, patients should begin intermittent use 30 to 45 seconds before peak contraction strength and take 4 to 5 consecutive breaths.\textsuperscript{88} If uterine contractions are regular in period, then analgesia could begin before onset of a contraction is sensed. Table 2 outlines a recommended technique for administration.

Table 2
Nitrous oxide analgesia: technique and patient instruction

<table>
<thead>
<tr>
<th>Steps</th>
<th>Action</th>
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| Assess parturient | Identify potential contraindications (see Box 2)  
Full discussion of benefits, limitations, side effects (dizziness, nausea)  
Confirm that parturient can self-administer using mask apparatus  
Determine if patients learn the technique while laboring |
| Prepare for administration | Inspect equipment before administration  
Provide patient instruction  
Hold mask to face, with complete seal to ensure effective drug administration  
Timing strategy: Initiate inhalation anticipating onset of contraction (if labor is regular) or as soon as contraction is sensed (if labor is irregular) |
| Monitor mother during use and provide feedback on technique | Confirm complete seal between face and mask during inspiration (drug uptake) and exhalation (ensure effective scavenging)  
Assess and record initial vital signs and oxygen saturation at beginning of use  
Assess for effectiveness and satisfaction; if not effective or dissatisfaction, remind parturient of alternative options  
Assess for and manage side effects (sedation, nausea) |
EQUIPMENT

The N₂O labor analgesia apparatus may include a single gas cylinder containing a one-to-one mix of N₂O and oxygen supplied at 2000 psi (both in gas phase, owing to the Poynting effect), most often used in Europe (eg, Entonox). In the United States, the apparatus most commonly draws the gases from separate sources (N₂O from an attached E cylinder and oxygen from a wall source or E cylinder) to provide a one-to-one ratio output. On a practical note, N₂O remains in a liquid phase inside a compressed gas cylinder, so long as the gas phase remains at 745 psi. Once the liquid is depleted, cylinder pressure decreases precipitously. If a parturient who was experiencing satisfactory analgesia develops a sudden increase in pain, an empty N₂O cylinder should be considered.

All devices should use a disposable circuit attached to a mask and demand valve that delivers N₂O only during negative pressure generated by patient inhalation. The demand valve limits N₂O flow only to those times when patients are actively inhaling (see Fig. 1). A scavenger device attached to the mask/demand valve assembly is essential to remove exhaled gas and minimize environmental contamination. Nearly 70% of exhaled N₂O can be captured with such systems. Finally, despite lack of reported instances, N₂O, as with other anesthetic agents, has abuse potential, either by health care workers or persons other than the patients to whom it is prescribed. Equipment should be stored in secure areas when not in use, and the institution’s substance abuse policy should apply.

COST

Several investigators have noted that N₂O administration is inexpensive, although specific costs of providing care have not been published. Disposable supply costs are similar to those for neuraxial blocks (approximately $20 hospital cost at Vanderbilt), and capital costs are not prohibitive (approximately $5000 per apparatus). The equipment is robust and has a long life expectancy. Personnel costs are probably lower than those involving neuraxial blockades if N₂O is administered by nurse midwives or labor and delivery nursing personnel, reflecting differences in labor costs versus that of anesthesia-trained persons. The cost-effectiveness of N₂O analgesia needs further investigation.

SUMMARY

Each parturient has personal preferences and needs, which are shaped by the uniqueness of her life experience. Furthermore, these preferences and needs are dynamic and often change during the course of her labor. Although N₂O is less effective in treating labor pain than neuraxial analgesic modalities, it has consistently served the needs and preferences of a small but significant subset of parturients. Including N₂O in the repertoire of modalities that obstetric anesthesiologists offer to alleviate pain and suffering, and to facilitate effective coping and maternal satisfaction, is consistent with a commitment to addressing the needs of all parturients.

REFERENCES

7. Cartwright FF. The English pioneers of anaesthesia. Bristol (United Kingdom): John Wright and Sons Ltd; 1952.


