Nitrous Oxide for Labor Pain: Is It a Laughing Matter?

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In the second season of the hit television series "Call the Midwife," the midwives who attend home births in East London in 1958 are introduced to what they call "gas and air" or 50%/50% nitrous oxide/oxygen (N_2O/O_2) mix. Soon all the expectant "mums" in East London start using it, and the midwives trade in their bicycles for cars, so gas and air can be transported to homes. It appeared that N_2O was the silver bullet laboring women desired. In fact, this 50/50 mixture of N_2O/O_2 is a common labor analgesic in Europe today. Although it has been used for labor pain management in a small number of labor and delivery units, until recently, N_2O/O_2 has been largely unknown in the United States. However, as clinicians and consumers alike look for alternatives to systemic opioid or neuraxial labor analgesia, and as public awareness of N_2O's potential use in labor and delivery expands, the time has come to look at use of gas and air in the childbirth setting more closely.

N_2O is a colorless, sweet-smelling, nonflammable gas with low potency, low solubility, and minimal metabolism that is used for inhaled analgesia/anesthesia. Overdose is unlikely as long as the concentration is controlled so that delivery of a hypoxic gas mixture is not possible. The low solubility facilitates rapid onset (30 to 50 seconds) and rapid offset of effect. These properties allow the gas to be self-administered with relative safety.

In 2011, the U.S. Agency for Health Care Research and Quality (AHRQ) Effective Health Care Program funded a comparative effectiveness review on use of N_2O for managing labor pain. This issue of *Anesthesia & Analgesia* includes an article derived from the AHRQ systematic review by Likis et al.,[1] authors of the original AHRQ report.[1] The review included studies of any type and design that addressed the effectiveness of N_2O for labor analgesia as well as women's satisfaction with the birth experience, adverse effects to the mother and child, and safety, including occupational hazards. The systematic review was well conducted with sound methodology. Unfortunately, of the 58 identified relevant publications, only 2 were of good quality. Given the paucity of good data, it is not surprising that the results are frustratingly inconclusive. The strength of the evidence for effectiveness of N_2O in managing labor pain was insufficient; there was a high risk of bias for all the analyzed outcomes, and findings were inconsistent across studies. In addition to poor-quality study designs, the studies varied in many aspects, including concentration and frequency of N_2O use, use of additional methods of analgesia, and type and timing of assessments. Older studies used comparator analgesic methods that are no longer available. Likis et al.[1] concluded that further research assessing N_2O use during childbirth is needed for all outcomes of interest, including adverse effects, effectiveness, and maternal satisfaction.

What do we know about the safety and effectiveness of this agent? In addition to the Likis et al.[1] study published in this issue, 3 other reviews of N_2O have been published using somewhat different methodologies.[2–4] The systematic review conducted by Rosen[2] found 19 mixed methods studies that were used to evaluate adverse effects and 11 randomized controlled trials that were used to evaluate effectiveness. Similar to the findings of Likis et al.,[1] Rosen[2] found that N_2O provides pain relief that is well tolerated and appears to be safe to the mother and fetus, but the varied comparisons and mix of doses among the studies precluded reaching any quantitative conclusions about the degree of pain relief that N_2O provides. Despite not being able to quantitate pain relief, Rosen[2] concluded that most women using N_2O reported positive results, and most would choose to use it again in a subsequent labor.

The review published by Rooks[3] examined the literature on safety of N_2O. She found that adverse effects of N_2O/O_2 were associated with large doses (concentration higher than 50%) and long duration exposures. In addition, when scavenging was appropriate, the occupational exposures were less than the standard set by the National Institute for Occupational Safety.

Finally, Collado et al.[4] conducted a literature review for the purpose of assessing the safety of N_2O/O_2. The authors identified 140 articles on 50%/50% N_2O/O_2 that addressed adverse events following perioperative use or chronic exposure of health care workers. Few of the studies prospectively determined the criteria used to define adverse events, and there was a great deal of heterogeneity among studies. Nonetheless, a consistent story emerged with regard to vertigo and hallucinations, which occurred in 1% of patients, and nausea and vomiting, which occurred in 0.8% of patients. The authors calculated that serious adverse effects related directly to N_2O/O_2 occur in 3/10,000 individuals.

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The Collado et al.[4] study did not conduct a separate analysis of obstetric use.

It is somewhat ironic that as interest in the use of N_2O/O_2 in the childbirth setting increases, N_2O use in operating rooms across the country is decreasing (http://www.hra-research.com/expertise/hospital-data-audits). For the past half century, the routine use of N_2O in anesthesia has been under "almost continuous challenge" because of concerns about neurologic and hematologic toxicity, adverse immunologic effects, genotoxicity, risk of myocardial ischemia, expansion of air-filled body cavities, and increased risk for postoperative nausea and vomiting.[5,6] In fact, new hospitals are being built without plumbing for central delivery of N_2O into operating rooms (personal communication: Tom Krejcie, Tony Gin, August 2013). In 2012 and 2013 (through August 14) alone, 6 editorials that addressed the controversies surrounding the use of N_2O as a component of general anesthesia have been published.[a]

Most labor studies have not identified adverse outcomes in the offspring of mothers who use N_2O during labor. However, as summarized by Likis et al.[1], study quality is poor. In addition, important outcomes have not been studied. For example, N_2O affects methionine synthase function. This enzyme plays an important role in the synthesis of DNA, RNA, myelin, and catecholamines, among other substances.[5] Relatively short periods of N_2O anesthesia (several hours) completely inhibit methionine synthase activity. Adverse clinical effects have been noted in individuals with cobalamin deficiency. Potential adverse effects may depend on diet (e.g., vitamin B_{12} and folate), and there is some evidence that common polymorphisms in the gene encoding an important enzyme in the folate cycle (5, 10-methylenetetrahydrofolate reductase [MTHFR]), may play a role.[5] What does this mean to the fetus/neonate with a rapidly developing nervous and hematologic system? To our knowledge, no studies have addressed this concern.

The mechanism of N_2O's anesthetic action is thought to relate to noncompetitive inhibition of the N-methyl-D-aspartate subtype of glutamate receptors. Evidence from animal studies shows that exposure of the developing nervous system to N-methyl-D-aspartate antagonists and γ-aminobutyric acid agonists may adversely affect neurologic, cognitive, and social development because of altered neuroapoptosis during periods of rapid synaptogenesis.[7,8] This period in humans extends from midgestation to several years after birth.[7] Studies in rodents and nonhuman primates have identified significant neuroapoptosis and postnatal functional changes after in utero exposure to clinically relevant mixtures of anesthetic drugs that include N_2O. Subanesthetic exposure to individual drugs such as ketamine, propofol, and isoflurane also results in these changes, although subanesthetic exposure to N_2O alone triggered little or no neuroapoptosis in rats.

The human relevance of these drug-induced changes is not clear.[7,8] Recent data suggest exposure to general anesthesia in early infancy may be associated with learning disabilities.[7] However, it is unclear whether the anesthetic per se is the cause of the learning disability, given that anesthesia is always associated with surgery and perhaps systemic illness. Although prospective studies are ongoing,[8] many will take years to complete and may still not definitively answer the question of whether the anesthetic is responsible for the adverse outcome. These studies will not determine whether in utero exposure to N_2O analgesia during labor has adverse short- or long-term effects on children.

Another final safety concern regarding use of N_2O in the childbirth setting is reproductive toxicity secondary to chronic occupational exposure. Waste gas scavenging may be more difficult in a labor ward than in an operating room because it depends on the parturient consciously exhaling through the mask. Although available data do not support toxicity due to occupational exposure to N_2O, no prospective, well-controlled epidemiologic studies exist.[5] One primary limitation to the use of N_2O/O_2 in the obstetric setting has been lack of equipment, including proper scavenging equipment. However, this year, the manufacturer Nitronox has resumed manufacturing and has begun selling the Nitronox delivery system to hospitals and birthing centers.

The Likis et al.[1] study also shows that we need to reassess measures of effectiveness. It seems self-evident that effectiveness of an analgesic agent is measured by the degree of pain relief. Likis et al.[1] noted that N_2O/O_2 is not as effective as epidural analgesia. This is an expected finding, and frankly, it is a comparison that one could argue does not require further study. Labor is a complex physiologic event in which multiple endogenous and exogenous mediators of pain play a role. We are nowhere near understanding this phenomenon in full. The complexity of the labor is underscored by the results of multiple studies of women's experiences. The systematic review of labor satisfaction studies by Hodnett[9] found that personal expectations, caregiver support, quality of caregiver–patient relationship, and involvement in decision making are stronger influences on the childbirth experience than is the type or degree of pain control achieved.[9] Additional studies have validated these findings, including the most recent Listening to Mothers survey.[10] The degree of pain relief achieved during labor is not the most salient component of women's experience of labor and birth.

It is clear from this body of literature that to comprehensively assess the effects of a pain relief technique such as N_2O/O_2, we need tools that assess women's experiences in more depth. As Angle et al.'s[11] work on labor pain relief after neuraxial analgesia indicates, an evaluation of the quality of labor analgesia must include measures of physical, cognitive, and emotional dimensions. This type of assessment is akin to a quality of recovery score in which the quality of postoperative recovery is assessed using a 40-question survey tool with several domains, including emotional state, physical comfort, psychologic support, physical independence, and pain.[12]

One option is to assess a woman's perception of her coping rather than her report of pain reduction on a scale of 0 to 10. Midwives at the University of Utah, Salt Lake City, Utah, have developed a coping scale that has been validated and accepted by The Joint Commission as a replacement for the verbal rating scale for pain in laboring women.[13,14] More importantly, it bypasses the problem of measuring only one component of a multifactorial experience. N_2O labor analgesia would be an ideal subject for studies that use more comprehensive measures of patient outcomes. Because N_2O/O_2 labor analgesia includes a degree of parturient control and

[a]Pubmed search using "nitrous oxide" and limiting the search to "editorials."

autonomy, part of its effectiveness is likely to be secondary to the value of personal control.

Where should we go from here? The systematic review by Likis et al.[1] as well as other reviews suggest that N_2O may be a safe agent to provide analgesia and improve coping and maternal satisfaction during labor. However, to date, there is virtually no good evidence that this is the case. The history of obstetric analgesia has a cycle wherein a new agent is introduced, widely adopted into clinical practice, found to have some adverse effects, and then withdrawn as the search for a new agent begins. Remember Twilight Sleep? This history should not be ignored.

Thus, if we want to use N_2O in the childbirth environment, additional rigorous study is necessary. Studies that assess low-hanging fruit should be done first. These might include rigorous case-controlled or randomized controlled trial(s) in various patient populations and practice environments, using a consistent N_2O dose and delivery system and using a validated tool(s) for maternal outcomes of the labor experience in additional to traditional pain scores. Suggested neonatal outcomes of interest include effects on lactation. Intermediate outcomes might include using umbilical cord blood for measurement of homocysteine[15] and leukocyte DNA damage[6] from mother/baby dyads exposed and not exposed to N_2O.

It may be almost impossible to perform human studies addressing whether in utero exposure to N_2O during labor has adverse effects on the infant central nervous system, although performing these studies in a nonhuman primate model may be helpful. Thus, women who ask to use N_2O/O_2 during labor should be informed that we lack data about this outcome.

Children are our best natural resource. To the best of our ability, we should carefully evaluate any procedures and drugs that might expose them to harm. N_2O for labor analgesia is one such drug.

RECUSE NOTE

Dr. Cynthia Wong is the Section Editor for Obstetric Anesthesiology for the Journal. This manuscript was handled by Dr. Steven L. Shafer, Editor-in-Chief, and Dr. Wong was not involved in any way with the editorial process or decision.

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Nitrous Oxide for the Management of Labor Pain: A Systematic Review

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BACKGROUND: We systematically reviewed evidence addressing the effectiveness of nitrous oxide for the management of labor pain, the influence of nitrous oxide on women's satisfaction with their birth experience and labor pain management, and adverse effects associated with nitrous oxide for labor pain management.

METHODS: We searched the MEDLINE, EMBASE, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases for articles published in English. The study population included pregnant women in labor intending a vaginal birth, birth attendees or health care providers who may be exposed to nitrous oxide during labor, and the fetus/neonate.

RESULTS: We identified a total of 58 publications, representing 59 distinct study populations: 2 studies were of good quality, 11 fair, and 46 poor. Inhalation of nitrous oxide provided less effective pain relief than epidural analgesia, but the quality of studies was predominately poor. The heterogeneous outcomes used to assess women's satisfaction with their birth experience and labor pain management made synthesis of studies difficult. Most maternal adverse effects reported in the literature were unpleasant side effects that affect tolerability, such as nausea, vomiting, dizziness, and drowsiness. Apgar scores in newborns whose mothers used nitrous oxide were not significantly different from those of newborns whose mothers used other labor pain management methods or no analgesia. Evidence about occupational harms and exposure was limited.

CONCLUSIONS: The literature addressing nitrous oxide for the management of labor pain includes few studies of good or fair quality. Further research is needed across all of the areas examined: effectiveness, satisfaction, and adverse effects. (Anesth Analg 2014;118:153–67)

Nitrous oxide is an inhaled anesthetic and analgesic gas commonly used in general anesthesia and dental care. Use of nitrous oxide during labor began in the late 1800s, and equipment for self-administration was introduced by Minnitt in England in 1934.[1] Nitrous oxide in a 50/50 mix with air, administered with a blender device (e.g., Nitronox) or premixed (e.g., Entonox), is the most common concentration of nitrous oxide used for labor pain management. Nitrous oxide is usually self-administered via a facemask or mouthpiece intermittently, beginning approximately 30 seconds before each contraction.[2]

Use of inhaled nitrous oxide for labor pain management is common in several countries. A 2002 systematic review cites evidence that nitrous oxide is used by 50% to 75% of women in the United Kingdom and 60% of women in Finland; use in Australia and New Zealand is also common.[1] Only 5 centers in the United States were known to provide nitrous oxide as an option for labor pain management at the time this review was conducted (J. P. Rooks, MPH, CNM, personal communication).

With widespread use of nitrous oxide during labor in some other countries and increasing interest in this method in the United States, we systematically reviewed the effectiveness of nitrous oxide for the management of labor pain, the influence of nitrous oxide on women's satisfaction with their birth experience and labor pain management, and adverse effects associated with nitrous oxide for labor pain management. Comparators included no analgesic/anesthetic intervention; other inhaled, epidural, or systemic opioid analgesia; paracervical or pudendal nerve block; transcutaneous electrical nerve stimulation; sterile water injections; hydrotherapy; and psychoprophylaxis.

METHODS

Search Strategy

Our searches, executed between July 2010 and July 2011 and not limited by date, included the MEDLINE (via PubMed), Embase, and Cumulative Index to Nursing and Allied Health

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Literature (CINAHL) databases. Searches used both controlled vocabulary and keyword terms representing nitrous oxide and known brand names (such as "nitrous oxide," "laughing gas," and "Entonox") and concepts of obstetric labor, pain, or analgesia (such as "labor pain," "labor, obstetric," "analgesia," "obstetrical," "labor," and "birth"). We excluded ineligible publication types (e.g., letters, editorials), animal or in vitro research, and non-English articles. Detailed search strategies, including complete search terms, search structure, limits, and numbers of results, are available.[3] We also hand searched the reference lists of included studies to identify additional potentially relevant items, and searched grey literature for relevant information, including sources of U.S. regulatory and occupational safety information, theses/dissertations, and meeting abstracts. A complete list of sources is available.[3]

Inclusion Criteria

Studies had to include pregnant women in labor intending a vaginal birth (any parity or risk status) and using nitrous oxide for labor pain management, birth attendees or health care providers who may be exposed to nitrous oxide during labor, and fetuses/neonates. We included studies of any type/design that reported outcomes on at least 20 women.

Study Selection and Data Extraction

Two reviewers separately evaluated abstracts for inclusion. If 1 reviewer concluded that an article could be eligible for the review based on the abstract, we retained it. Full publications were then dually reviewed for final inclusion, with discrepancies resolved by third party adjudication. Two reviewers independently extracted outcomes data, including pain management, satisfaction with pain management, satisfaction with birth experience, and adverse effects associated with the use of nitrous oxide for the management of labor pain, and entered this information into evidence tables.[3] The team evaluating the literature included 3 physicians (2 obstetrician-gynecologists and an anesthesiologist), 2 certified nurse-midwives, 2 health services researchers, and 2 library scientists.

Rating Quality of Individual Studies

We used the Cochrane Risk of Bias tool[4] to assess the quality of randomized controlled trials (RCTs). Fundamental domains include sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting bias. The Newcastle-Ottawa Quality Assessment Scale[5] was used to assess the quality of nonrandomized studies. This scale's 3 broad perspectives include the selection of study groups, the comparability of study groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Four investigators independently assessed the quality of individual studies; the Senior Scientist (JCA) reviewed and resolved any discrepancies. A description of both tools and the thresholds for converting their results to the Agency for Healthcare Research and Quality's standard of "good," "fair," and "poor" quality designations is available.[3]

Evidence Synthesis and Grading Strength of Evidence

Once data extraction and quality assessment were complete, we developed an extended analysis of the research evidence, including text and summary tables.[3] We graded available evidence for each of the following domains: risk of bias, consistency of findings, directness, and precision. We combined the grades of each domain to develop the strength of evidence for each key outcome and assigned one of the following grades: high, moderate, low, or insufficient. Two reviewers independently graded the body of evidence; disagreements were resolved through discussion or a third reviewer adjudication.

RESULTS

We identified 1428 nonduplicate titles or abstracts, with 574 proceeding to full text review (Fig.1). Fifty-eight publications were included in the review; one publication reported on 2 distinct study populations. Thus, there are 59 distinct study populations: 13 RCTs, 7 crossover RCTs, 4 nonrandomized clinical trials, 14 prospective cohorts, 1 retrospective cohort, 3 case series, 4 case-control studies, 11 cross-sectional studies, and 2 trend studies. Tables 1, 2, and 3 provide an overview of included studies; the summary in this section focuses on the studies for which quality was assessed as good or fair. Seven studies of occupational exposure to nitrous oxide[6–12] and 4 studies of outcomes in offspring following maternal nitrous oxide

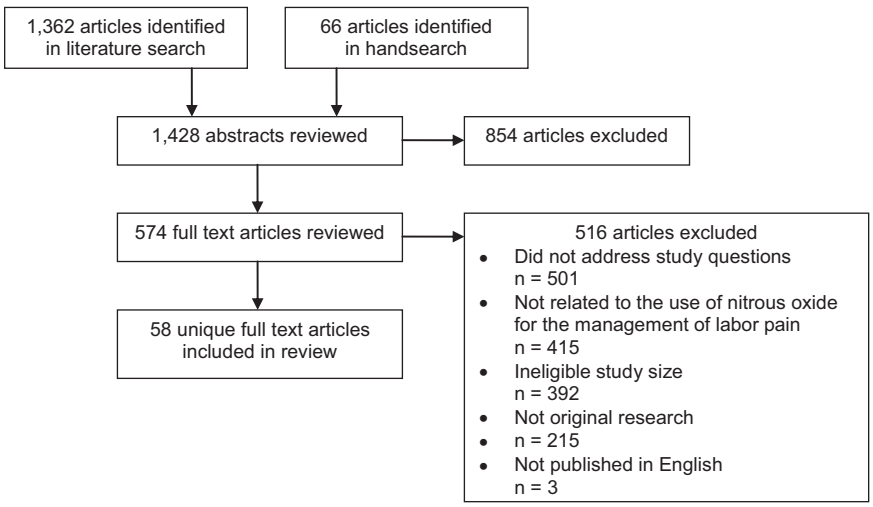

Figure 1. Study selection. Some articles fit multiple exclusion categories.

Table 1. Summary of Randomized Controlled Trials

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Comparator(s)	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
Talebi et al.,[42] 2009, Iran	523	RCT	Poor	50%;self-administered via facemask	50% oxygen	None reported
Yeo et al.,[23] 2007, United Kingdom	32	Crossover RCT	Poor	Entonox (50%); self-administered	0.8% sevoflurane	Effectiveness for labor pain management • Pain relief significantly better with sevoflurane than Entonox in the first ($P = 0.01$) and second ($P < 0.001$) crossovers. • Pain intensity significantly higher with Entonox than sevoflurane in the first crossover ($P = 0.04$) but not different in the second crossover. • 97% of participants preferred sevoflurane over nitrous oxide ($P < 0.001$).
Einarsson et al.,[43] 1996, Sweden	24	RCT	Poor	50%, 70%; administered via mouthpiece	The alternate nitrous oxide mixes were compared (50% vs 70%)[a]	None reported
Abboud et al.,[17] 1995, United States	80	RCT	Poor	30 - 60%; administered by an anesthesiologist	1.0%–4.5% desflurane	Effectiveness for labor pain management • Satisfactory analgesia scores were comparable among women, anesthesiologists, and obstetricians. Satisfaction with labor pain management • The proportion of women who were satisfied or very satisfied with nitrous oxide was not statistically different than desflurane (63% for both).
Carstoniu et al.,[24] 1994, Canada	26	Crossover RCT	Poor	50%; self-administered	Compressed air	Effectiveness for labor pain management • No statistically significant differences in the mean visual analogue scores for pain between the 2 groups.
Arora et al.,[44] 1992, United Kingdom	41	RCT	Fair	Entonox (50%); administration method not reported	Entonox and isoflurane	None reported
Westling et al.,[48] 1992, Sweden	24	Crossover RCT	Poor	40% and 70% (intermittent), 40% (continuous); administered via facemask	Intermittent oxygen, alternate nitrous oxide mixes, intermittent vs continuous	None reported
Chia et al.,[18] 1990, Singapore	121	RCT	Poor	Entonox (50%); administration method not reported	TENS	Effectiveness for labor pain management • Proportion of women randomized to Entonox or TENS who chose a different method because initial method was inadequate was comparable as were pain ratings. • The difference in pain relief with the 2 methods was nonsignificant.

(*Continued*)

Table 1. (*Continued*)

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Comparator(s)	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
Abboud et al.,[19] 1989, United States	60	RCT	Poor	30%–60%	0.7% isoflurane	Effectiveness for labor pain management • Proportion of satisfactory pain scores did not differ significantly between groups among mothers (87% for nitrous oxide, 83% for isoflurane), anesthesiologists (97% for nitrous oxide, 90% for isoflurane), and obstetricians (83% for nitrous oxide, 87% for isoflurane). Satisfaction with labor pain management • The proportion of women who were satisfied or very satisfied with nitrous oxide was not statistically different than isoflurane (87% vs 83%).
Constantine et al.,[45] 1989, United Kingdom	149	RCT	Poor	Entonox (50%); administered via facemask, mouthpiece, or humidifier	The alternate administration methods were compared[a]	None reported
McLeod et al.,[25] 1985, United Kingdom	32	Crossover RCT	Poor	Entonox (50%); administered via facemask	0.75% isoflurane	Effectiveness for labor pain management • Mean pain scores were 63.0 (range 24–92) with Entonox and 46.6 (range 19–86) with isoflurane ($P < 0.001$). • When women asked which agent they preferred at the end of the study, 69% chose isoflurane, 25% chose Entonox, and 6% were undecided.
McGuinness and Rosen,[26] 1984, United Kingdom	20	Crossover RCT	Poor	Entonox (50%); administered by an anesthesiologist via mouthpiece	1% enflurane	Effectiveness for labor pain management • Pain scores with enflurane (median 50, range 13–79) were significantly lower than the scores with nitrous oxide use (median 52, range 29–79, $P < 0.02$).
Abboud et al.,[20] 1981, United States	105	RCT	Poor	30%–60%; administered by an anesthesiologist	0.25%–1.25% enflurane	Effectiveness for labor pain management • Most women had satisfactory analgesia according to scores from the women, anesthesiologists, and obstetricians. • The difference in satisfactory analgesia scores for the 2 gases was significant only for the obstetricians ($P < 0.05$). Satisfaction with labor pain management • The proportion of women who were satisfied or very satisfied with nitrous oxide was not statistically different than enflurane (76% versus 89%).
Rosen et al.,[46] 1972, United Kingdom	250	RCT and prospective cohort	Poor	Entonox (50%); administration method not reported	0.35% methoxyflurane	None reported

(*Continued*)

Table 1. (*Continued*)

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Comparator(s)	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
Bergsjo and Lindbaek,[27] 1971, Norway	63	Crossover RCT	Poor	50%; administered via facemask	0.5%–0.8% methoxyflurane	Effectiveness for labor pain management • After using both, a higher proportion of mothers chose nitrous oxide (63%) than methoxyflurane (35%) with 2% undecided ($P < 0.05$). • Analgesic effect of nitrous oxide (rated by physician): excellent for 8%, good for 82%, moderate for 4%, and poor for none. • Analgesic effect of methoxyflurane (rated by physician): good for 95% and moderate for 5%.
Phillips and Macdonald,[47] 1971, United Kingdom	152	RCT	Poor	Entonox (50%); administration method not reported	Trichloroethylene and meperidine, meperidine only	None reported
NA,[41] 1970, United Kingdom	778	RCT	Fair	50%, 70%; administration method not reported	The alternate nitrous oxide mixes were compared (50% vs 70%)[a]	None reported
Jones et al.,[21] 1969, United Kingdom	50	RCT	Poor	50%; administration method not reported	0.35% methoxyflurane	Effectiveness for labor pain management • Mean proportion of time the anesthetists assessed the women's reactions to contractions as satisfactory was significantly ($P < 0.05$) higher for methoxyflurane (79.3% ± 20%) than nitrous oxide (62.3% ± 30%). • Most midwives and women reported pain relief was complete or considerable.
Jones et al.,[22] 1969, United Kingdom	48	RCT	Poor	0%–80%; administration method not reported	60% methoxyflurane	Effectiveness for labor pain management • Mean proportion of time the anesthetists assessed the women's reactions to contractions as satisfactory did not differ significantly between groups. • Most midwives and women reported pain relief was complete or considerable.

RCT = randomized controlled trial; TENS = transcutaneous electrical nerve stimulation.
[a]Studies that assessed nitrous oxide and no other pain management methods are only included in the adverse effects section.

use[13–16] are not included in the tables but are described in the section on adverse effects.

Effectiveness of Nitrous Oxide for Labor Pain Management

Twenty-one publications representing 22 studies of distinct populations addressed the effectiveness of nitrous oxide for labor pain management (see Tables 1–3). These studies included 6 RCTs,[17–22] 6 crossover RCTs,[18,23–27] 4 cross-sectional studies,[28–31] 2 nonrandomized clinical trials,[32,33] 2 prospective cohort studies,[34,35] 1 case series,[36] and 1 trend study.[37] One study included an RCT and a crossover RCT with 2 distinct populations.[18] Four studies were of fair quality,[28,29,36,37] and 17 were of poor quality.[17–27,30–35]

One study compared nitrous oxide with methoxyflurane, which is no longer used for labor pain management in the United States.[36] Three cross-sectional studies retrospectively assessed the effectiveness of labor pain management methods.[28,29,37] In 1 study, 2482 women completed a questionnaire 2 months after labor and birth that included assessment of their pain management methods as very effective, some effect, or no effect.[37] The proportion of very effective responses for primiparas and multiparas respectively was 84% and 72% for epidural analgesia, 38% and

Table 2. Summary of Nonrandomized Trials and Cohort Studies

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Comparator(s)	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
Stirk et al.,[51] 2002, United Kingdom	115	Prospective cohort	Poor	Entonox (50%); administration method not reported	Diamorphine	None reported
Leong et al.,[38] 2000, Malaysia	118	Prospective cohort	Good	Entonox (50%); administration method not reported	Epidural and bupivacaine and/or fentanyl	Satisfaction with labor pain management • Only 6% of women who had epidural analgesia were not satisfied with their pain relief compared with 46% of women who had Entonox and meperidine.
Arfeen et al.,[52] 1994, United Kingdom	40	Prospective cohort	Poor	Entonox (50%); administration method not reported	Epidural analgesia and bupivacaine	None reported
Ranta et al.,[34] 1994, Finland	1091	Prospective cohort	Poor	50%; administered by an anesthesiologist	Epidural, water block, meperidine, multiple analgesics, no analgesia	Effectiveness for labor pain management • Median pain scores decreased significantly ($P < 0.01$) from preanalgesia values with epidural analgesia and paracervical block and increased significantly ($P < 0.01$) after water block, nitrous oxide, and meperidine. • None of the women who had epidural analgesia rated it as poor ($P < 0.01$ for comparison with other groups) compared with 28% who used nitrous oxide. Satisfaction with labor pain management • 33% of women who chose Entonox rated their pain relief adequacy as good compared with 94% of those who chose epidural analgesia, 60% of those who chose meperidine, 59% of those who chose injections of water in their lower back, and 59% of those who chose paracervical block.
Landon et al.,[53] 1992, United Kingdom	58	Prospective cohort	Poor	Entonox (50%); administration method not reported	No nitrous oxide	None reported
Zelcer et al.,[54] 1989, Australia	75	Prospective cohort	Poor	% not reported, administration method not reported	Epidural, meperidine	None reported
Deckardt et al.,[55] 1987, Germany	55	Prospective cohort	Poor	50%; administration method not reported	Lumbar peridural anesthesia, no analgesic drugs	None reported
Harrison et al.,[35] 1987, Ireland	170	Prospective cohort	Poor	Entonox (50%); self-administered	Epidural, TENS, meperidine, and promazine	Effectiveness for labor pain management • Women and midwives rated epidural analgesia as providing the most pain relief, and meperidine and promazine as providing the least ($P < 0.001$).

(*Continued*)

Table 2. (*Continued*)

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Comparator(s)	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
						Satisfaction with birth experience • Of the women who chose Entonox, 80% would request Entonox again, compared with 88% of women who chose epidural analgesia, 38% of women who chose meperidine and promazine, and 60% of women who chose TENS. Satisfaction with labor pain management • 60% of women who chose Entonox reported pain relief was adequate compared with 90% of women who chose epidural analgesia, 80% of women who chose TENS, and 18% of women who chose meperidine-promazine.
Harrison and Cullen[56] 1986, Ireland	110	Prospective cohort	Poor	Entonox (50%); self-administered	Epidural, meperidine and promazine, TENS, TENS placebo, general anesthesia	None reported
Soyannwo,[57] 1985, Nigeria	150	Prospective cohort	Poor	Entonox (50%); self-administered	Entonox and meperidine or pethilorphan	None reported
Murphy et al.,[59] 1984, United Kingdom	8392	Retrospective cohort	Poor	Entonox (50%); administration method not reported	Epidural, meperidine	None reported
Arthurs et al.,[50] 1979, United Kingdom	49	Prospective cohort	Poor	Entonox (50%); self-administered intermittently via facemask, or continuously via nasal cannula	Facemask and nasal cannula versus facemask only[a]	None reported
Rosen et al.,[32] 1969, United Kingdom	1257	Nonrandomized trial	Poor	Entonox (50%); administration method not reported	0.35%, 0.5% trichloroethylene; 0.35% methoxyflurane	Effectiveness for labor pain management • No significant difference between groups in the women's assessment of their pain relief in interviews immediately after the birth and 2 days later. • Midwives rated pain relief good or excellent more frequently with methoxyflurane (53%, $P < 0.01$) and trichloroethylene (49%, $P < 0.02$) than nitrous oxide (42%).
Beppu,[58] 1968, Japan	667	Prospective cohort	Poor	5%–80%; administration method not reported	Trichloroethylene, halothane	None reported
Smith et al.,[33] 1968, United States	2066	Nonrandomized trial	Poor	25%–50%; administration method not reported	0.2%–0.5% methoxyflurane, 1%–5% cyclopropane, pudendal, spinal	Effectiveness for labor Pain management • Participant and physician pain ratings did not differ significantly across groups.

(*Continued*)

Table 2. (*Continued*)

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Comparator(s)	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
Clark et al.,[36] 1968, United States	94	Nonrandomized trial	Fair	50% oxygen with nitrous oxide and methoxyflurane[b] administered via inhaler	Methoxyflurane	Effectiveness for labor pain management • Proportion of women who had excellent or good pain relief was comparable in both groups.
McAneny and Doughty,[49] 1963, United Kingdom	501	Nonrandomized trial	Poor	50%, 60%, 70%, 75%, 80%; self-administered	Alternate nitrous oxide mixes[a]	None reported

TENS = Transcutaneous electrical nerve stimulation.
[a]Studies that assessed nitrous oxide and no other pain management methods are only included in the adverse effects section.
[b]Nitrous oxide concentration not reported.

49% for nitrous oxide, 39% and 47% for psychoprophylaxis, 41% for both groups for meperidine, 29% and 35% for bath or shower, and 10% and 23% for acupuncture. In a study with 278 women who were interviewed 1 day after giving birth, the proportion who rated their pain as worst imaginable (7 on a 7-point scale) was 86% for nitrous oxide, 46% for bath, 39% for epidural analgesia, 27% for local infiltration, 26% for breathing technique, and 24% for acupuncture.[28] The third study used graphical data from which nitrous oxide results could not be clearly determined.[29]

Effect of Nitrous Oxide on Women's Satisfaction with Their Birth Experience and Labor Pain Management

Nine studies addressed the effect of nitrous oxide on women's satisfaction (Tables 1–3). These studies included 3 RCTs,[17,19,20] 3 prospective cohorts,[34,35,38] and 3 cross-sectional studies.[31,39,40] One study was of good quality,[38] 1 of fair quality,[40] and 7 of poor quality.[17,19,20,31,34,35,39]

One fair quality study assessed women's satisfaction with their birth experience.[40] This cross-sectional study surveyed 1111 women about their birth experience at 2 months postpartum.[40] Of 362 women who had nitrous oxide, 57% reported a positive or very positive birth experience compared with 49% of women who had meperidine (n = 94) and 34% of women who had epidural analgesia (n = 129). One good quality study assessed women's satisfaction with their labor pain management.[38] In this prospective cohort study, only 6% of women who had epidural analgesia were not satisfied with their pain relief compared with 46% of women who had Entonox and meperidine.[38]

Adverse Effects of Nitrous Oxide for Labor Pain Management

Forty-nine publications addressed maternal, fetal, neonatal, and occupational adverse effects related to nitrous oxide for labor. These studies include 12 RCTs,[17,19–22,41–47] 6 crossover RCTs,[23–27,48] 4 case-control studies,[13–16] 4 nonrandomized clinical trials,[32,33,36,49] 13 prospective cohorts,[10,12,34,38,50–58] 1 retrospective cohort,[59] 3 case series,[60–62] 5 cross-sectional studies,[6,7,9,11,63] and 1 trend study.[8] Two were of good quality,[16,38] 7 of fair quality,[6,10–12,36,44,63] and 40 of poor quality.[7–9,13–15,17,19–27,32–34,41–43,45–62]

Maternal Adverse Effects

In 32 studies reporting maternal adverse effects related to nitrous oxide, the most clinically significant and frequently reported harms were nausea, vomiting, dizziness, and drowsiness (Table 4). Historically, nitrous oxide for labor was coadministered with other analgesic, anesthetic, anxiolytic, and sedative drugs in various combinations titrated to induce sedation and amnesia. These co-agents have a significant impact on the rate and degree of adverse effects associated with nitrous oxide for labor analgesia. To maintain consistency with contemporary practice, 13 studies published before 1980 in which nitrous oxide was given in combination with unspecified doses of opioids and sedatives are not included in Table 4.[21,22,27,32,33,36,46,47,49,50,58,62,64]

One fair quality study of nitrous oxide as a sole drug reported nausea and vomiting in 13% (95% confidence interval [CI], 9–19) of women.[63] In 2 fair quality studies with nitrous oxide as a sole drug,[44,63] the incidence of dizziness was 3% to 5% (95% CI, 0.1–15). In another fair quality study, the incidence of drowsiness incidence was 4%, reduced awareness of experience was 18%, and mask phobia was 5% with nitrous oxide used as a sole drug.[63] No good or fair quality but several poor quality studies reported data on unconsciousness,[21,32,41,48–50,57,60] amnesia or hazy memory of labor or birth,[17,19–22,33,41,49,50] hypoxia and/or maternal oxygen saturation,[23,24,43,52,54,55,61] diffusion hypoxia,[24,43,50] restlessness,[21,22,32,41,49,50] dreams,[21,22,41,49,50] dry mouth or nose,[27,42,45,50] tingling or pins and needles,[42,45] numbness,[27] paresthesias,[50] bothersome smell,[22,27] euphoria,[27] hiccups,[27] inactivation of methionine synthase,[53] and effects on maternal circulation.[48]

Fetal and Neonatal Adverse Effects

Twenty-nine studies reported fetal and neonatal adverse effects. The most clinically significant and frequently reported outcomes were umbilical cord blood gases and Apgar scores. In a good quality study comparing nitrous oxide and meperidine with epidural analgesia, there were no statistically significant differences in Apgar scores or special care nursery

Table 3. Summary of Other Study Designs

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Other pain management method(s) assessed	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
Waldenström and Irestedt,[37] 2006, Sweden	2482	Trend	Fair	% not reported; administration method not reported[a]	Epidural block, meperidine, paracervical block, pudendal block	Effectiveness for labor pain management • Women completed a questionnaire 2 months after their births that included assessment of their pain management methods as very effective, some effect, or no effect. • Epidural analgesia had the highest proportion highest proportion of very effective responses (84% for primiparas, 72% for multiparas) followed by nitrous oxide (38% primiparas, 49% multiparas), psychoprophylaxis (39% primiparas, 47% multiparas), meperidine (41% primiparas and multiparas), bath or shower (29% primiparas, 35% multiparas), and acupuncture (10% primiparas, 23% multiparas).
Henry and Nand,[39] 2004, Australia	496	Cross-sectional	Poor	% not reported; administration method not reported	Meperidine, epidural, local anesthesia, nonpharmacological methods	Satisfaction with labor pain management • 30% of women who chose nitrous oxide were very satisfied with the relief of pain, compared with 49% of those who chose epidural analgesia.
Paech,[63] 1991, Australia	1000	Cross-sectional	Fair	% not reported; administration method not reported	Epidural, meperidine, nonpharmacological (alone and in combination)	None reported
Ross et al.,[60] 1999, United Kingdom	221	Case series	Poor	Entonox (50%) with isoflurane; administration method not reported	None	None reported
Waldenström,[40] 1999, Sweden	1148	Cross-sectional	Fair	Entonox (50%); administration method not reported	Epidural, meperidine	Satisfaction with birth experience • Of women who had nitrous oxide, 57% reported a positive or very positive birth experience compared with 49% of women who had meperidine and 34% of women who had epidural analgesia.
Waldenström et al.,[28] 1996, Sweden	385	Cross-sectional	Fair	Entonox (50%); administration method not reported	Epidural, local anesthesia, acupuncture, bath, breathing techniques	Effectiveness for labor pain management • Proportion who rated their pain as worst imaginable (7 on a 7-point scale) was highest for nitrous oxide (86%) followed by bath (46%), epidural analgesia (39%), local infiltration (27%), breathing technique (26%), and acupuncture (24%).
Ranta et al.,[29] 1995, Finland	1091	Cross-sectional	Fair	50%; administered via facemask	Epidural, meperidine, paracervical block, bupivacaine	Effectiveness for labor pain management • Reported graphical data from which nitrous oxide results could not be clearly determined.

(*Continued*)

Table 3. (*Continued*)

Study, country	Total *N*	Study type	Quality	Nitrous oxide mix and administration method	Other pain management method(s) assessed	Primary outcomes for effectiveness of nitrous oxide for labor pain management and effect of nitrous oxide on women's satisfaction with their birth experience and labor pain management
Reed et al.,[61] 1989, United Kingdom	41	Case series	Poor	Entonox (50%); administration method not reported	Meperidine	None reported
Morgan et al.,[30] 1982, United Kingdom	1000	Cross-sectional	Poor	Entonox (50%); self-administered	Epidural, meperidine, pudendal block	Effectiveness for labor pain management • Women who had epidural analgesia had the lowest mean (± SD) pain score (29 ± 3.7) followed by meperidine plus epidural analgesia (30 ± 3.8), epidural analgesia plus Entonox (51 ± 4.2), meperidine plus Entonox (57 ± 3.4), meperidine (58 ± 3.1), Entonox (61 ± 3.1), pudendal block (68 ± 1.9), miscellaneous (69 ± 3.3), and no analgesia (70 ± 2.6).
Holdcroft and Morgan,[31] 1974, United Kingdom	705	Cross-sectional	Poor	Entonox (50%); administration method not reported	Entonox and meperidine, meperidine only	Effectiveness for labor pain management • When nitrous oxide was compared with meperidine, more women had complete (4% vs 0) or satisfactory (46% vs 22%) pain relief with nitrous oxide. • Nearly half of the women who used meperidine reported no pain relief compared with one-third of the women who used nitrous oxide. Satisfaction with labor pain management • 50% of women who received Entonox reported satisfactory or complete pain relief compared with 22% of those receiving meperidine alone.
Marx et al.,[62] 1970, United States	40	Case series	Poor	50%–70%; administered via facemask	None	None reported

[a]Survey of the prevalence of pain management methods.

admission rates between the 2 groups, and no newborn had an Apgar score lower than 7 at 5 minutes (95% CI, 0%–4%).[38] One fair quality study that reported umbilical cord blood gases and Apgar score data had unspecified coadministration of opioids, pudendal nerve block, or spinal or lumbar epidural in all groups.[36] No good or fair quality studies reported fetal resuscitation,[57,60] asphyxia,[58] depressed neonates,[20] sleepy neonates,[58] prolonged time to sustained respiration,[62] treatment for apnea,[60]or neurobehavioral status.[17,19,56,58]

Long-term offspring outcomes were addressed in 4 retrospective case-control studies;[13–16] no prospective studies were identified. One of these 4 studies was of good quality; the multivariate odds ratio for childhood leukemias after *in utero* exposure to nitrous oxide was 1.3 (95% CI, 1.0–1.6). These results may be coincidental because the increased odd ratios was not observed in all subgroups (e.g., the odds ratio was increased for boys but not girls).[16]

Occupational Exposure

Occupational exposure in labor and birth settings was addressed in 7 studies.[6–12] Three studies of poor quality examined occupational exposure-related adverse effects in midwives.[7–9] The measurement of nitrous oxide exposure is addressed in 4 fair quality studies, which report nitrous oxide levels but not specific adverse effects.[6,10–12] A study in the United Kingdom collected data on midwives wearing exposure badges for 242 shifts (each 7.5–11 hours) in labor wards without scavenging and with standard room ventilation only.[12] Midwives had exposure greater than 100 ppm (the Swedish occupational exposure limit) during 23% of shifts and >25 ppm (the U.S. limit) during 53% of shifts. An evaluation of scavenging systems in Swedish labor wards found a 4-fold reduction in nitrous oxide levels with use of efficient scavenging systems. Nitrous oxide concentrations in diffusive air samplers varied from 2.5 to 260 mg/m^3, and mean

Table 4. Clinically Relevant and Frequently Reported Maternal Adverse Effects Associated with Nitrous Oxide Use During Labor

Author, y, country, study type	Intervention (*N*)	Nausea (%)	Vomiting (%)	Dizziness (%)	Drowsiness (%)
Talebi et al.,[42] 2009, Iran, RCT	50% nitrous in oxygen (260)	8	2	23	8
	50% oxygen (249)	0	0	0	0
Arora et al.,[44] 1992, United Kingdom, RCT	Entonox (39)	NR	NR	3	NR
	Entonox and 0.25% isoflurane (39)	5	NR	10	NR
Constantine et al.,[45] 1989, United Kingdom, RCT	Entonox, via mask (49)[a]	45	NR	NR	NR
	Entonox, via mask and humidifier (36)[a]	25	NR	NR	NR
	Entonox, via mouthpiece (37)[a]	36	NR	NR	NR
	Entonox, via mouthpiece and humidifier (27)[a]	41	NR	NR	NR
Yeo et al.,[23] 2007, United Kingdom, Crossover RCT	Entonox (22)	28	14	NR	0
	Sevoflurane (22)	3	0	NR	0
Westling et al.,[48] 1992, Sweden, Crossover RCT	40% nitrous oxide in oxygen, intermittent (24)	0	0	NR	NR
	70% nitrous oxide in oxygen, intermittent (24)	0	0	NR	NR
	40% nitrous oxide in oxygen, continuous (24)	4	0	NR	NR
	Oxygen, intermittent (24)	0	0	NR	NR
McGuinness et al.,[26] 1984, United Kingdom, Crossover RCT	50% nitrous in oxygen (20)	5	NR	NR	NR
Paech,[63] 1991, Australia, Cross-sectional	Nitrous oxide (220)	13[b]	13[b]	5	4
	Epidural (112)	14[b]	14[b]	0	0
	Meperidine (83)	16[b]	16[b]	6	11
	Nonpharmacological (140)	0	0	0	0
	Enflurane in air (20)	15	NR	NR	NR
McLeod et al.,[25] 1985, United Kingdom, Prospective cohort	50% nitrous oxide in oxygen (32)	3	NR	6	More drowsy with Entonox: 10
	0.75% Isoflurane in oxygen (32)	3	NR	0	More drowsy with isoflurane: 58
Abboud et al.,[20] 1981, United States, RCT	30%–60% nitrous in oxygen (50)[c]	NR	2	NR	NR
	0.25%–1.25% Enflurane in oxygen (55)[c]	NR	0	NR	NR
Soyannwo,[57] 1985, Nigeria, Prospective cohort	Entonox (114)	NR	4[d]	NR	Mild: 67 Moderate: 31 Severe: 2
	Entonox with 100 mg meperidine or pethilorphan (36)	NR	4[d]	NR	Mild: 56 Moderate: 44 Severe: 0.0

Studies are grouped by drug(s) administered. Studies of nitrous oxide as a sole drug are listed first, followed by nitrous/opioid, nitrous/other anesthetic, nitrous/opioid/sedatives, and nitrous/other anesthetic gases/opioids/sedatives or combinations thereof. Within each drug designation, randomized controlled trials are listed first followed by nonrandomized clinical trials and observational studies, and each group of study type is in reverse chronological order. Studies published before 1980 are not included in this table. Numerous studies did not provide the *N* for these outcomes; therefore, only percentages are reported in this table.

[a]Some patients used meperidine.

[b]Nausea and vomiting results combined.

[c]Some patients used additional meperidine or alphaprodine.

[d]Results combined for entire study population.

Table 5. Strength of Evidence for Nitrous Oxide for the Management of Labor Pain

Total studies (total participants)	Domains pertaining to strength of evidence[a]				Strength of evidence[b]
	Risk of bias	Consistency	Directness	Precision	
Effectiveness of nitrous oxide versus other, nonepidural labor pain management methods for the management of labor pain					
22 (15,991)	High	Inconsistent	Indirect	Imprecise	Insufficient; includes 6 RCTs; 4 studies of fair quality and 18 studies of poor quality total
Equivalence or superiority of nitrous oxide versus other labor pain management methods for women's satisfaction with their birth experience					
2 (1303)	High	Consistent	Direct	Imprecise	Low; includes no RCTs; 1 study of fair quality and 1 study of poor quality total
Equivalence or superiority of nitrous oxide versus other labor pain management methods for women's satisfaction with their pain management					
8 (2825)	High	Consistent	Direct	Imprecise	Low; includes 2 RCTs; 1 study of good quality and 7 studies of poor quality total
Adverse effects associated with nitrous oxide for the management of labor pain are primarily unpleasant side effects that affect tolerability (KQ4)					
48 (27,530)[c]	High	Consistent	Direct	Imprecise	Moderate; includes 18 RCTS; 2 studies of good quality, 6 studies of fair quality, and 40 studies of poor quality total

RCT = randomized controlled trials.

[a]Domains pertaining to strength of evidence are taken for the Agency for Healthcare Research and Quality Methods Guide.[65]

[b]High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates. Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate. Insufficient: Evidence is either unavailable or does not permit a conclusion. When no studies were available for an outcome or comparison of interest, we assessed the evidence as insufficient. Two reviewers independently graded the body of evidence; disagreements were resolved through discussion or a third reviewer adjudication.

[c]One study did not provide an *N* and is not included in this calculation.[12]

8-hour time weighted averages were 17 mg/m^3 for midwives and 42 mg/m^3 for assistant midwives, respectively.[10] The 8-hour time weighted averages exceeded the American Conference of Industrial Hygienists' average threshold limit value (50 ppm or 90 mg/m^3) in 16% of midwives and 45% of assistant midwives. The authors attribute these differences to the fact that assistant midwives have a longer average exposure time and are also working more closely with women earlier in labor when nitrous oxide is used more frequently.[10]

Another study in the United Kingdom correlated nitrous oxide exposure to urine nitrous oxide levels in a descriptive study of unscavenged and poorly ventilated delivery suites.[6] Environmental levels exceeded 100 ppm over 8-hour time weighted averages in 35 of 46 midwife shifts monitored. Notably, 22 of 46 midwives had nonzero baseline values of nitrous oxide in their urine, which the authors propose may indicate tissue clearance occurs over a longer time period than previously thought.

Newton et al.[11] evaluated 8-hour time weighted average nitrous oxide exposure (in ppm) for 15 midwives at a newly built hospital in the United Kingdom with a ventilation system incorporating 6 to 10 air changes per hour, comparing the results with historical data from an older building in which there was no ventilation (Entonox machines were unscavenged in both hospitals). Nitrous oxide levels in the new hospital were significantly lower, and none of the 15 midwives in the new hospital was exposed to levels of nitrous oxide greater than 100 ppm. Six of the 15 midwives were exposed to levels of nitrous oxide >25 ppm (the U.S. limit).

DISCUSSION

Fifty-nine distinct studies reported in 58 publications met our review criteria: 2 of good quality; 11 fair; and 46 poor. One-third of the studies are RCTs, 7% are clinical trials without clear evidence of randomization, and the majority is observational research. Overall, the strength of the evidence was insufficient for effectiveness in managing labor pain, low for satisfaction, and moderate for harms (Table 5). Deficiencies in the strength of evidence most often related to a preponderance of study designs with a high risk of bias, inconsistent findings across studies and inconsistencies among outcomes that would be expected to show corresponding benefit, use of intermediate outcomes, and studies with poor precision.

Twenty-one studies that addressed the effectiveness of nitrous oxide using some measurement of pain or pain relief varied in many aspects including the concentration of nitrous oxide and frequency (continuous versus intermittent) administered, additional pain management methods used, and methods and persons (i.e., women, obstetricians, midwives, and anesthesia providers) assessing pain and pain relief. The substantial variation in timing of assessment may have affected the reported outcomes because women's opinions about pain relief change with time lapsed after birth.[21,22,32] Most of the effectiveness studies (12 of 21) had as comparators other inhaled anesthetic gases that are no longer used to manage labor pain. Only 1 study compared nitrous oxide with placebo and found no significant difference in pain scores.[24] Epidural analgesia provided more effective pain relief than nitrous oxide. These studies are unable to demonstrate whether nitrous provided adequate pain relief for women who knowingly accept less effective pain relief in exchange for increased mobility and less intervention and monitoring. In addition, it may be counterproductive to evaluate pain scores, which require focusing on the level of pain, in women using nitrous oxide, which is intended to produce dissociation from pain. Generally speaking, therefore, pain relief is likely to be an inadequate measure of effectiveness for nitrous oxide in the absence of other outcomes such as women's satisfaction.

In 9 studies that addressed women's satisfaction with their birth experience or pain management, measurements of satisfaction were not uniform, making it impossible to synthesize findings. Satisfaction may be a more relevant measure of effectiveness than assessment of pain because nitrous oxide is not intended to provide complete pain relief.

Of 49 studies reporting adverse effects, one-third (n = 16) were conducted before 1980 when nitrous oxide was often used in combination with sedatives and other inhaled anesthetics in labor, a largely abandoned practice. Studies reporting harms associated with sedative analgesic regimens may not translate effectively to contemporary labor analgesia practice. For example, in older studies, amnesia in labor was considered to be a positive outcome.

Most maternal adverse effects reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness). Some maternal adverse effects of analgesia (e.g., nausea) are common in all laboring women regardless of whether analgesia is used. Study sizes were inadequate to assess unusual or rare harms that might be more serious in terms of morbidity.

Nitrous oxide is transmitted via the placenta and is rapidly eliminated by the neonate after birth once breathing begins. Apgar scores in newborns whose mothers used nitrous oxide did not differ significantly from those of newborns whose mothers used other labor pain management methods or no analgesia. Follow-up of newborns was short, most frequently lasting only to birth or discharge of the neonate from the hospital.

Limited data on occupational adverse effects are available, thus drawing conclusions regarding potential occupational harms of exposure is difficult. Evidence about occupational levels of nitrous oxide is limited, and some studies were conducted before the use of room ventilation systems or scavenging systems. The implementation of these systems in clinical practice appears to reduce occupational exposure, which should in turn mitigate potential risks of exposure.

Nitrous oxide provides analgesia, decreases women's perception of pain, and has an anxiolytic effect that may be helpful if women are restless or doubt their ability to cope as commonly occurs near the end of the first stage of labor.[2] Although nitrous oxide is not as effective for pain relief as epidural analgesia, nitrous oxide has other benefits including that it is inexpensive and noninvasive. Nitrous oxide has a rapid onset and offset. Women who do not like nitrous oxide or find it inadequate for pain management can easily discontinue its use and switch to another method for pain management, unlike the prolonged effects of epidural analgesia and systemic opioids that diminish gradually over a much longer time period. Nitrous oxide preserves mobility and does not require additional monitoring and potential anesthesia-related interventions (e.g., bladder catheterization). Women self-administer nitrous oxide, which allows them to control the amount they need.[2] Nitrous oxide may not be an ideal method for women who want maximum pain relief but may

Table 6. Priorities for Future Research

Methodologic Priorities

- Clearly documenting the mix of nitrous oxide used and the timing and mode of administration.
- Performing studies that use doses and equipment consistent with contemporary U.S. maternity care.
- Developing outcome measures that assess effectiveness as defined by women choosing nitrous oxide (e.g., adequate pain relief may be a more meaningful measure than pain scores because nitrous oxide is not expected to relieve pain completely).
- Using standardized and validated outcome measures to assess pain and women's satisfaction.
- Including women's assessment of pain, rather than only providers', in all studies that report this outcome.
- Performing qualitative research in addition to quantitative studies.
- Conducting sequential analysis trials in which women can opt-in and opt-out of nitrous oxide.
- Conducting studies in out-of-hospital birth settings (i.e., freestanding birth centers and home births).
- Building consensus about critical maternal, fetal, neonatal, childhood, and occupational exposure outcomes, developing a minimal core data set for future research.
- Designing human studies that examine apoptosis, which has been observed in rodents exposed to high doses of systemic anesthetics.
- Developing electronic medical record approaches to long-term surveillance for adverse effects.

Priorities for Clinical Care

- Exploring antianxiety effects of nitrous oxide during labor.
- Examining the influence of nitrous oxide on whether and when women choose to use other labor pain management methods.
- Investigating the impact of nitrous oxide on use of cointerventions, route of birth, maternal-newborn bonding, and breastfeeding.
- Assessing fetal/neonatal clearance of nitrous oxide.
- Determining optimal methods for minimizing occupational exposures, such as room ventilation and scavenging measures.
- Assessing potential occupational harms, including nitrous oxide abuse and addiction.
- Identifying health system factors influencing the use of nitrous oxide for the management of labor pain, including but not limited to provider preferences, availability, setting, and resource utilization.
- Determining provider and patient education needed for nitrous oxide use in labor.
- Analyzing cost effectiveness of nitrous oxide and other labor pain management methods.

be preferable to other pharmacologic pain management methods for women who want increased mobility with less intervention and monitoring. Nitrous oxide can also be useful when a woman wants to delay use of epidural analgesia until later in labor, when epidural analgesia is not immediately available (e.g., in hospitals that do not have 24-hour anesthesia service), when a woman arrives at the hospital too late in labor to allow for epidural analgesia to be placed and take effect, or when epidural analgesia is ineffective or inadequate.

In summary, the literature addressing nitrous oxide for the management of labor pain includes few studies of good or fair quality. Suggested priorities for future research are identified in Table 6. Research assessing nitrous oxide is needed across all of the areas examined: effectiveness, satisfaction, and adverse effects.

DISCLOSURES

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