



# Effective Health Care Program

## Nitrous Oxide for the Management of Labor Pain

### Executive Summary

#### Background

More than 4 million births occur in the United States each year; in 2008, there were 4,247,694 births.<sup>1</sup> The most commonly used labor pain management method in the United States is epidural analgesia (hereafter epidural).<sup>2</sup> Use of inhaled nitrous oxide is a common option for labor pain management in several countries outside the United States, including the United Kingdom, Finland, Sweden, Canada, Australia, and New Zealand. Only five centers in the United States are known to currently provide nitrous oxide as an option for labor pain management: the Birth Center at the University of California San Francisco Medical Center; the University of Washington Hospital in Seattle; St. Joseph Regional Medical Center in Lewiston, ID; Okanogan Douglas Hospital in Brewster, WA; and Vanderbilt University Medical Center in Nashville, TN (which began offering nitrous oxide in June 2011 after this review was under way). A significant barrier to use in the United States is limited availability of equipment to blend and deliver a mixture of nitrous oxide and oxygen for self-administration by laboring women.

#### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

Nitrous oxide, sometimes called “laughing gas” because it can produce euphoria, is

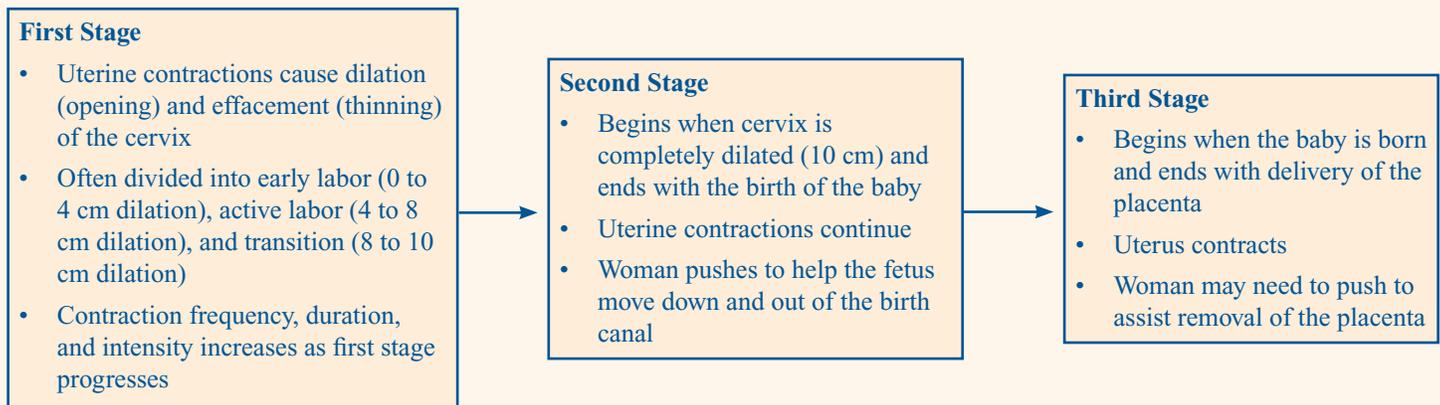


an inhalational anesthetic and analgesic gas. Nitrous oxide has been used in dental care since the mid-1800s<sup>3</sup> and is commonly used for this indication today. Use of nitrous oxide during labor began in the late 1800s, and equipment for self-administration was introduced by Minnitt in England in 1934.<sup>4</sup>

The mechanism of action of nitrous oxide is thought to be an increased release of endorphin, dopamine, and other natural pain relievers in the brain, which modulate pain

stimuli via descending spinal cord nerve pathways. Nitrous oxide does not completely relieve the pain of labor but creates “diminished pain, or a continued awareness of pain without feeling bothered by it.”<sup>5</sup> Nitrous oxide also has an antianxiety effect, which may be helpful if laboring women are restless and doubt their ability to cope, emotions that are not uncommon, especially during transition (see Figure A for an overview of the stages of labor).

**Figure A. Stages of labor**



The most common concentration of nitrous oxide administration for labor pain management in the biomedical literature and in current clinical practice is 50 percent nitrous oxide in oxygen, which can be mixed from two separate gas sources with a blender device (e.g., Nitronox<sup>®</sup>) or premixed in a single cylinder (e.g., Entonox<sup>®</sup>). Nitrous oxide is usually self-administered via a facemask or mouthpiece on an intermittent basis, beginning about 30 to 60 seconds before each contraction.<sup>6</sup>

A variety of pain management methods were described in studies in this review (Table A). Epidural analgesia is the most commonly used method in the United States and may block pain entirely. Although epidurals are more effective for pain relief than other pain management methods, epidurals are associated with increased risk of assisted (vacuum or forceps) vaginal birth, use of oxytocin, maternal hypotension, motor blockade, urinary retention, maternal fever, and cesarean for maternal distress.<sup>7</sup> Women who have epidurals must have additional monitoring and may need confinement to bed, which limits mobility and options for positioning, and placement of a Foley catheter.

Although nitrous oxide would not be expected to be as effective for analgesia as an epidural because of the differences in their mechanism of action, nitrous oxide has other benefits, including its lower cost and less invasive nature. Nitrous oxide has a rapid onset and end of action. Thus women who do not like nitrous oxide or find it inadequate for pain management can easily discontinue its use and switch to another method, unlike epidurals and systemic opioids, which diminish gradually over a much longer period. Mobility and options for positioning are not limited and nitrous oxide 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.<sup>8</sup> Nitrous oxide may not be an ideal method for women who want maximum pain relief, but it could be preferable to other pharmacologic pain management methods for women who want increased mobility with less intervention and monitoring. Nitrous oxide might also be useful when a woman wants to delay use of epidural anesthesia until later in labor, when epidural anesthesia is not immediately available (e.g., in hospitals that do not have in-house anesthesia staff and must call in an

anesthesia provider), when a woman arrives at the hospital too far along in labor to allow for an epidural to be placed and take effect, and when a woman finds epidural analgesia ineffective or inadequate.

One concern with nitrous oxide use is the potential for the gas to escape into the room and potentially affect health care workers as well as other individuals present with laboring women. For this reason, multiple organizations are responsible for regulating the use of nitrous oxide, and factors other than clinical outcomes are important to decisionmaking about its use (Appendix F). Room ventilation systems and scavenging systems that remove waste gases are used to reduce exposure to caregivers and

others present for labor. Equipment capable of scavenging provides constant negative pressure so that the woman’s exhalations, which contain nitrous oxide, are captured and removed from the room and facility.<sup>6</sup>

Finding the appropriate measure of effectiveness on which to assess nitrous oxide with other pain management methods is challenging. Nitrous oxide is not intended to provide the extent of pain relief expected with epidural. Therefore, rather than a direct comparison of effectiveness, the more important questions are whether women are satisfied with the use of nitrous oxide for labor pain management and if it is safe for the woman and her fetus/newborn.

**Table A. Labor pain management methods used in studies included in this review**

<b>Method</b>	<b>Description</b>	<b>Timing and Frequency of Administration</b>
Nitrous oxide	<ul style="list-style-type: none"> <li>Anesthetic and analgesic gas usually inhaled intermittently via a facemask or mouthpiece, can be given continuously via nasal cannula</li> <li>Reduces the perception of pain, alters consciousness, decreases anxiety</li> </ul>	<ul style="list-style-type: none"> <li>Can be used for first- and second-stage labor pain</li> <li>Self-administered between and/or during contractions</li> <li>May be continued into third stage if procedures, such as perineal repair or manual removal of the placenta, are needed</li> </ul>
Other inhalational anesthetic gases (desflurane, sevoflurane, isoflurane, enflurane, methoxyflurane, trichloroethylene, cyclopropane)	<ul style="list-style-type: none"> <li>Anesthetic gas usually inhaled intermittently via a facemask or mouthpiece, can be given continuously via nasal cannula</li> <li>Reduces the perception of pain, alters consciousness</li> </ul>	<ul style="list-style-type: none"> <li>None is used currently used for management of labor pain in the United States</li> <li>Desflurane, sevoflurane, and isoflurane are used for other types of anesthesia in the United States</li> </ul>
Epidural	<ul style="list-style-type: none"> <li>Injection of medications (usually a combination of local anesthetic and opioid) into the epidural space around the spinal cord</li> <li>Blocks pain in lower half of body May partially or fully block voluntary motor control in lower half of body</li> </ul>	<ul style="list-style-type: none"> <li>Initiated during first stage of labor with infusion usually continuing into second stage</li> <li>May be continued into third stage if procedures, such as perineal repair or manual removal of the placenta, are needed</li> </ul>
Opioids (for example, pethidine/meperidine)	<ul style="list-style-type: none"> <li>Medication given intravenously or by intramuscular injection</li> <li>Provides some relief of labor pain and causes sedation, which can also alter perception of pain</li> <li>Opioids commonly used in labor include meperidine/pethidine, morphine, fentanyl, remifentanyl, butorphanol, and nalbuphine</li> </ul>	<ul style="list-style-type: none"> <li>Used during the first stage of labor Administered at regular intervals as needed for pain (usually every 1 to 4 hours depending on specific medication)</li> </ul>

**Table A. Labor pain management methods used in studies included in this review (continued)**

<b>Method</b>	<b>Description</b>	<b>Timing and Frequency of Administration</b>
Paracervical block	<ul style="list-style-type: none"><li>• Injection of local anesthetic at lateral cervix</li><li>• Provides some relief from the pain of cervical dilation</li></ul>	<ul style="list-style-type: none"><li>• Rarely used in the United States because it causes fetal bradycardia (slow heart rate)</li><li>• Used during the first stage of labor Can be repeated</li></ul>
Pudendal block	<ul style="list-style-type: none"><li>• Injection of local anesthetic in the vaginal wall near the pudendal nerves, bilaterally</li><li>• Relieves pain in the lower vagina, perineum, and external genitalia that occur when the woman is pushing</li></ul>	<ul style="list-style-type: none"><li>• Used during the second stage of labor Administered once</li></ul>
Transcutaneous electrical nerve stimulation (TENS)	<ul style="list-style-type: none"><li>• Low-voltage electrical impulses are sent from a handheld device controlled by the woman to electrodes placed on the skin of the lower back</li></ul>	<ul style="list-style-type: none"><li>• Used during the first stage of labor Used as needed</li></ul>
Sterile water injections	<ul style="list-style-type: none"><li>• Injection of sterile water intradermally (just below the skin) in four locations on the lower back</li></ul>	<ul style="list-style-type: none"><li>• Used during the first stage of labor, most commonly for low back pain Can be repeated</li></ul>
Hydrotherapy	<ul style="list-style-type: none"><li>• Immersion of the laboring woman in water</li></ul>	<ul style="list-style-type: none"><li>• Can be used during the first and second stages of labor Used as needed</li></ul>
Psychoprophylaxis	<ul style="list-style-type: none"><li>• Use of breathing and relaxation techniques taught during pregnancy</li></ul>	<ul style="list-style-type: none"><li>• Can be used during the first and second stages of labor Used as needed</li></ul>

## Scope of this Report

Most women in the United States use some type of medication for labor pain management. However, the option of using nitrous oxide to relieve labor pain is limited by its lack of availability. Use of nitrous oxide during labor is common in other countries, increasing interest in this method in the United States, in part because it is less expensive and invasive than widely used regional anesthesia. This review attempts to assess the effectiveness of nitrous oxide in managing labor pain and to identify potential factors that may influence its availability and use within the United States. Our Key Questions have been structured with this goal in mind. The primary questions include the comparative effectiveness of nitrous oxide for the management of labor pain, the influence of nitrous oxide on women's satisfaction with their birth experience, the health system factors influencing its use within the United States, and any adverse effects associated with this intervention. With the rate of cesarean birth continuing to rise—32.3 percent of all U.S. births reported in 2008<sup>1</sup>—it is also important to address whether the use of nitrous oxide during labor influences the route of birth in women initially intending a vaginal birth.

## Objectives

### Population

We focused this review on pregnant women in first and second stages of labor, other attendees and health care providers present during labor, and the fetus/neonate.

### Intervention(s)

We examined the use of nitrous oxide for the management of labor pain.

### Comparators

We compared nitrous oxide with the following pain management methods: no analgesic/anesthetic intervention, other inhalational anesthetic gases, epidural, opioids, paracervical block, pudendal block, transcutaneous electrical nerve stimulation (TENS), sterile water injections, hydrotherapy, and psychoprophylaxis (see Table A).

### Outcomes

Our primary outcomes included pain management, satisfaction with pain management, satisfaction with birth experience, effect of nitrous oxide on the route of birth,

adverse effects associated with the use of nitrous oxide for the management of labor pain, and health system factors associated with the use of nitrous oxide for the management of labor pain.

### Timing

Intermediate outcomes include associated labor outcomes, while long-term outcomes include associated birth outcomes. We did not place a restriction of the duration of followup.

### Setting

We considered all birth settings, including hospital, birth center, and home.

## Key Questions

1. What is the effectiveness of nitrous oxide when compared with other methods for the management of labor pain among women intending a vaginal birth?
2. What is the comparative effectiveness of nitrous oxide on women's satisfaction with their birth experience and pain management?
3. What is the comparative effectiveness of nitrous oxide on the route of birth?
4. What is the nature and frequency of adverse effects associated with the use of nitrous oxide for the management of labor pain, including but not limited to:
  - Maternal adverse effects, such as nausea and vomiting, dizziness, unconsciousness, and postpartum complications.
  - Fetal/neonatal adverse effects, such as low Apgar scores and abnormal fetal cord blood gases.
  - Childhood adverse effects, such as drug dependency and developmental complications.
  - Adverse effects on health care providers and other individuals present for labor.
5. What are the 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?

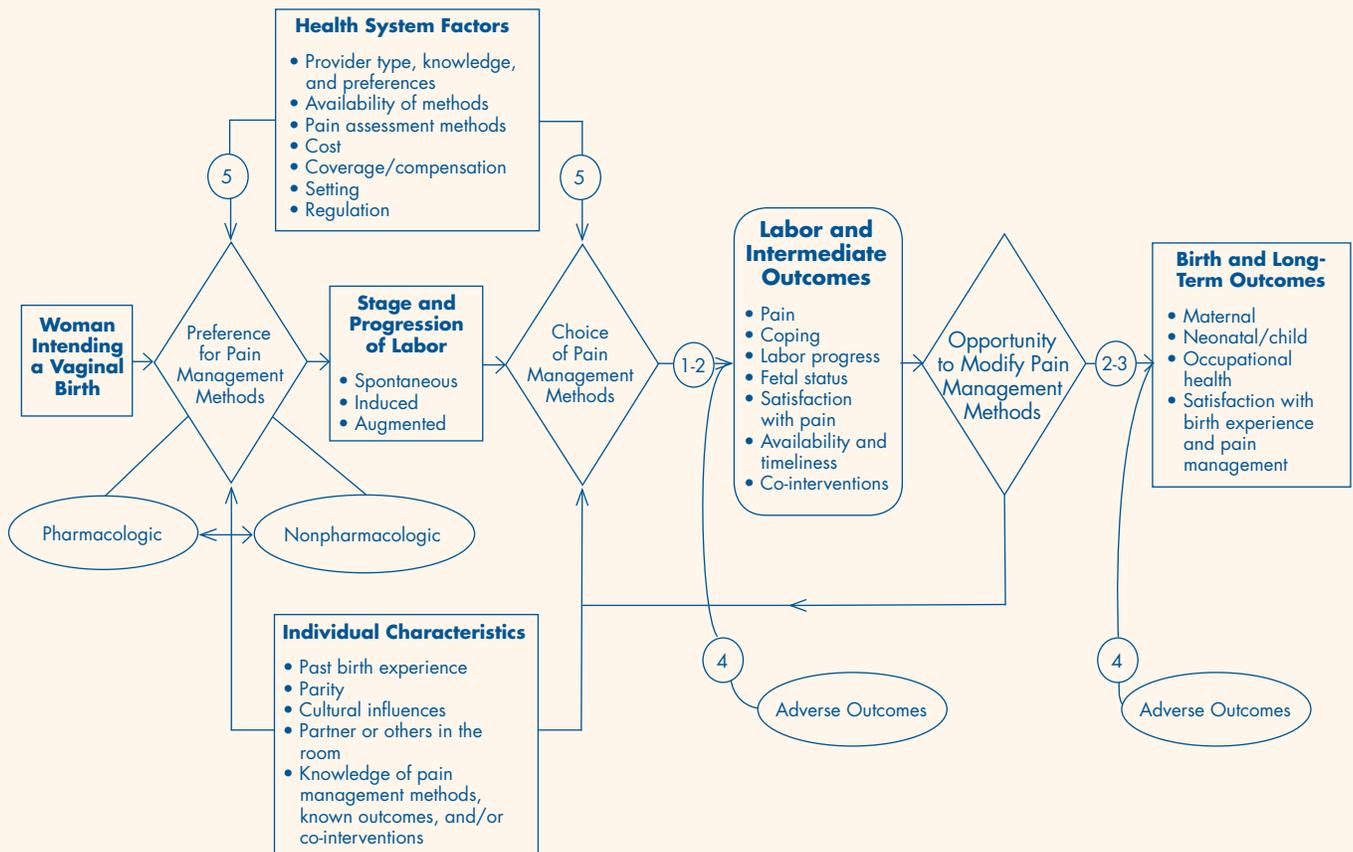
## Analytic Framework

We developed the analytic framework (Figure B) based on clinical expertise and refined it with input from our key informants and Technical Expert Panel (TEP) members.

The figure represents the population of interest, women intending a vaginal birth, and the factors and decision points that influence the use of nitrous oxide for the management of labor pain. The initial preference for pain management methods, which is often determined prior to the onset of labor, can be shaped by past birth experience, cultural or familial influence, and knowledge of various pain management options. Women acquire knowledge about pain management options from a variety of sources including health care providers, childbirth educators, patient education books and other materials, popular media, friends, and family. Once labor begins, health system factors such as availability, setting, and provider preference may affect the utilization of the desired pain

management methods (Key Question [KQ] 5). The first two decision points reflect the initial preference for and actual implementation of pain management methods. A third decision point occurs after the onset of labor but prior to birth, at which point the woman in labor may opt to modify the pain management method. We sought to examine how the administration of nitrous oxide at various mixes, routes, and intervals affects outcomes that occur during labor, after birth, and in the long term (KQs 1–3). Adverse effects of treatment are examined in KQ4. Portions of the framework that are unexplored in the scientific literature are highlighted in the discussion of future research needs.

**Figure B. Analytic framework for nitrous oxide for the management of labor pain**



## Methods

### Input From Stakeholders

The topic was nominated in a public process. With key informant input, we drafted initial KQs, which were reviewed by the Agency for Healthcare Research and Quality (AHRQ) and posted to a public Web site for public comment. Using public input, we drafted final KQs, which were reviewed by AHRQ. We convened a technical expert panel to provide input during the project on issues such as setting inclusion/exclusion criteria and refining the analytic framework

### Literature Search

Our search included the MEDLINE<sup>®</sup>, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. Reviews conducted by the Cochrane Collaboration are indexed in the MEDLINE database and were also included in the search. We also hand-searched references of included articles to identify additional studies. Controlled vocabulary terms served as the foundation of our search, complemented by additional keyword phrases to represent the myriad ways in which nitrous oxide is referred to in the clinical literature. We also employed indexing terms within each database to exclude ineligible publication types and articles in languages other than English.

### Inclusion and Exclusion Criteria

- We excluded studies that:
- Were not original research
- Did not include 20 or more pregnant women in labor
- Did not address adverse effects or occupational exposure during labor
- Did not report information pertinent to any KQ
- Were not published in English

### Article Selection Process

We examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts for inclusion or exclusion. If one reviewer concluded the article could be eligible for the review based on the abstract, we retained it. Full publications were then dually reviewed for final inclusion, with disagreements resolved via adjudication by an independent third reviewer. Reasons and process for exclusions are described in the full report.

### Data Extraction

All team members shared the task of entering information into evidence tables. After initial data extraction, another member checked table entries for accuracy, completeness, and consistency. Abstractors reconciled inconsistencies.

### Quality Assessment

The quality of individual studies was assessed using existing, widely accepted tools for each type of study. For randomized controlled trials (RCTs), the Cochrane Risk of Bias tool was employed. Fundamental domains include: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and free of selective reporting bias. For nonrandomized and observational studies, the Newcastle-Ottawa Quality Assessment Scale was utilized. The scale assesses three broad perspectives: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Both tools are presented in the full report. Additionally, the thresholds for converting the Cochrane Risk of Bias tool and Newcastle-Ottawa Quality Assessment Scale results to the AHRQ standard of “good,” “fair,” and “poor” quality designations are presented in the full report.

### Evidence Synthesis

Text that summarizes the research evidence is organized by KQ. Within each KQ, evidence is organized by aspects of the question, such as the compared intervention and outcomes. In the full report, we include evidence tables for individual studies and summary tables of common outcomes and provide extended analysis.

### Grading Strength of Evidence

We evaluated the overall strength of the evidence for the primary outcomes. We graded available evidence for each key outcome for each of the following domains:

- risk of bias (low, medium, or high),
- consistency of findings (inconsistency not present, inconsistency present, or unknown or not applicable),
- directness (direct comparison of influence on outcomes in RCT, or indirect information from observational research), and
- precision (precise or imprecise based on outcomes rates, size of the individual studies and the total number of women in the studies for the category of intervention).

We combined the grades of each domain to develop the strength of evidence for each key outcome. Possible grades for each domain were: low, moderate, or high risk of bias; consistent or inconsistent; direct or indirect; and precise or imprecise. We considered additional domains, including publication bias and large effect size, on a per-KQ basis.

We graded the body of literature for effectiveness of nitrous oxide, women's satisfaction with their birth experience and pain management, effect of nitrous oxide on route of birth, and adverse effects associated with nitrous oxide. The possible grades were:

**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.

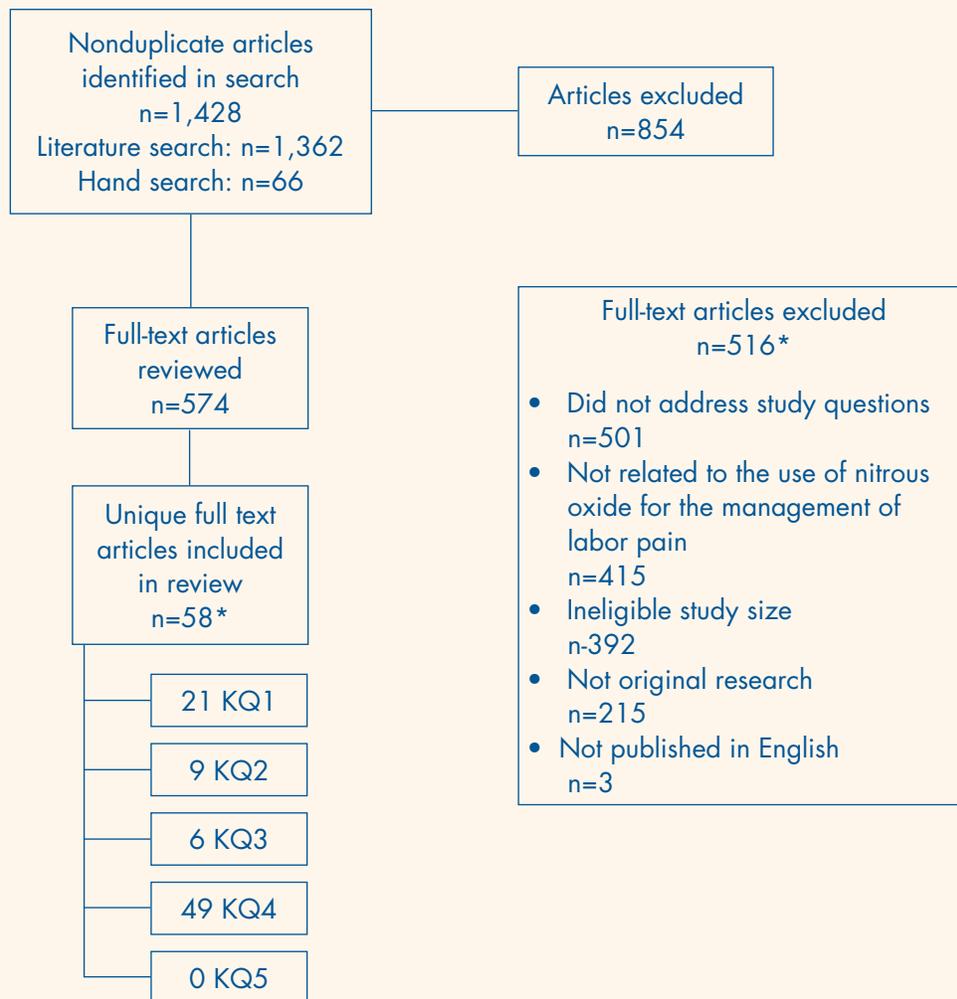
When no studies were available for an outcome or comparison of interest, we assessed the evidence as insufficient. Two reviewers independently graded the body of evidence; disagreements were resolved through discussion or a third reviewer adjudication.

## Results

### Literature Search Yield

We identified 1,428 nonduplicate titles or abstracts. Fifty-eight publications were included in the review (Figure C), representing 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. The most common reasons for exclusion were irrelevance to the topic and ineligible study size. Twenty-one articles pertain to KQ1, 9 articles to KQ2, 6 articles to KQ3, 49 articles to KQ4, and 0 articles to KQ5.

**Figure C. Disposition of articles identified by the search strategy**



KQ = Key Question

\*The number of articles addressing Key Questions and those excluded exceed the total number of articles in each category because some articles fit multiple exclusion categories or addressed more than one Key Question.

## **KQ1. Effectiveness of Nitrous Oxide for Labor Pain Management**

Twenty-one studies addressed the effect of nitrous oxide on pain or pain relief.<sup>9-29</sup> Four studies were of fair quality,<sup>19, 22-23, 25</sup> and 17 were of poor quality.<sup>9-18, 20-21, 24, 26-29</sup>

There was considerable variation in the concentration of nitrous oxide and frequency (continuous vs. 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.<sup>10-11, 14</sup>

The majority of the effectiveness studies (12 of 21) had as comparators other inhalational anesthetic gases that are not used to manage labor pain in the United States. Only one study compared nitrous oxide with placebo and found no significant difference in pain scores. As expected, epidurals provide more effective pain relief than nitrous oxide. The evidence is insufficient to determine the effectiveness of nitrous oxide for the management of labor pain compared with other, nonepidural labor pain management methods because the studies are predominately of poor quality, use heterogeneous outcome measures, and have inconsistent findings.

## **KQ2. Effect of Nitrous Oxide on Women's Satisfaction**

Nine studies addressed women's satisfaction with their birth experience or pain management.<sup>16-17, 20-21, 24, 27, 30-32</sup> One study was of good quality,<sup>31</sup> one of fair quality,<sup>32</sup> and seven of poor quality.<sup>16-17, 20-21, 24, 27, 30</sup> Measures of satisfaction were not uniform, making it difficult to synthesize studies. The strength of the evidence is low for equivalence or superiority of nitrous oxide compared with other pain management methods for women's satisfaction with their birth experience and pain management.

## **KQ3. Effect of Nitrous Oxide on the Route of Birth**

Six studies compared the route of birth in women who used nitrous oxide with that in women who used other pain management methods.<sup>10, 14, 17, 24, 27, 31</sup> Two of these included only women who had vaginal births,<sup>10, 17</sup> and five were of poor quality.<sup>10, 14, 17, 24, 27</sup> The evidence is insufficient to determine the effect of nitrous oxide on the route of birth because the studies are predominately of poor quality and have inconsistent findings.

## **KQ4. Adverse Effects of Nitrous Oxide for Labor Pain Management**

Forty-nine studies addressed the maternal, fetal, neonatal, and occupational harms related to nitrous oxide use during labor.<sup>9-14, 17-21, 24, 26, 29, 31, 33-65</sup> Two were of good quality,<sup>31, 54</sup> 7 of fair quality,<sup>19, 33, 45, 47, 57, 59, 66</sup> and 40 of poor quality.<sup>9-14, 17-18, 20-21, 24, 26, 29, 34-44, 46, 48-53, 55-56, 58, 60-65</sup> Although these 49 studies report data from more than 27,000 women, only 6 were conducted in the United States (n = 2,445 women).

One-third (16 of 49) of studies reporting harms were conducted prior to 1980, when nitrous oxide was often used in combination with sedatives, tranquilizers, and other inhaled anesthetics in labor, a practice that has largely been abandoned. 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 harms reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness). Some maternal harms (e.g., nausea and oxygen desaturation) are common in all laboring women regardless of the type of analgesia used. Study sizes were inadequate to assess for unusual or rare harms that might be more serious.

Nitrous oxide is transmitted via the placenta and is rapidly eliminated by the neonate following 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. Followup of newborns was short, most frequently lasting only to birth or discharge of the neonate from the hospital.

Few data are available to draw conclusions regarding potential occupational harms as a result of exposure to nitrous oxide. Evidence about occupational levels of nitrous oxide is limited, and some studies were conducted prior to the use of room ventilation systems or scavenging systems. The implementation of these systems in clinical practice has reduced occupational exposure, which should mitigate potential risks.

## **KQ5. Effects of Provider and Health System Factors**

No studies addressed KQ5.

## Discussion

### Summary Strength of Evidence and Findings

Overall, the strength of evidence to answer the KQs was insufficient for effectiveness for the management of labor pain (KQ1), route of birth (KQ3), and health system factors (KQ5); low for satisfaction with birth experience and pain management (KQ2); and moderate

for harms (KQ4) (Table B). Deficiencies in the strength of evidence most often related to a preponderance of study designs with 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 small studies with poor precision.

<b>Table B. Strength of evidence for nitrous oxide for the management of labor pain</b>					
<b>Total Studies (Total Participants)</b>	<b>Domains Pertaining to Strength of Evidence</b>				<b>Strength of Evidence</b>
	<b>Risk of Bias</b>	<b>Consistency</b>	<b>Directness</b>	<b>Precision</b>	
<b>Effectiveness of nitrous oxide vs. other, nonepidural labor pain management methods for the management of labor pain (KQ1)</b>					
25 (15,991)	High	Inconsistent	Indirect	Imprecise	Insufficient; includes 6 RCTs; 5 studies of fair quality and 20 studies of poor quality total
<b>Equivalence or superiority of nitrous oxide vs. other labor pain management methods for women's satisfaction with their birth experience (KQ2)</b>					
2 (1,303)	High	Consistent	Direct	Imprecise	Low; includes no RCTs; 1 study of fair quality and 1 study of poor quality total
<b>Equivalence or superiority of nitrous oxide vs. other labor pain management methods for women's satisfaction with their pain management (KQ2)</b>					
8 (2,825)	High	Consistent	Direct	Imprecise	Low; includes 2 RCTs; 1 study of good quality and 7 studies of poor quality total
<b>Effect of nitrous oxide for the management of labor pain on route of birth (KQ3)</b>					
6 (33,031)	High	Inconsistent	Direct	Imprecise	Insufficient; includes 2 RCTs; 1 study of good quality and 5 studies of poor quality total
<b>Adverse effects associated with nitrous oxide for the management of labor pain are primarily unpleasant side effects that affect tolerability (KQ4)</b>					
48 (27,530)	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

Note: Domains pertaining to SOE are taken from the AHRQ methods guide and are explained in the Methods section.

KQ = Key Question, RCT = randomized controlled trial

## Applicability

Applicability describes the extent to which study populations and characteristics in the literature reviewed apply to the larger population. In this report, the study populations were healthy women in labor who should be similar to the target population. Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox<sup>®</sup>. The 50/50 mix is available, although Entonox is not used in the United States and has not been reviewed by the U.S. Food and Drug Administration. In addition, mechanical equipment for administration of nitrous oxide in labor and delivery has very limited availability in the United States at the time of this writing. The comparators include standard pain management methods, such as epidural, narcotics, and nonpharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women, such as other inhalational anesthetic gases.

For KQ1, the most frequent outcome was an assessment of pain, generally during labor but sometimes in the immediate postpartum period and/or weeks to months after birth. Those assessing outcomes included participants, obstetricians, midwives, and anesthesia providers.

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, less intervention and monitoring, and avoidance of potential complications associated with epidurals. 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. Satisfaction with pain management and the birth experience were assessed in KQ2. Satisfaction is a more relevant measure of effectiveness than assessment of pain because nitrous oxide is not intended to provide complete pain relief. The outcomes for KQ3 were vaginal birth, assisted vaginal birth, and cesarean. For KQ4, the most frequent outcomes were assessments of nausea, vomiting, dizziness, drowsiness, hypoxia, oxygen saturation, Apgar scores, and cord blood gases.

Only 6 of 58 studies were conducted in the United States. The options for labor pain management in the United States are somewhat dissimilar to those in other countries because nitrous oxide for laboring women is widely available outside of the United States, whereas in this country its availability is extremely limited. All of the studies were conducted in hospitals; thus, the effectiveness, women's satisfaction, route of birth, and harms associated with nitrous oxide in birth centers and the home setting have not been reported.

## Conclusions

The literature addressing nitrous oxide for the management of labor pain has few studies of good or fair quality. Synthesis of effectiveness and satisfaction studies was challenging because of heterogeneous interventions, comparators, and outcome measures. Satisfaction may be a more relevant measure of effectiveness than assessment of pain because nitrous oxide is not intended to provide complete pain relief. The strength of evidence for the effect of nitrous oxide on route of birth was insufficient. Most maternal harms reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness), and Apgar scores did not differ significantly across labor pain management methods. Data for occupational harms were limited. Research assessing nitrous oxide is needed across all of the KQs examined: effectiveness, women's satisfaction, route of birth, harms, and health system factors affecting use.

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