HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: NITROUS OXIDE USE FOR LABOR PAIN MANAGEMENT

Approved January 14, 2016

HERC Coverage Guidance

Nitrous oxide for labor pain is recommended for coverage *(weak recommendation).*

Note: Definitions for strength of recommendation are provided in Appendix A GRADE-Informed Framework – Element Description.

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

GRADE-INFORMED FRAMEWORK

The HERC develops recommendations by using the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for carrying out the steps involved in developing recommendations. There are several elements that determine the strength of a recommendation, as listed in the table below. The HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by the Commission based on assessment of two independent reviewers from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of the Commission.

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Fetal/neonatal adverse effects *(Critical outcome)*	No significant differences in Apgar scores at 1 and 5 minutes, or umbilical cord gasses after birth when maternal N2O is compared to epidural anesthesia use. ●●●○ *(Moderate certainty, based on multiple RCTs and other studies with consistent findings)*	Use of N2O is likely to be cost-saving compared to epidural anesthesia. The cost of N2O is low. Use of N2O is associated with lower rates of assisted vaginal birth and cesarean delivery, and shorter length of stay on labor and delivery units.	High variability: Some women would want this additional option because of the reduced risk of caesarean section or assisted delivery. Concerns about harms would be mitigated because they could easily discontinue it and consider an epidural if adverse events occur or if analgesia is insufficient. Other	There is no specific CPT code for this service, other than an anesthesia code, so reimbursement to providers may require use of a non-specific code that may require manual review.
Mode of birth *(Critical outcome)*	Compared to women using epidural anesthesia, for those using N2O: 15 to 34 more women per 100 are likely to have an unassisted vaginal birth; 9 to 27 fewer women per 100 would experience assisted vaginal (forceps/vacuum) birth; and there would be about 6 fewer Cesarean births per 100 compared to those using epidural anesthesia for labor pain. ●●○○ *(Low certainty based on prospective cohort and cross sectional studies with consistent findings)*			

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
Maternal adverse effects *(Important outcome)*	Women may experience unpleasant side effects when using N2O. (These data come from studies of women using N2O as the sole form of labor analgesia and are not compared to any other methods.) Nausea (0-28%), vomiting (0-14%), dizziness/lightheadedness (3-23%), and drowsiness/sleepiness (0-67%) were commonly reported side effects. Effects dissipated quickly when N2O use is stopped. ●●●○ (*Moderate certainty based on multiple RCTs and other studies with consistent findings*)		women may prefer epidural anesthesia because of its greater effect in reducing labor pain.	
Maternal satisfaction *(Important outcome)*	70 to 80% of women who used N2O said they would want to use it in a subsequent pregnancy compared to 45 to 88% of women who would request an epidural again. (These data come from studies where multiple labor pain management modalities are readily available and women using N2O or epidural were asked if they would want to use that method for a future birth.) ●●○○ (*Low certainty based on prospective cohort and cross-sectional studies with consistent findings*)			
Use of neuraxial (e.g., epidural) anesthesia *(Important outcome)*	When multiple pain management methods are available for women 13% to 79% will use N2O, compared to 34 to 42% who will select epidural anesthesia. There is no direct evidence on whether			

Coverage question: Should nitrous oxide (50% N2O) be recommended for coverage for labor pain management?				
Outcomes	**Estimate of Effect for Outcome/ *Confidence in Estimate***	**Resource allocation**	**Values and Preferences**	**Other considerations**
	availability or use of N2O changes the use of neuraxial anesthesia. ●○○○ (*Very low certainty based on cross-sectional studies with consistent findings*)			
Rationale: On balance, there are potential benefits to the use of N2O and no serious harms to its use. Costs are low and variable maternal preferences argue for increased availability of N2O for management of labor pain. Coverage is recommended because of the potential benefits of fewer cesarean and assisted deliveries, the lack of significant harms, maternal preferences, and low costs. The recommendation is a weak recommendation because there are few studies available for benefit outcomes, and the external validity of the data and its applicability in U.S. settings is limited. The confidence in the quality of evidence for most outcomes is low to moderate certainty.				
Recommendation: Nitrous oxide for labor pain is recommended for coverage (*weak recommendation*).				

Note: GRADE-informed framework elements are described in Appendix A. Appendix B provides a GRADE Evidence Profile.

EVIDENCE OVERVIEW

Clinical background

Annually, approximately 45,000 births occur in Oregon (Oregon Health Authority, 2015) and childbirth pain is a major concern among women (Likis et al., 2012). Pain relief is most commonly delivered through epidural anesthesia in the United States, with 61% of women who had singleton births through vaginal delivery electing an epidural anesthesia (Centers for Disease Control and Prevention, 2011; Likis, et al., 2012). For women interested in other types of pain relief or in delaying the timing of an epidural, there are several options including inhaled nitrous oxide (N2O, also known as "laughing gas"), other inhaled anesthetic gases, opioids, paracervical or pudendal block, transcutaneous electrical nerve stimulation, hydrotherapy, sterile water injections, and psychoprophylaxis (Likis et al., 2012).

Inhaled nitrous oxide is a non-invasive form of pain relief. Commonly used in dentistry, nitrous oxide provides a diminished sense of pain and provides some antianxiety effects (Likis et al., 2012). In comparison to epidural anesthesia, women using nitrous oxide for pain management retain their full mobility. Individuals experience the maximum effect of nitrous oxide 30 to 60 seconds after inhalation. The effects of nitrous oxide wear off quickly and other types of pain management methods can be used in a relatively short time period after the use of nitrous oxide (Likis et al., 2012).

In the Portland-Metro region, an epidural adds an additional $1,050 to $2,400 to the cost of a hospital birth (Providence Health Services, 2015). The use of nitrous oxide costs significantly less with estimates ranging from $15 to $100 per patient.

Indications

Inhaled nitrous oxide can be used in the first or second stages of labor and is indicated for pregnant women in labor intending a vaginal birth. Nitrous oxide can also be used in the third stage of labor to assist with managing pain that may occur during immediate postpartum procedures (e.g., perineal repair, manual placenta removal).

Technology description

Inhaled nitrous oxide is widely used for childbirth pain relief outside of the United States and is a common form of non-invasive pain relief during childbirth (Klomp, van Poppel, Jones, Lazet, Di Nisio & Lagro-Janssen, 2012). Nitrous oxide is a non-flammable, tasteless, odorless gas that is self-administered on demand by laboring women through a mouth piece or facemask (Collins, Starr, Bishop, Baysiner, 2012; Klomp et al., 2012). Inhaled nitrous oxide is typically administered as a 50% nitrous oxide / 50% oxygen combination. It can be administered at this concentration using a blender device (e.g., Nitronox®) or as a premixed gas (e.g., Entonox®). Entonox® is not currently available in the U.S., but appropriate types of blender equipment are available for hospital and out-of-hospital use.

Key questions

The following key questions (KQ) guided the evidence search and review described below. For additional details about the review scope and methods please see Appendix C.

> KQ1: What are the effects on mode of birth, use of neuraxial (e.g. epidural) analgesia and maternal satisfaction when nitrous oxide is used for labor analgesia?
>
> KQ2: What are the maternal and fetal/neonatal harms of nitrous oxide used for labor pain?

Evidence review

Two systematic reviews (SR) (Klomp et al., 2012; Likis et al., 2012) identified in the core source search address the use of nitrous oxide for pain management during labor. Both SRs were of good methodological quality. The AHRQ SR (Likis, 2012; Likis, 2014) was selected as the index SR and is the primary evidence source for this coverage guidance because it is more comprehensive and matches the scope of the HERC's key questions better. In addition, the Cochrane SR (Klomp, 2012) did not add eligible studies or other information which were not included in the AHRQ SR. For further details on the methods of this evidence review please see Appendix B. The included study characteristics for the AHRQ SR are outlined below in Table 1.

Table 1. Overview of Index Systematic Review

Citation	Total Studies Included	Included Studies Specifically Addressing Coverage Guidance Scope
Likis et al (2012, 2014) [AHRQ SR]	59 studies (13 RCTs, 7 crossover RCTs, 4 non-randomized clinical trials, 14 prospective cohorts, 1 retrospective cohorts, 3 case series, 4 case-control studies, 11 cross sectional studies, and 2 trend studies)	• 14 studies (5 RCTs; 8 prospective cohorts 1 case-series) for fetal/neonatal harms • 3 studies (2 prospective cohort studies, 1 cross-sectional study) for mode of delivery • 10 studies (7 RCTs; 2 prospective cohorts; 1 cross-sectional study) for maternal adverse effects • 2 studies (both cross-sectional studies) for use of neuraxial (e.g. epidural) anesthesia

Evidence from additional sources

No additional evidence sources were included in this review. A MEDLINE® (Ovid) search based on the search strategy of the AHRQ SR did not locate any additional eligible studies.

EVIDENCE SUMMARY

The AHRQ SR (Likis, 2012) included a total of 59 studies reported in 58 publications (13 RCTs, 7 crossover RCTs, 4 non-randomized clinical trials, 14 prospective cohorts, 1 retrospective cohorts, 3 case series, 4 case-control studies, 11 cross sectional studies, and 2 trend studies) to answer five key questions on the following issues: 1) effectiveness for pain (21 studies); 2) comparative effectiveness for women's satisfaction with their birth experience and pain management (9 studies); 3) effect on mode of birth (6 studies); 4) maternal and fetal/neonatal adverse effects (49 studies); and 5) health system factors influencing the use of nitrous oxide (no studies). Key Questions 2, 3 and 4 are directly applicable to this coverage guidance.

Most of the studies in the full AHRQ SR included comparator interventions that are not of interest for this guidance (comparators included other inhaled anesthetic gasses, most of which are not used in the U.S., alternative concentrations of N2O; parenteral opioids and non-pharmacologic techniques not widely available or used in the U.S.). Many of the studies used different concentrations of N2O compared to the 50% N2O/50% oxygen mix that is used in most labor and delivery settings in countries such as the United Kingdom (U.K.) and which is the concentration used in U.S. settings that have adopted it for obstetric use. Most included studies did not report on populations or outcomes of interest for this guidance (e.g. pain scores, occupationally exposed workers). Some populations of interest (e.g. women in the third stage of labor requiring procedural analgesia such as for manual placental removal) were not explicitly included among the studies identified in the AHRQ SR. No study directly addressed or was designed to address whether availability or use of N2O reduces the use of neuraxial (e.g. epidural) analgesia; we were only able to address this outcome descriptively. None of the included studies that did address the questions of interest for this evidence review were conducted in the U.S., although all were conducted in developed countries with modern maternity care systems. However, differences in health systems, provider training, hospital routines and patient expectations may limit the applicability of these studies to the U.S. context.

Although pain was not selected as a key outcome for this guidance, for background context, the AHRQ SR found that N2O is less effective than epidural anesthesia for measures of pain in labor, but that the evidence was insufficient to determine the effectiveness compared with other, non-epidural pain management interventions. The studies are limited because of poor quality, use of varying outcome measures, and inconsistency. The review found no studies that met inclusion criteria and studied the systems factors related to using N2O for management of labor pain, including provider preferences, availability, settings and resource utilization.

Critical Outcome: Fetal/neonatal adverse effects

The AHRQ SR (Likis, 2012) noted that while 49 studies reported on maternal, fetal, neonatal, or occupational harms associated with N2O use in labor, that 16 of these were conducted prior to 1980 when it was usual practice to combine N2O with other sedative, tranquilizing and anesthetic agents. Although N2O is transmitted via the placenta to the fetus, it is also quickly eliminated via maternal circulation and neonatal respiration. Twenty-nine studies included fetal or neonatal harms as outcomes. The SR found no significant differences between any comparison groups in Apgar scores at either one or five minutes after birth. Eight studies reported umbilical cord blood gasses. There was one study that compared infants of women using 50% N2O/50% oxygen to epidural anesthesia. It found that 7% of the N2O group had Apgar scores less than or equal to seven at one minute after birth compared to 6% of infants of women who used epidurals. At five minutes, the proportions with low Apgar scores were 1% and 4%, respectively (p values not reported). There was a statistically significant finding in one study of lower arterial cord blood gasses among infants of primiparous women who used N2O plus meperidine (a parenteral opioid) compared to those who used an epidural (pH 7.21 vs. pH 7.29, $p<0.01$). Use of meperidine alone has been associated with lower umbilical cord gasses and so it is not clear whether this finding can be attributed to N2O use or only to use of meperidine. The AHRQ SR was unable to analyze neonatal intensive care unit admission because of the varying definitions of intensive care across countries and lack of reporting of this outcome.

Only one study included in the AHRQ SR compared neonatal neurobehavioral outcomes among infants of women using N2O and who used other methods of labor pain management, including epidurals, opioids, TENS, and non-pharmacologic methods. This study reported no significant differences between groups in neonatal adaptive capacity scores (NACS).

Critical Outcome: Mode of birth

Six studies in the AHRQ review compared the mode of birth among women who used N2O to women who used other methods of pain relief and determined that there was insufficient evidence, primarily due to poor quality studies and inconsistent results. However, only three studies compared the intervention and comparator of interest for this guidance. One prospective cohort study from Ireland, published in 1987, enrolled primiparous women in an academic hospital. Twenty women used N2O and 50 women used epidural anesthesia. Other comparison groups in the study used TENS or parenteral opioids. Another prospective cohort study from Finland, published in 1994, included 210 women (27% primiparas) using N2O and 82 women (71% primiparas) using epidural anesthesia. This study also found higher rates of vaginal birth among women using N2O. No analysis of the results by parity was provided in the AHRQ SR. These two studies found the following proportions of women with vaginal, assisted vaginal (vacuum or forceps), Cesarean, or vaginal breech births as described in Table 2 below. No statistical testing of differences between pain management groups were reported in either study.

Table 2. Mode of Birth According to Pain Management Approach

Mode of Birth	Nitrous Oxide*	Epidural*
Vaginal	60%/95%	26%/80%
Assisted	35%/2%	62%/11%
Cesarean	0%/3%	6%/9%
Breech	5%/NR	6%/NR

NR: not reported

* The first percentage in each cell represents the Irish study and the second percentage is from the Finnish study.

One cross sectional study conducted in the U.K. and published in 1982 also reported the mode of birth. This U.K.-based study included women (51.4% primiparous) who had vaginal births and found that women who used N2O (n=128) were more likely to have a spontaneous vaginal birth and less likely to have an assisted vaginal birth compared with women who used epidural anesthesia (n=423) or women who used an epidural and N2O together (n=38). Proportions who had a vaginal birth for each of these three groups were 93.7%, 48.7%, and 60.5% and for assisted vaginal birth the proportions were 6.3%, 51.3%, and 39.5%.

Consistent with reported mode of birth outcomes, three of these studies (two prospective cohort studies and one cross sectional study) also reported shorter duration of labor for women in the N2O groups compared to the epidural groups. The reported duration of labor in the N2O groups ranged from a mean of 5.2 hours +/- 1.7 (standard deviation [S.D.]) to 6.7 +/- 3.0 hours. The reported range among women using epidural anesthesia was 7.7 +/- 2.4 hour to 10.8 +/- 4.9 hours.

Important Outcome: Maternal adverse effects

Most harms reported by studies included in the AHRQ SR were unpleasant side effects of N2O such as nausea, vomiting, dizziness and drowsiness. Some commonly reported adverse effect outcomes (e.g. nausea and oxygen desaturation) are reported often among women in labor regardless of pain management strategies used. Studies did not have adequate power to detect rare outcomes. Eight studies of women receiving N2O as the sole pain management agent report rates of nausea from 0% to 28%. Four of these studies also reported vomiting with a range of 0% to 14%. Four studies of women using N2O as the sole analgesia agent reported dizziness or lightheadedness, with rates ranging from 3% to 23%. Four studies reported drowsiness or sleepiness with sole use of N2O and proportions ranged from 0% to 67%.

Important Outcome: Maternal satisfaction

Nine studies in the AHRQ SR evaluated women's satisfaction with their birth experience or pain management, although most were of poor quality and reported varying outcome measures, making it difficult to synthesize results. However, the AHRQ authors concluded that there was low strength of evidence to support the equivalence or superiority of N2O relative to maternal satisfaction outcomes.

Among the three studies that specifically evaluated use of 50% N2O / 50% oxygen compared with epidural anesthesia, two studies (two prospective cohorts) evaluated women's satisfaction with labor pain management at various points in time between one hour and three days post-delivery. They both reported that women who used N2O were somewhat less satisfied with the adequacy of pain relief for N2O compared to epidural anesthesia. Satisfaction scores ranged from 60% to 90% for the N2O group and 98% to 100% for the epidural group in the prospective cohort study. Because N2O is not assumed or designed to achieve the same degree of pain relief as epidural anesthesia this is not considered by the AHRQ researchers to be as robust of an outcomes as is women's assessment of whether they would use the method again. One prospective cohort study conducted in Ireland found that 80% of women who used N2O would request the method again in a subsequent pregnancy compared with 88% of women who used an epidural. In a cross-sectional study performed in Sweden that evaluated this outcome, 69.9% of women who used N2O would request it in another pregnancy compared to 45.3% of women who used an epidural.

Important Outcome: Use of neuraxial analgesia in labor

The AHRQ SR did not report on this outcome. However, the two cross sectional studies (one from the U.K. and one from Sweden) that reported outcomes for groups of women choosing N2O and epidural anesthesia, respectively, do give some information on the methods that women choose when both choices are freely available. The U.K. based study, published in 1982, included only women who had a vaginal birth and approximately half were primiparous. Of 1000 women, about 13% used N2O, 42% used epidurals, and 4% used both methods. Other methods used in this study included parenteral opioids, pudendal or regional anesthetic blocks, no pharmacologic pain management, and combinations of these methods. The Swedish cross-sectional study, published in 1996, gathered data on women who had used N2O, epidural, local anesthesia, acupuncture, hydrotherapy, and breathing techniques as their primary pain management technique. About 79% of women used N2O and 34% used epidural (categories were not mutually exclusive and thus some women who started with N2O may have also used epidurals or other techniques).

OTHER DECISION FACTORS

Resource Allocation

The cost of N2O for labor is low ($15 to $100 per patient). The major cost is for the delivery equipment, which is borne by the facility or provider. The costs of the comparator intervention are relatively high ($1,050 to $2,400 per patient per epidural in the Portland metropolitan area). Use of N2O is associated with lower rates of assisted vaginal birth and cesarean delivery which would potentially result in significantly lower intrapartum costs. For some women who use both N2O and an epidural during the same labor, anesthesia costs of care could increase over use of an epidural alone. However, this combination may still result in higher vaginal birth rates and thus lower total costs of care. The literature review found that the length of labor was consistently shorter (about 2 to 4 hours shorter) among

women using N2O analgesia compared to women using epidural anesthesia such that increased use of N2O may also result in somewhat shorter length of stay on labor and delivery units.

Values and preferences

Some women and clinicians have a strong preference to avoid or delay neuraxial anesthesia and would potentially desire an intervention that may decrease their risk of assisted vaginal delivery or cesarean section. If N2O were available in Oregon facilities, many women would likely try it. Most women would not be concerned about potential harms because there do not appear to be adverse fetal/neonatal harms and women who experience adverse effects themselves can stop using N2O and their symptoms would resolve. Its quick onset would also be desired by women who are waiting for an epidural in labor and who would use it as a bridging technology. However, other women may strongly prefer neuraxial anesthesia (epidural) because of its greater effect in reducing labor pain, so the net assessment is that values and preferences would be highly variable.

Other considerations

There is currently no specific CPT code for N2O use in labor except for an anesthesia-specific code. Benefit plans may need to consider alternative payment methodologies and/or innovative mechanisms to encourage use by providers. Facilities and clinicians may have to invest in equipment and staff training to implement N2O for labor pain. Facilities may experience shorter length of stay on labor and delivery units with increased use of N2O that may result in higher bed availability and/or decreased staffing needs in some hospitals.

POLICY LANDSCAPE

Quality measures

No quality measures related to the use of nitrous oxide during labor were identified when searching the National Quality Measures Clearinghouse.

Payer coverage policies

No public or private payer coverage policies[1] were identified for the use of nitrous oxide during labor.

Professional society guidelines

The National Institute for Health and Care Excellence (NICE) found there to be moderate evidence of benefit for the use of nitrous oxide during labor (NICE, 2014). The guideline notes that nitrous oxide can cause nausea and light-headedness for the mother. NICE did not find any evidence of harm to the baby. The use of 50:50 mixture oxygen and nitrous oxide is recommended to be available in all birth settings in the United Kingdom.

[1] Washington Medicaid, Aetna, Cigna, Regence Blue Cross Blue Shield, and Moda

The American College of Nurse-Midwives (ACNM) has a Position Statement that supports the increased availability and use of nitrous oxide analgesia (ACNM, 2011).

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APPENDIX A. GRADE INFORMED FRAMEWORK - ELEMENT

Element	Description
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issue about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

DESCRIPTIONS

Confidence in the quality of the evidence, across studies, about an outcome

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

***Low*:** The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

***Very low*:** The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Strong recommendation

In Favor: The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Against: The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

APPENDIX B. GRADE EVIDENCE PROFILE

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Fetal/Neonatal Adverse Effects (Apgar scores, Cord gasses)[1]							
14	5 RCTs; 8 Prospective cohorts; 1 Case-series	High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
Mode of Birth[3]							
3	2 Prospective cohort; 1 Cross-sectional	High	Consistent	Direct	Imprecise	Moderate magnitude of effect and some evidence of dose-response relationship	Low confidence in estimate of effect ●●○○
Maternal Adverse Effects (Nausea, Vomiting, Dizziness/Lightheadedness, Drowsiness/Sleepiness)[2]							
10	7 RCTs; 2 Prospective cohorts; 1 Cross-sectional	High	Consistent	Direct	Imprecise	None	Moderate confidence in estimate of effect ●●●○
Maternal Satisfaction[3]							
4	2 Prospective cohort; 2 Cross-sectional	High	Consistent	Direct	Imprecise	None	Low confidence in estimate of effect ●●○○

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Use of Neuraxial Anesthesia[3]							
2	2 Cross-sectional	High	Consistent	Indirect	Imprecise	None	Very low confidence in estimate of effect (●○○○)

[1] Studies from Tables 9, 10, 11 (AHRQ, 2012). Strength of evidence assessment based on AHRQ SR, Table 12 (AHRQ, 2012).

[2]Studies from Table 8 (AHRQ, 2012). Strength of evidence assessment based on AHRQ SR, Table 12 (AHRQ, 2012).

[3]Studies for benefit outcomes selected from AHRQ SR based on HERC review PICO only (neuraxial anesthesia comparator studies only) (AHRQ, 2012). Strength of evidence based on risk of bias assessments included for individual studies in AHRQ SR, Table 6 (AHRQ, 2012) and assessment of other GRADE elements by staff.

APPENDIX C. METHODS

Scope Statement

Populations

Pregnant women intending a vaginal birth in the first and second stages of labor and their fetus/neonate, women in the third stage of labor or immediate postpartum period

Population scoping notes: *Exclude women planning a Cesarean birth*

Interventions

Self-administered nitrous oxide used for labor analgesia or third stage/immediate postpartum management

Intervention exclusions: *Concentration of nitrous oxide blended with oxygen for analgesia other than 50%; non-self-administration of nitrous oxide*

Comparators

Neuraxial analgesia (e.g. epidural, combined spinal/epidural)

Outcomes

Critical: Mode of birth; Fetal/neonatal adverse effects (e.g. low Apgar score, low cord blood gasses)

Important**:** Maternal adverse effects (e.g. nausea/vomiting, dizziness, loss of consciousness); Use of neuraxial (e.g. epidural) analgesia; Maternal satisfaction

Considered but not selected for the GRADE table: Use of non-neuraxial analgesia

Key Questions

KQ1: What are the effects on mode of birth, use of neuraxial (e.g. epidural) analgesia and maternal satisfaction when nitrous oxide is used for labor analgesia?

KQ2: What are the maternal and fetal/neonatal harms of nitrous oxide used for labor pain?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, technology assessments, and clinical practice guidelines using the terms “nitrous oxide,” and “labor pain management.” Searches of core sources were limited to citations published after 2004.

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Health Technology Assessment (HTA) program
BMJ Clinical Evidence
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Interscience)

Hayes, Inc.
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

Based on this initial search, the AHRQ report (Likis, 2012) was selected as the index systematic review.

We also identified another good quality SR from the Cochrane Collaboration in the core source search. The Cochrane SR (Klomp, 2012) included four RCTs that were not included in the AHRQ SR. They were excluded from the AHRQ SR because they were not published in English. In total, five RCTs in the Cochrane SR, compared varying or unspecified concentrations of N2O to oxygen alone or no treatment. Only one of these RCTs evaluated the comparison, relevant to this coverage guidance, of 50% N2O/50% oxygen with epidural anesthesia. This RCT also included a no treatment control group. The Cochrane SR did not present outcomes for the comparison of N2O vs. epidural groups, but only the comparison of the N2O and no treatment groups. We were unable to incorporate the results of the N2O vs. epidural comparison to this evidence report due to this RCT being published in Chinese.

A MEDLINE® (Ovid) search was then conducted to identify systematic reviews, meta-analyses, and technology assessments published after the search dates of the AHRQ report (Likis, 2012). The search was limited to publications in English published after 2010 (the end search date for the AHRQ SR).

Searches for clinical practice guidelines were limited to those published since 2010. A search for relevant clinical practice guidelines was also conducted, using the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Centers for Disease Control and Prevention (CDC) – Community Preventive Services
Choosing Wisely
Institute for Clinical Systems Improvement (ICSI)
National Guidelines Clearinghouse
New Zealand Guidelines Group
NICE
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DOD)

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, or clinical practice guidelines.

APPENDIX D. APPLICABLE CODES

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
760.0-760.5,760.61-760.9,761.0-761.9,762.0-762.9,763.0-763.7,763.81-763.9,764.00-764.99,765.20-765.29,779.32,779.81-779.82,779.84,779.89,V30.00-V30.2,V31.00-V31.2,V32.00-V32.2,V33.00-V33.2,V34.00-V34.2,V35.00-V35.2,V36.00-V36.2,V37.00-V37.2,V39.00-V39.2	Birth of Infant
ICD-10 Diagnosis Codes	
P00.0-P00.7,P00.81-P00.9,P01.0-P01.9,P02.0-P02.1,P02.20-P02.9,P03.0-P03.6,P03.810-P03.9,P04.0-P04.3,P04.41-P04.9,P05.00,P05.10,P05.9,P29.0,P29.11-P29.2,P29.4,P29.81-P29.9,P36.0,P36.10-P36.9,P78.89,P92.01-P92.09,P94.1-P94.9,P96.0,P96.3-P96.5,P96.82-P96.89,Q27.0, Z38.00-Z38.8	Birth of Infant
CPT Codes	
01960	Anesthesia for vaginal delivery only
01961	Anesthesia for cesarean delivery only
01967	Neuraxial labor analgesia/anesthesia for planned vaginal delivery
01968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia
01969	Anesthesia for cesarean hysterectomy following neuraxial labor analgesia/anesthesia
01996	Daily management of epidural, not to include the day that the catheter is placed

Note: Inclusion on this list does not guarantee coverage