

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Nitrous Oxide for the Management of Labor Pain*

Draft review available for public comment from November 29, 2011 to December 27, 2011.

Research Review Citation: Likis FE, Andrews JC, Collins MR, Lewis, RM, Seroogy JJ, Starr SA, Walden RR, McPheeters ML. Nitrous Oxide for the Management of Labor Pain. Comparative Effectiveness Review No. 67. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 12-EHC071-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Reviewer #2	Abstract	Structured Abstract: Page V, Im 22: Please refer to the techniques of providing analgesia by inhalation of nitrous oxide and epidural administration of medication as inhalational (or inhaled) nitrous oxide and epidural analgesia, and not as 'nitrous oxide,' and 'epidural.' This is too colloquial and inappropriate for a scholarly presentation. "Inhaled nitrous oxide provided less effective pain relief than epidural analgesia, but the quality of studies was predominately poor."	This change has been made.
Reviewer #2	Executive Summary	Structured Abstract: Page V, Im 24: "... their birth experience and labor pain management made..."	This change has been made.
Reviewer #2	Executive Summary	Page ES-1, Im 32: Change to: "Inhalational analgesia with nitrous oxide is a commonly available..." or "Use of inhaled nitrous oxide is a common option for labor pain management ..."	This change has been made.
Reviewer #2	Executive Summary	Page ES-1, Im 43: Please reference statement that nitrous oxide produces euphoria.	We believe a reference is unnecessary as this is a widely known effect and would only serve to complicate the sentence and confuse readers.
Reviewer #2	Executive Summary	Page ES-1, Im 45: Regarding reference #8, it seems incongruous to cite a reference from nearly 50 years ago in a sentence that ends "... commonly used for this indication today."	This has been updated.
Reviewer #2	Executive Summary	Page ES-1, Im 46: Reference 9 is the same as Reference 4.	This has been corrected.
Reviewer #2	Executive Summary	Page ES-1, Im 49: Is Reference 11 an appropriate citation for this report?	This is an appropriate reference for this statement.
Reviewer #2	Executive Summary	Page ES-1, Im 48-49: "The mechanism of action of nitrous oxide is thought..." In fairness to more original (and accurate) attribution, the reference for this should be any of the three citations below, rather than the Rooks article. Fujinaga M, Maze M. Mol Neurobiol 2002;25:167-89 and/or Sanders RD, Weimann J, Maze M. Anesthesiology 2008; 109:707-22 and/or Emmanouil DE, Quock RM. Anesth Prog 2007, 54:9-18	This has been changed.
Reviewer #2	Executive Summary	Page ES-2, Im 17-21 (and ES10, Im 29): "Nitrous oxide in a 50/50 mix..." is too colloquial. Please change to "The most common concentration of nitrous oxide administration for labor pain management described in the biomedical literature and used in current clinical practice is 50% nitrous oxide in oxygen, either mixed from two separate gas sources with blender devices (e.g. Nitronox TM) or premixed in single cylinder (Entonox)." [Note: Nitronox is no longer an available option]	This change has been made.

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Reviewer #2	Executive Summary	Page ES-2, Im 22: This is not quite accurate. Ideally, inhalation of nitrous oxide should begin at least 50-60 seconds before the onset of a labor contraction, not 30 seconds, at normal ventilation. (Waud B, Waud D. Calculated kinetics of distribution of nitrous oxide and methoxyflurane during intermittent administration in obstetrics. <i>Anesthesiology</i> 1970;32:306-16) Personal experience: Clinically, I encouraged women to begin inhalation of nitrous oxide 1 minute beforehand for better efficacy.	This has been edited to reflect a range (30-60 seconds).
Reviewer #2	Executive Summary	Page ES-2, Im 26 and 27 and 39 and Page ES-3, Im 8 and throughout the entire text: 'epidural analgesia', instead of "epidurals" or "epidural" (the use of the word 'epidural' is too colloquial for this scholarly review)	This has been clarified in the introduction and shortened for brevity.
Reviewer #2	Executive Summary	Page ES-2, Im 42-48: Aren't these two sentences more conclusive remarks, rather than background information.	We hope our changes throughout the report have addressed appropriate placement of content.
Reviewer #2	Executive Summary	Page ES-5, Im 35: Key Question 5 is not listed separately, but embedded as a bulleted point into Key Question 4.	This has been updated.
Reviewer #2	Executive Summary	Page ES-7, Im 11: Does this mean studies that only addressed efficacy and not adverse effects or occupational exposure were excluded?	No, it means we excluded studies of adverse effects or occupational exposure outside labor pain management (e.g. dental use).
Reviewer #2	Executive Summary	Page ES-10, Im 47: What is meant that the standards of care are not comparable between the United States and other countries? Again, what's the point being made that only six of the studies originate in the United States?	The standards of care are not comparable because the labor pain management options differ. This has been clarified in the text. We identified the number of studies conducted in the US because the target audience is US readers.
Reviewer #2	Executive Summary	Page ES-9, Im 45: What's the significance of the observation that only six of the forty-nine studies were conducted in the United States? And the next sentence begins "In addition..." 'In addition' to what? In addition to the studies being old (prior to 1980), not many were conducted in our country where nitrous oxide isn't much used?	The point is to illustrate why applicability to current US practice may be limited.
Reviewer #2	Executive Summary	Although the scope of this report is stated as an attempt to assess the effectiveness of nitrous oxide in managing labor pain, in the Results section (Page ES-9, Im 11-16), it is reported 'what these studies are unable to demonstrate.' This belongs in a Discussion or Conclusion, it is not a Result. These sentences are not appropriate in the Results section: Page ES-9, Im 11-16: "What these studies are unable..." "Generally speaking, therefore, pain relief..." Page ES-9, Im 26-27: "Satisfaction is a more relevant measure..."	These changes have been made.

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Reviewer #5	Executive Summary	Executive Summary: Page 9, lines 31=32: The authors cite 2 articles to address the prevalence of the use of epidural analgesia for pain relief. A new vital statistics report, perhaps not available at the writing of this review, provides more recent data (Osterman MJK, Martin JA. Epidural and spinal anesthesia use during labor:27 state reporting are, 2008. National vital statistics reports; vol 59 no 5, 2011).	The reference has been updated.
Reviewer #8	Executive Summary	In the Executive Summary of Methods: ES-7 The Inclusion and Exclusion Criteria states that studies were excluded that “Did no address adverse effects of occupational exposure during labor”. If this is the case then it would exclude potentially valuable studies. This needs to be clarified.	We only included studies related to labor pain management and excluded studies in which nitrous oxide was used to manage other types of pain (e.g. dental use).
Reviewer #11	Executive Summary	Applicability, p. 18: Line 28, p. 18, refers to “healthy” women. Some women who have medical problems are not be able to have an epidural and may have a special need for N2O. There are very few medical problems other than ear problems and inadequate Vitamin B12 blood levels and stores that would make a woman high risk for use of N2O labor analgesia.	Healthy refers to the study populations, and not the potential users of nitrous oxide.
Reviewer #11	Executive Summary	Applicability, p. 18: Re. line 31. The FDA has never been asked to approve a premixture of 50% N2O and 50% O2. Take care not to give the impression that FDA was asked to approve it and refused.	This point has been added.
Reviewer #11	Executive Summary	Applicability, p. 18: Re. line 33, please as “at this time” to the end of the sentence re availability of equipment. It would be good to add that an American medical equipment company is currently developing a prototype of new equipment to be submitted to FDA.	We have clarified that equipment is not currently available.
Reviewer #11	Executive Summary	Applicability, p. 18: Re. line 34. TENS is only used for first stage labor. It would be better to give continuous woman-to-woman support and submersion in a tub of warm water as nonpharmacologic methods, since both of them can be used in both stage of labor—or sterile water injections. You don’t want to give the impression that you are only impressed with methods that require equipment.	This is not an exhaustive list and refers to the comparators in the studies.
Reviewer #11	Executive Summary	Applicability, p. 18: Re. line 48: Nitrous oxide itself is widely available in the US; it is only N2O labor analgesia that is extremely limited.	This has been clarified.
Reviewer #11	Executive Summary	Applicability, p. 18: Re. lines 35-37. This sentence gives the impression that other inhalational anesthetic gases are in use in other countries. They aren’t. The only method that is being used to any extent in other countries and isn’t being used here is N2O.	This sentence describes applicability in the US.
Reviewer #11	Executive Summary	Re. line 51: “Harms” (plural) have not been reported, not has (singular) not be reported.	This has been corrected.
Reviewer #11	Executive Summary	Applicability, p. 18: I don’t see what the second paragraph, lines 38-46, has to do with applicability?	The purpose of this paragraph is to list the most frequent outcomes, which are relevant to how the report can be applied.

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Reviewer #11	Executive Summary	Summary Strength of Evidence and Findings, pp. 18 & 19: Re. lines 4 & 5 on p. 19, what is meant by “inconsistencies among outcomes that would be expected to show corresponding benefit”?	A description of SOE methodology and a table describing these results have been added to the Executive Summary to clarify this section.
Reviewer #11	Executive Summary	Summary Strength of Evidence and Findings, pp. 18 & 19: Re. line 6 on p. 19, It would be better to say “small studies with inadequate power to find true differences and thus may result in beta errors, where no statistically significant difference is found although there is a true difference. would request	A description of SOE methodology and a table describing these results have been added to the Executive Summary to clarify this section.
Reviewer #11	Executive Summary	Conclusions, p. 19: It might be useful to note that it has been used for that purpose for 100 years and it is harder to garner the interest and financial support for studies of methods that have been used for so long. Because N2O is an off-patent drug, no drug companies are interested in investing the resources necessary to study it.	We cannot speculate on the reasons for the lack of research.
Reviewer #11	Executive Summary	Internet Citation, p. 19: Good that you provide that.	Thank you.
Reviewer #2	Introduction	The Introduction could more clearly state the reason for this review, which is most succinctly revealed on page 55, first paragraph.	The reason for the review has been further clarified in the scope of the report.
Reviewer #2	Introduction	Further, it would be more accurate to write: “The mechanism of action of nitrous oxide is thought to involve activation of opioidergic neurons in the periaqueductal gray matter and noradrenergic neurons in the locus ceruleus, with analgesia mediated by descending spinal cord neural pathways that inhibit nociceptive transmission.” Or “Nitrous oxide induces release of endogenous opioid peptides in the midbrain, stimulating descending neuronal pathways that modulate pain processing by in the spinal cord.” Or “Nitrous oxide affects the brain, which modulates pain stimuli by way of descending spinal cord nerve pathways.”	This change has been made.
Reviewer #2	Introduction	Page 1, paragraph 1: This paragraph would read more logically if the sentences were effectively reordered 1, 5, 6, 2, 4, 3	Thank you. This change has been made.
Reviewer #2	Introduction	Page 1, lm 16: Wouldn't it be more accurate to call this a systematic review, rather than a 'chapter'?	The term "chapter" is used to refer to the sections of this review.
Reviewer #2	Introduction	Page 1, lm 30 and 41: This reviewer suggests deletion of author names here (Irestedt, Bishop). They are not included elsewhere in the text. Also, delete the title of the Bishop article. Suggested rewrite: Patient preparation, contraindications, documentation and competency requirements for midwives were described for the clinical practice at UCSF, where 50% nitrous oxide in oxygen is self-administered by patients after initial instruction on use and potential side effects. ⁷	Thank you. This change has been made.

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Reviewer #2	Introduction	Page 2, lm 4: As above: Regarding reference #8, it seems incongruous to cite a reference from nearly 50 years ago in a sentence that ends "... commonly used for this indication today."	Thank you. This change has been made.
Reviewer #2	Introduction	Page 2, lm 4: As above: Reference 9 is the same as Reference 4.	Thank you. This change has been made.
Reviewer #2	Introduction	Page 2, lm 6-7: As above for Page ES-1, lm 48-49.	This change has been made.
Reviewer #2	Introduction	Page 2, lm 7: As above: Is Reference 11 an appropriate citation for this report?	This is an appropriate reference for this statement.
Reviewer #2	Introduction	Page 2, lm 29-36: The paragraph, "Nitrous oxide in a 50/50 mix..." would be better placed before the preceding paragraph.	Thank you. This change has been made.
Reviewer #2	Introduction	Page 2, lm 29: As above: Nitrous oxide in a 50/50 mix..." is too colloquial. Please change to "The most common concentration of nitrous oxide administration for labor pain management described in the biomedical literature and used in current clinical practice is 50% nitrous oxide in oxygen, either mixed from two separate gas sources with blender devices (eg. Nitronox TM) or premixed in single cylinder (Entonox)." [Note: Nitronox is no longer an available option]	This change has been made.
Reviewer #2	Introduction	Page 2, lm 36: As above: This is not quite accurate. Ideally, inhalation of nitrous oxide should begin at least 50-60 seconds before the onset of a labor contraction, not 30 seconds, at normal ventilation. (Waud B, Waud D. Calculated kinetics of distribution of nitrous oxide and methoxyflurane during intermittent administration in obstetrics. Anesthesiology 1970;32:306-16) Personal experience: Clinically, I encouraged women to begin inhalation of nitrous oxide 1 minute beforehand for better efficacy.	Thank you. This has been edited to reflect a range (30-60 seconds).
Reviewer #2	Introduction	Page 2, lm 37: Move parenthetical comment to see Table 1 to the end of the sentence.	This change has been made.
Reviewer #2	Introduction	Page 2, lm 55: "... are gone within five minutes after discontinuation." Better to say 'rapid offset.' Lm 58: "...must wear off over time." Better to say "... unlike the effects of epidural analgesia and systemic opioids, which diminish gradually over a much longer time period."	This change has been made.
Reviewer #2	Introduction	Page 3, lm 23: It is arguable whether epidural analgesia is "intended" to provide "complete pain relief," as stated in this review. The reality is that expectations and desires of parturient women and anesthesia providers are highly variable, and there are many different regimens for epidural analgesia that range from minimal analgesia to anesthesia. Epidural administration of opioids alone or ultra-low concentrations of local anesthetic agents are not same as administration of 0.25% bupivacaine, for example.	The text has been updated to read: Nitrous oxide is not intended to provide the extent of pain relief expected with epidural

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Reviewer #2	Introduction	Further, although nitrous oxide (similar to intravenous or epidural administration of opioids) is not intended to provide “complete pain relief,” it is still intended to provide labor relief, whether that’s analgesia or some other coping relief, and despite the limitations of the methodology, it is still appropriate to compare pain relief with nitrous oxide analgesia to other modalities. The sentence that begins “Therefore, the more important questions are…” seems like a conclusion, and belongs in the Discussion or Conclusions, but not here.	We feel this information is necessary to frame the review, based on comments from other reviewers.
Reviewer #2	Introduction	Perhaps what’s missing here is the background information that previous reviews (such as the one I wrote a decade ago) fail to demonstrate significant analgesic efficacy for nitrous oxide labor analgesia. Yet, use of nitrous oxide for labor analgesia is popular in other countries. Then, it would be more appropriate to opine whether measures of satisfaction, or other measures would be more important or appropriate than simply assessing analgesia.	We address this in the discussion chapter.
Reviewer #2	Introduction	Page 4, Table 1: Interesting that for opioids, the description states “Relieves labor pain…” and for paracervical block it states “Provides some relief from pain of cervical dilation.” The data for efficacy of intravenous opioid labor analgesia would suggest this description for “opioids” is optimistic. (Bricker L, Lavender T. Parenteral opioids for labor pain relief: a systematic review. Am J Obstet Gynecol. 2002 May;186(5 Suppl Nature):S94-109.)	The description of opioids in this table has been revised.
Reviewer #2	Introduction	Page 6, Im 10: The sentence would be better as “It will be of interest to individual women and the general public because millions of women per year give birth in the United States.” Otherwise the reader might think millions of women give birth repetitively (annually).	This change has been made.
Reviewer #2	Introduction	Page 7, Im 6: As above: “chapter” should be review (?)	The term “chapter” is used to refer to the sections of this review.
Reviewer #3	Introduction	A well-written and comprehensive overview of nitrous oxide analgesia in labor with some data and statistics about other methods of analgesia for delivery.	Thank you.
Reviewer #5	Introduction	The introduction explicitly lays out the background information needed, the key questions and organization of the report as well as the intended audiences.	Thank you.

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Reviewer #5	Introduction	Specific comment: Background (page 20, paragraph 1: The authors use the Listening to Mothers Survey to estimate the proportion of women who use nitrous oxide, which was noted to be 3%. They then note that “the percentage who used nitrous oxide is likely an overestimate considering this is a nationally representative sample and only a few US facilities offer this method.” This rationale for this statement is unclear. If it is truly a nationally representative sample, then the estimate is likely the best one can do. I agree that, given the small number of centers where it is N2O is available, it is possible that the survey estimated the rate with less precision. However, unless the sampling scheme was flawed, it should be as likely to underestimate as overestimate the use of N2O. The authors should explain why they believe an overestimate is more likely.	We have revised the text to clarify this may be inaccurate without suggesting whether it is likely an overestimate or underestimate.
Reviewer #5	Introduction	There is a fair overview of nitrous oxide which sets the scene for the rest of the report. However, the section on epidurals needs addressing (Page 2, lines 41-49). This section reads with heavy bias against epidurals and should be more balanced, especially if this report is to be used to facilitate decision-making regarding labor analgesia. Major issues, such as the increased risk of assisted vaginal delivery need to be quantified. While the increased duration of second stage labor may be statistically significant, it needs to be put in context. This increased time is usually 15-30 minutes only.	The wording of the sentence on second stage labor has been revised. A detailed review of the risks of epidurals is outside the scope of this review. The information presented is supported by the references cited.
Reviewer #6	Introduction	Women who have epidurals do NOT necessarily have to be confined to bed or have a Foley catheter. Many hospitals use "walking epidurals" and the large majority use very low concentrations of local anesthetic in their infusions, which minimizes motor block allowing ambulation or changing positions and reduces the need for catheterization. I refer the authors to the following articles which address these issues: Stewart a, Fernando R. Maternal ambulation during labor. Curr Opin Anesthesiol 2011;24:268-273 Hawkins JL. Epidural analgesia for labor and delivery. NEJM 2010;362:1053-10.	The wording has been revised to reflect that confinement to bed and catheterization are not always required.
Reviewer #6	Introduction	The incidence of spinal headache needs to be quantified. See Hawkins paper above.	We do not want to single out incidence for this specific complication. The reference to the Hawkins article has been added so that reviewers can find more detailed information.
Reviewer #6	Introduction	There is NO evidence that epidurals cause residual back/leg pain. I refer the authors to the following book chapter: Chapter 17 Epidural analgesia and back pain. Evidence-based Obstetric Anesthesia. Editors: Stephen H. Halpern, M. Joanne Douglas. BMJ Books, Blackwell Publishing.	This has been removed.

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Reviewer #6	Introduction	Page 3, Table 1. Labor Pain management methods. Epidurals. Under description - "partially or fully blocks voluntary motor control...." This should be changed to read "may partially block voluntary motor function..." It is uncommon for a patient to be completely unable to move their legs with an epidural. If receiving higher concentrations of local anesthetic for a forceps delivery, it is more likely.	This text has been revised.
Reviewer #6	Introduction	Under timing. Epidurals are often continued for the third stage of pregnancy and beyond is laceration repairs are necessary.	This point has been added.
Reviewer #6	Introduction	Page 4. Table 1 continued. Opioids. Under description - "causes sedation, which can also relive pain". They "may" cause sedation but this does not relieve pain, only alter the perception or emotional response to pain.	This point has been added.
Reviewer #6	Introduction	Page 6, lines 12-13. This report does not contain sufficient information about the different pain management modalities for labor to act as a tool for making the best decisions for labor analgesia options. It is really a tool to help patients and their careers decide if nitrous oxide may be an appealing analgesic option.	Providing a comprehensive review of different pain management modalities for labor is outside of the scope of this report.
Reviewer #7	Introduction	Very clear and easy to read. See specific comments in attached document.	Thank you.
Reviewer #8	Introduction	It is important for the authors to explain why nitrous oxide is not offered to most women in the USA and how this situation came about historically.	The most significant barrier to use in the United States, appropriate equipment, is noted at the end of the Background section.
Reviewer #8	Introduction	It would also be useful to briefly discuss the rationale used by the limited number of US hospitals/health services who made decisions to re-introduce nitrous oxide as an option for women, and to outline whether there is ongoing research regarding the success or otherwise of their use of nitrous oxide.	We do not have a method to determine the rationale of hospitals using nitrous oxide. Ongoing research is addressed in the discussion chapter.
Reviewer #8	Introduction	To further set the context regarding comparative availability of various methods of pain relief for women experiencing labor in the US, the background should also outline the degree to which epidural services are available to women. This may include availability according to different types of birthing services (obstetrician versus nurse-midwifery), health insurance (private versus public), time of day (24hr service vs 9am- 5pm), locality (urban vs rural or remote) and differences by state. This may provide some insight into where gaps may exist for US women in terms of adequate labor pain management services.	Summarizing the availability of epidural services is outside the scope of this report.

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Reviewer #8	Introduction	There is a message communicated in the introduction/background that epidural is the most effective method of pain relief for women in labor. This needs to be further explained in terms of the underlying assumption that the 'optimal' level of pain for women in labor is zero. In addition, the emphasis that epidural is the most effective method of pain relief should be substantiated with specific information regarding the degree to which all women who elect epidural will experience complete pain relief versus partial pain relief and for how long the relief can be achieved for women who select epidural.	Thank you. We hope our changes have addressed this.
Reviewer #8	Introduction	What specific agent and dosage are the authors referring to in this statement regarding 'optimal' epidural effectiveness?	We are not referring to a specific agent or dosage.
Reviewer #10	Introduction	page 9, lines 41-42 and page 20 lines 40-41 delete "(which began offering nitrous oxide in June 2011 after this review was underway") This is an irrelevant statement.	We think this is important to address any concerns regarding conflict of interest.
Reviewer #10	Introduction	page 9, line 50 -- "nitrous oxide does not completely relieve the pain of labor but instead" --> change to nitrous oxide does not completely relieve the pain of labor, surgery, or dental extraction.	This report focuses on labor pain.
Reviewer #10	Introduction	page 10 & 21 -- figure es-1 is confusing, particularly the second stage and third stage boxes. Recommend splitting all three boxes into some type of figure that notes when the stage starts and ends -- and then the common features. Right now as presented, it is difficult to follow the bullets point as you read down -- particularly in the second and third stage boxes.	We believe this figure is the most efficient way to present this information. It is intended to provide only a brief background on the different stages of labor.
Reviewer #10	Introduction	page 10 -- line 22 -- "ideally beginning about 30 seconds before each contraction" -- has the ideal timing been substantiated in the literature? The reference given doesn't provide this information. If this is not established, say so or delete the statement.	The word "ideally" has been deleted, and the timing has been edited to a range
Reviewer #10	Introduction	page 10 -- line 29-30 -- there is an updated version of reference 16 -- Cochrane review dated Dec 2011. This should be cited in place of reference 16.	We have updated the reference and content.
Reviewer #10	Introduction	page 10 -- line 29-31 & page 21 lines 46-48, and page 22 lines 4-5 -- "women who have epidurals must have additional monitoring and precautions, including confinement to bed..." -- this is not correct and inaccurate and reflects a problematic bias on the part of the authors. Many centers routinely perform CSAE -- the modern day approach to allowing a walking epidural. See Curr Opin Anaesthesiol. 2011 Jun;24(3):268-73. Maternal ambulation during labor. Stewart A, Fernando R. and also Acta Anaesthesiol Belg. 2004;55(1):29-34. Ambulation with combined spinal-epidural labor analgesia: the technique. Kuczkowski KM. The statement as written is much too strong and needs to be revised.	The wording has been revised to reflect that confinement to bed and catheterization are not always required.

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Reviewer #10	Introduction	Page 10 -- lines 40-41 "nor does nitrous oxide require concurrent intervention and additional monitoring" -- what is the scientific basis for this statement? recommend delete or revise.	This has been revised to read "...but it could be preferable to other pharmacologic pain management methods for women who want increased mobility with less intervention and monitoring"
Reviewer #10	Introduction	page 17 -- lines 15-16 -- "generally speaking, therefore, pain relief is likely to be an inadequate measure of effectiveness for nitrous oxide in the absence of other outcomes ... " -- This statement is too broad and should be deleted. Key Question 2 addresses the issue of nitrous oxide's impact on women's satisfaction.	We feel this information is necessary to frame the review, based on comments from other reviewers.
Reviewer #11	Introduction	The 1st bullet under the 4th question (Maternal adverse effects) should reflect concerns about maternal-newborn alertness, interaction and bonding during the critical period immediately after birth and possible maternal pp cardiovascular problems and deaths caused by hyperhomocysteinemia caused by an effect of N2O on maternal vitamin B-12 function. Would the included studies have picked up these problems if they had occurred? If not, future studies should look for them. But the studies you used would have noted severe maternal morbidity and mortality, wouldn't they? There should also have been collection of data on rapid breathing, cyanosis, executing poor judgment or a diagnosis of O2 desaturation, bradycardia, hyperventilation apnea, dystocia, length of active first-stage labor, length of second-stage labor, and length of third-stage labor. All of those may be signs and symptoms of potential maternal morbidity. I understand that some of these observations were not collected in any of the studies, but one purpose of this review is to give best advice for future studies.	This is not an exhaustive list of adverse effects. We have edited the list of future research priorities, which already notes the need to build consensus about critical adverse effects to be studied in future research.
Reviewer #11	Introduction	The 2nd bullet under the 4th question (Fetal/neonatal adverse effects), beginning with line 29, should include non-reassuring EFM findings, a diagnosis of fetal distress, meconium-stained amniotic fluid, neonatal seizures, admission to a NICU, and assessments of breastfeeding success.	This is not an exhaustive list of adverse effects.

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Reviewer #11	Introduction	<p>Re the 3rd bullet under the 4th question (Childhood adverse effects), lines 31 & 32, the concerns about drug dependency refer specifically to methamphetamine and do not occur during childhood; rather the concern is that children whose mothers used extremely high doses (pure [100%] of N2O administered by a health care worker who held the mask to the woman's face in the study that raised this concern) might become addicted to methamphetamine after the child grows up. Also, you need to be much more specific if you want to address concerns that maternal use of N2O during labor would lead to developmental complications in her child. A great deal of research is now on-going to do that in relation to fetal and early childhood exposure to anesthetics during long surgeries (Rappaport B, Mellon RD, Simone A, Woodcock J. Defining safe use of anesthesia in children. N Engl JMed. 2011;364(15):1387-1390.) I think that you should reference that paper, and my review, ref. 10, and point out that a great deal of research is being done. We need to make sure that it includes observation of children whose mothers used N2O during labor.</p>	<p>The reference on anesthesia use in children is outside the scope of this report. We have addressed the need for research on fetal exposure in the future research section.</p>
Reviewer #11	Introduction	<p>Re the 4th bullet under the 4th question (Adverse effects on health care providers and other individuals present for labor), line 34. It should be explained that the real concern has to do with repetitive exposures to the very low exposures that caregivers and others in the same room as a woman using N2O labor might be exposed to. The concern is really only appropriate for caregivers who spend time in close contact with women during N2O for prolonged periods of time on a repetitive basis. I suggest that you refer to pp. 562-3 of ref. 10, which explains the basis for this concern.</p>	<p>This concern is described in the "Nitrous Oxide as a Labor Pain Management Option" section of the Introduction.</p>

Commentator & Affiliation	Section	Comment	Response
Reviewer #11	Introduction	The 5th bullet under the 4th question, lines 35-27, should be presented as question #5. In addition to the health system factors mentioned in the draft, the report should cite day of the week, time of day, and access to other analgesic methods. Access to continuous care by a midwife, doula, nurse or other trained woman throughout the labor. Financial considerations (does offering N2O reduce or increase incomes of physicians and hospitals? Does that depend on the kind of hospital, such as a private for-profit hospital versus a true HMO?). The effect of needing to provide care to women who are experiencing pain during labor on staff? E.g., it requires a more intimate, intensive form of care-giving that takes more time and may require more energy, especially interpersonal energy. It may make a labor unit noisier, including sounds made by women who are not entirely pain-free. If most of the women in a particular obstetric unit are using epidurals, a woman who is not using an epidural may be seen as disruptive and noisy. If a large percentage of parturients are using epidurals, labor care in a hospital may become based on the assumption that all women will have an epidural and the staff may not be open to providing care to a woman who needs a different kind of care.	These are examples of concerns that have been raised that we sought evidence for in the literature. Several of these factors are noted in the analytic framework. This level of detail is beyond what could be identified in the current literature.
Reviewer #11	Introduction	The review only looked at the effectiveness of N2O as an analgesic, effects on overall satisfaction with labor, and “harms” (which is an inappropriate word for many of the side effects). The review did not look for studies that measured effects of N2O on anxiety (although N2O is an anxiolytic and anxiety is a major problem during labor) or effects on use of obstetric procedures such a Pitocin and restrictions on the mother, e.g., restriction to bed, restricted movement, which are important advantages of N2O labor analgesia. These are important limitations of the review and should be noted as such. Effects on use of other procedures and restrictions imposed on the woman may be intermediary outcomes that effect satisfaction with the birth experience, but each intervention and restriction is also is associated with the risk of complications, and interventions and complications are both expensive. If there had been key questions about these outcomes Figure ES-2 would have a box for effects of the labor management method on use of other procedures and restrictions on the mother, with feedback loops to complications.	Unfortunately, this is not part of the key question. The anxiolytic effects of nitrous oxide are noted as a priority for future research, as is the impact on cointerventions.
Reviewer #11	Introduction	This review does not consider costs, but costs are going to become increasing important in AHRQ research. I recommend that a short paragraph with an appropriate heading be adding to identify these limitations and note the need for both of them to be addressed in future research.	Cost is noted as a Health System Factor in the Analytic Framework; however, cost-effectiveness analysis is outside the scope of this review. The need for this analysis is noted in the future research section.

Commentator & Affiliation	Section	Comment	Response
Reviewer #11	Introduction	Regarding the Analytic Framework, pp. 13 & 14: The sentence on lines 55-56 notes that a woman may opt to modify her pain management during labor. Yes, and one modification may be to use two or more methods simultaneously. N2O is often used with another pharmacologic or non-pharmacologic method to ease the pain of labor.	Thank you.
Reviewer #11	Introduction	p. 20: Re. lines 10-14, on p. 20, There is every reason to doubt the estimate on the percent of women who use N2O during labor in the US in 2005 based on the LTM's survey. I contacted key persons from every hospital that provided N2O in the US in 2010. They only provided it to about 300 women. It is clear that many women misunderstood the question and responded "yes" for N2O if they had been given O2 by mask during labor. Based on data from every hospital that provides N2O labor analgesia, I KNOW THAT THE ESTIMATE FROM THE LTM'S SURVEY IS WRONG	We have clarified that this estimate may be inaccurate.
Reviewer #11	Introduction	Key Questions, p. 24: Here there are 5 key questions. In the ES, there are only 4. Get it together!	This has been corrected.
Reviewer #11	Introduction	Uses of This Report, p. 24: Re. 51, American College not Congress of Obstetricians and Gynecologists.	They have changed their name from College to Congress.
Reviewer #11	Introduction	Technical Expert Panel, p. 26: Re. line 24, p. 26, Appendix E was not included.	TEP members have been added to the report, and the note referring to Appendix E has been removed.
Reviewer #2	Methods	Yes.	Thank you.
Reviewer #3	Methods	The inclusion criteria are careful and appropriate. The exclusion criteria are mixed. It is probably acceptable to eliminate non-English articles because of the difficulty of translation though important insights may be lost. The major difficulty is the exclusion of studies of less than 20 parturients. Bad outcomes in anesthesia are extremely rare and may only be found in case reports. Death for example is commonly accepted to be 1:300K anesthetics. I would revisit this. Theoretically the combination of pethidine (meperidine) and 50% nitrous oxide in a pregnant patient might approach 1MAC. Then nausea + aspiration?	The criteria were identified a priori with input from our Technical Expert Panel and vetted through several stages of public comment. We believe the sample size criterion is appropriate for a review of comparative studies.
Reviewer #3	Methods	Definitions are appropriate and well thought-out. No statistics.	Thank you.
Reviewer #5	Methods	The methods carefully lay out the process of the review and the rationale for the method of search and inclusion/exclusion of specific studies. The authors appropriately decide not to do formal meta-analyses due to lack of consistency in study methodologies.	Thank you.
Reviewer #5	Methods	Page 26, paragraph 2: The authors indicate that Appendix E includes the TEP members, but that appendix reports excluded studies.	TEP members have been added to the report, and the note referring to Appendix E has been removed.

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Commentator & Affiliation	Section	Comment	Response
Reviewer #5	Methods	Page 30, Table 2: In the reporting of other outcomes, the distinction between the sub-categories for 'labor and immediate outcomes', 'birth and long-term outcome' and 'adverse effects' is sometimes a bit unclear. For example, childhood drug dependency is listed under both birth and long-term outcomes and adverse outcomes. I understand the challenges of categorization, but wonder if the outcomes might be more easily categorized as either (1) related to labor and birth and measurable during labor or in the immediate postpartum period; or, (2) Longer term outcomes including adverse events as well as satisfaction measured more distant from delivery.	Thank you. We have revised the table according to these suggestions.
Reviewer #5	Methods	Page 32, paragraph 2 (and Appendix E): Perhaps I missed it, but I did not see the codes defining the reasons for exclusion either in the text or in Appendix E, where the articles are listed.	The exclusion codes have been added to the beginning of Appendix E.
Reviewer #5	Methods	Page 32, last line (and Appendix C and page 67, paragraph 1): The acronym for NACS is defined as the Neonatal Psychological Assessment; it should be listed as the Neonatal Neurologic and Adaptive Capacity Score, which more accurately describes the assessment being performed.	Thank you. This change has been made.
Reviewer #5	Methods	Page 33, paragraph 1: Both the Cochrane Risk of Bias tool and the Newcastle-Ottawa Quality Risk Assessment Scale should have references attached to them. Similarly, in paragraph 2, we should be provided with more information on the Distiller Systematic Review online reference manager.	Thank you. These citations have been added.
Reviewer #7	Methods	As noted in attached comments, I would like to have seen attempt to include non-English studies that Judith Rooks mentioned on TEP call. Not sure why economic studies were not included.	We have explained the rationale for why we could not include non-English studies. Economic studies are outside the scope of this review.
Reviewer #8	Methods	Regarding Inclusion/Exclusion Criteria: The key questions are posed to compare nitrous oxide with other methods of pain management among women intending a vaginal birth. However the report does not provide a comprehensive assessment of the benefits and risks of other methods of pain relief if the evidence is excluded on the grounds that it "did not relate to the use of nitrous oxide for the management of labor pain n= 415" (p. 18). Therefore what results is very limited evidence about the use of epidural, a key comparator in this study. An alternative exclusion criteria would be to "exclude studies not related to the management of pain relief in labor". This way a broader base of evidence about the effectiveness of other methods of pain relief could be explored.	A comprehensive assessment of all labor pain management methods is outside the scope of this review.

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#8	Methods	Regarding Inclusion/Exclusion Criteria: The most recent Cochrane review on the topic of “epidural versus non-epidural or no analgesia” should have been referred to in this review. The evidence contained in this review is relevant to the questions being answered about how well nitrous oxide compares to other methods of pain relief. The conclusions of this recent Cochrane review are relevant in terms of evidence about benefits of the effectiveness of epidural (effective pain relief) as well as risks including a greater likelihood of instrumental birth, maternal hypotension, fluid retention, fever during labor, need for oxytocin administration and cesarean section for fetal distress. There was little difference found for maternal satisfaction with pain relief and long-term backache. Neonatal status as determined by Apgar scores did not appear to be adversely affected. The full citation for this review is; Anim-Somuah M, Smyth RMD, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD000331. DOI: 10.1002/14651858.CD000331.pub3	Thank you. We have updated the reference from the earlier version of this review used in the draft report.
Reviewer #8	Methods	Regarding Search Strategy: Given there was no evidence found to answer question 5, a detailed explanation should be provided regarding the search strategy for this question. In particular it is not clear whether the health economics literature was explored. Resource utilization associated with the use of different forms of analgesia for birth may fall outside the biomedical literature and therefore a note about lack of evidence despite the search for literature in the field of health economics should be included? The following two articles did not seem to appear in the reference list for either included or excluded studies. Huang C, and Macario A. (2002) ‘Economic Considerations Related to Providing Adequate Pain Relief for Women in Labour: Comparison of Epidural and Intravenous Analgesia’ <i>PharmacoEconomics</i> , Volume 20, Number 5, 2002 , pp. 305-318(14) Bell E, Penning D, Cousineau E, et al (2000) ‘How Much Labor Is in a Labor Epidural?: Manpower Cost and Reimbursement for an Obstetric Analgesia Service in a Teaching Institution’ <i>Anesthesiology</i> : Volume 92 - Issue 3 – pp. 851-858	The search strategies are detailed in Appendix A. Cost-effectiveness analysis is outside the scope of this review. The need for this analysis is noted in the future research section.
Reviewer #10	Methods	The inclusion and exclusion criteria are justifiable, except the authors did not adequately address the issue of abuse potential among health care workers which is critically important. There are no statistical methods that warrant review or comment at this time.	We sought evidence for any health care provider adverse effects, which would include abuse.
Reviewer #11	Methods	Input from Stakeholders, p. 14: very good.	Thank you.

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Reviewer #11	Methods	Note that “stakeholders” is capitalized in line 36 but “search” is not capitalized in line 45, although both headings are of the same order, I believe.	Thank you. This has been fixed.
Reviewer #11	Methods	Literature Search, p. 14: Lines 54 & 55 note that you excluded articles in languages other than English. In the body of the report itself, lines 4 & 5, p. 32, you said that the “TEP agreed that the vast majority if not all of the relevant literature would be published in English.” This member of the TEP did not and does not agree that all of the relevant literature was published in English. I regret that the big study from China is missing (Su F, Wei X, Chen X, Hu Z, Xu H. Clinical study on efficacy and safety of labor analgesia with inhalation of nitrous oxide in oxygen [published in Chinese with an English abstract]. Zhonghua Fu Chan Ke ZaZhi 2002;37[10]:584-587.) 1300 cases of term primiparous women in labor divided into two groups with 658 women in each group. Compared 50% N2O to intermittent inhaling of O2. Big numbers with a no-other-method-of-analgesia control group, and found significantly shorter active stage labor and cesarean section rate in the group that used N2O (11.6% vs 19.3% Cesarean rates, P < 0.05 and 153 min vs 187 min active phase labor, P < 0.05). And, with much larger numbers than most of the studies in the review, there were no significant differences meconium stained amniotic fluid, postpartum bleeding volume, neonatal Apgar score, and blood gas analysis between two groups (P > 0.05). These findings should be included in the review, which is much weaker without them.	Thank you. We have clarified there may be relevant literature not published in English; however, we did not have translation services available to us.
Reviewer #11	Methods	With China and some other “less developed” countries becoming more important, there is going to be a lot of interest in providing women in those countries with labor analgesia. I think it was a loss to the paper, which should be looking to the future as well as to the past. I understand that translating a single paper with great findings while not translating all of them would have constituted bias. But only 3 papers were excluded because they were not published in English. I’d bet that Vanderbilt has grad students who speak of the languages involved who would be happy to translate those articles for a minimal sum. It would really add to the strength of the review is the Su paper could be included. Please discuss this.	Our search excluded studies not published in English. We did not explore foreign language citation databases; therefore, it is likely that there are more than 3 excluded papers. As you note, translating a single paper from an excluded category would constitute bias.

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Reviewer #11	Methods	Inclusion/Exclusion Criteria, pg. 15: Re line 10, I regret that the smallest study N that you would accept for inclusion was set at ± 20 instead of ± 15 , because it caused the only RCT comparing N ₂ O and remifentanyl to be excluded (Volmanen P, Akural E, Raudaskoski T, Ohtonen P, Alahuhta S. Comparison of remifentanyl and nitrous oxide in labour analgesia. Acta Anaesthesiol Scand. 2005 Apr;49(4):453-8). As the current review and earlier less extensive reviews have found, most of the opioids that have been used during labor are not very effective unless they are used at doses that are high enough to cause respiratory and general depression of the newborn.	These criteria were developed in conjunction with the TEP members and cannot be revised at this point.
Reviewer #11	Methods	A search for better opioids has been going on for several years. IV remifentanyl is the most popular opioid being used for that purpose currently, but it can cause blood oxygen desaturation problems for the mother, and it is not exactly clear what happens to the drug, which is lipophilic, when it is removed (quite quickly) from the mother's circulation. The primary investigator for the N ₂ O/remifentanyl RCT is a Finnish anesthesiologist who seems committed to finding the best possible method(s) of analgesia that can be used safely under the control of the pregnant women during labor. He has stated concern about potentially serious side effects that may limit remifentanyl's use in obstetrics (Volmanen P, Akural EI, Raudaskoski T, Alahuhta S. Remifentanyl in obstetric analgesia: a dose-finding study. Anesth Analg. 2002 Apr;94(4):913-7).	Thank you for this information.
Reviewer #11	Methods	Literature Search Yield, pp. 15-17: The small para that starts at the bottom of p. 15 and ends at the top of p. 16 is very good, as is figure ES-3. Excellent.	Thank you.
Reviewer #11	Methods	Key Question 1, pp. 16 & 17: Very well done. Kudos.	Thank you.
Reviewer #11	Methods	Key Question 1, pp. 16 & 17: You should also note that the methods used to measure pain objectively (smiling-to-frowning face, least-to-worst pain every experienced or imagined, 1 = least to 10 = worst) all require a women using N ₂ O, who is benefiting from dissociating from the pain, to stop what she is concentrating on and focus on her pain. This is not a valid way to assess the effectiveness of N ₂ O for limiting the perception of pain, which, after all, is a perception and therefore susceptible to what the woman is thinking about.	This limitation of objective pain measurements applies to all pain management methods. We have acknowledged this limitation in the discussion section of KQ1.
Reviewer #11	Methods	Key Question 1, pp. 16 & 17: It was striking to me that after an elaborate process to find the studies eligible to be considered, only 4 were judged to be of fair quality. None pertinent to effectiveness were, it seems, were judged be of good quality. I read the abstracts for the 4 judged to be fair.	Thank you for your input.

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Reviewer #11	Methods	Key Question 1, pp. 16 & 17: One was a 1968 study to evaluate use of methoxyflurane analgesia and anesthesia for OB. It is too old to have its abstract included in PubMed, methoxyflurane has been ruled out as an analgesic for labor, so it is not really relevant to the issue at hand today (Clark RB, Cooper JO, Brown WE, et al. An evaluation of methoxyflurane analgesia and anesthesia for obstetrics. South Med J. 1968 Jul;61(7):687-91.)	This study met the inclusion criteria.
Reviewer #11	Methods	Key Question 1, pp. 16 & 17: The 2nd study was a prospective survey of 1091 Finnish parturients conducted to ascertain mothers' expectations for labour pain relief and correlated them with measures of the pain they experienced during all three stages of labour and with their satisfaction regarding the adequacy of pain relief on the third day postpartum. Although 80% of women described their pain as very severe to intolerable, dissatisfaction with the childbirth experience was very low and was associated with instrumental deliveries but not with usage or method of analgesia. Ranta P, Spalding M, Kangas-Saarela T, et al. Maternal expectations and experiences of labour pain options of 1091 Finnish parturients. Acta Anaesthesiologica Scandinavica. 1995;39(1):60-66.4	Thank you for your input.
Reviewer #11	Methods	Key Question 1, pp. 16 & 17: The 3rd study asked all women giving birth in Stockholm during a 2-week period except those who didn't speak Swedish or had an elective cesarean (N = 278) about their experience of pain 2 days after the birth. Although 91% reported high levels of pain, 41% the worst imaginable pain, in spite of wide use of pharmacological pain relief (only 9% had no analgesia, pain was not an entirely negative experience. Twenty-eight percent assessed it as more positive than negative, "suggesting that coping with pain is a rewarding experience for some women." .Anxiety during labor, expected pain, expected birth experience, midwife support and duration of labor were the most important variables associated with intensity of remembered pain. This study points to the need to focus on anxiety as well as pain as important factors.(Waldenstrom U, Bergman V and Vasell G. The complexity of labor pain: Experiences of 278 women. Journal of Psychosomatic Obstetrics and Gynaecology 1996;17(4):215-228.)	Thank you for your input.

Commentator & Affiliation	Section	Comment	Response
Reviewer #11	Methods	Key Question 1, pp. 16 & 17: The aim of the 4th study was to investigate the association between epidural analgesia and other forms of pain relief, and memory of pain at two months and one year after birth based on national sample of 2482 Swedish speaking women with vaginal delivery or emergency cesareans preceded by labor were followed from early pregnancy to one year after birth. Recollection of intense pain at two months and one year was associated with high rates of pain relief, especially epidural analgesia in first-time mothers (Waldenstrom U and Irestedt L. Obstetric pain relief and its association with remembrance of labor pain at two months and one year after birth. J Psychosom Obstet Gynaecol. 2006 (3):147-56.	Thank you for your input.
Reviewer #11	Methods	Key Question 1, pp. 16 & 17: The abstracts didn't provide data to compare effectiveness of N2O labor analgesia with the other methods, but they gave a lot of information showing how complex labor pain is. I think that some of those findings are worth noting, in order to make the review more meaningful.	A discussion of the complexity of labor pain is outside the scope of this review.
Reviewer #11	Methods	Key Question 2, p. 17. Good	Thank you.
Reviewer #11	Methods	Key Question 4, pp. 17-18: Re. statement that only 6 of the studies were from the US, line 44, p. 17. Why does that matter? Did you discount data from studies conducted in countries that actually use N2O labor analgesia?	We identified the number of studies conducted in the US because the target audience is US readers. We analyzed every article that met our inclusion criteria.
Reviewer #11	Methods	Key Question 4, pp. 17-18: I question the term "harms" to describe nausea and drowsiness, line 52, p.17.	"Harms" is standard terminology for AHRQ reports.
Reviewer #11	Methods	Key Question 4, pp. 17-18: On p. 18, line 6. Apgar scores did not differ significantly. How big would differences have to be to be statistically significant? Were any of the studies big enough? Were there any trends even if not statistically significant?	Thank you. We can report only what is in the literature and recognize that larger studies are needed, as noted in the future research section.
Reviewer #11	Methods	Key Question 4, pp. 17-18: You have only described the limitations of the evidence. I don't agree that there is nothing else noteworthy from the findings of these 2 studies.	This is meant to be an overview of the results. Individual studies are elaborated on in the full report.
Reviewer #11	Methods	Key Question 4, pp. 17-18: Re lines 11-13 on page 18: What findings are available from situations in which room ventilation systems or scavenging were used?	This is noted in the description of the studies.
Reviewer #11	Methods	Literature Synthesis, Development of Evidence Tables and Data Abstraction Process, p. 32: Lines 31 & 32 on p. 32 begin a description of the team that abstracted the data and decided on how to present the data in tables. I think that readers (including me) would like to know the professional backgrounds of the staff members and clinical experts who conducted this review.	This is listed in the article selection process section of the methods chapter.

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Reviewer #11	Methods	Literature Synthesis, Development of Evidence Tables and Data Abstraction Process, p. 32: Individual studies are identified in the tables by the last name of the first author and the country in which the study was conducted. I would like to have the grade assigned to the study as per the process described in the section on Rating Quality of Individual Studies at the top of page 33 also given for each study in a table, "G, F or P" if there isn't enough space for the actual words. That would be very helpful.	The quality ratings have been added to Tables 3, 4 and 5.
Reviewer #11	Methods	Inhalational Anesthetic Gases, p. 44: It would be worthwhile to reiterate that none of these methods is being used except during research for labor analgesia anywhere in the world. It might be worthwhile to quote or paraphrase Mark Rosen's explanation for that: "Although most inhalation anesthetic agents have been studied for labor analgesia, few were adopted for widespread use. Trichloroethylene in air had been used by midwives in the UK and methoxyflurane and cyclopropane were also widely used. Nitrous oxide in oxygen has been studied in conjunction with 0.2–0.25% isoflurane by use of a draw-over vaporizer ^{5,6} and by adding isoflurane to a nitrous oxide/oxygen mixture in a single cylinder, inhaled through a standard Entonox valve. ⁷ However, at present the use of halogenated inhaled anesthetics is very uncommon, possibly non-existent; only nitrous oxide inhalation analgesia is currently used to any great extent in obstetric practice. The reasons for this are not entirely clear, but probably relate to the ease of nitrous oxide administration, its lack of flammability, absence of pungent odor, minimal toxicity, minimal depression of the cardiovascular system, and lack of effect on uterine contractility." (Rosen M. Another choice for Queen Victoria? Int J Obstet Anesth. 2003 Apr;12(2):71-3.)	This is noted in the background section and clarified.
Reviewer #11	Methods	Observational Studies of Multiple Pain Management Methods, p. 47-48: In line 51, p. 47, I think it would be helpful to note that pethidine is known as Demerol in the US and is an opioid and that promazine is an anti-emetic.	Both of these items are noted in the key points section of KQ1.
Reviewer #11	Methods	Observational Studies of Multiple Pain Management Methods, p. 47-48: In line 8 on p. 48, it would be useful to know the time elapse between the sterile water injections and first scoring of pain after the injections, since the injections cause pain.	We did not report this information for any intervention, as it was not consistently available.

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Reviewer #11	Methods	Observational Studies of Multiple Pain Management Methods, p. 47-48: Also in line 8, it would be useful to inform readers of the time elapse between the first measure and the subsequent ones for all methods, since first stage labor usually becomes more painful as it progresses. As written, a reader could surmise that the pain management methods causes more pain, when they really just did not reduce the pain enough to compensate for the increase in the strength of labor contractions and the pain associated with them.	We did not report this information for any intervention, as it was not consistently available.
Reviewer #11	Methods	Observational Studies of Multiple Pain Management Methods, p. 47-48: For all studies, it is essential to note what stage of labor and fix the circumstances during which the pain assessments were made as much as possible.	We did not report this information for any intervention, as it was not consistently available. We have identified this as a methodological priority for future research.
Reviewer #11	Methods	Key Question 2, Detailed Synthesis, Overview of the Literature, Women's Satisfaction with their Birth Experience, p. 48-50: There is no summary of the findings from these studies. Some of these studies have very interesting findings, i.g., "Of the women in the prospective cohort study who chose Entonox, 80 percent (16/20) would request Entonox again, compared with 88 percent (44/50) of women who chose epidural. ⁵⁷ In the postpartum survey, 57 percent of women who had nitrous oxide (n = 362) reported a positive or very positive birth experience compared with 34 percent of the women (n = 129) who had epidural analgesia. ⁶⁹ " You can say something of interest and value about the findings from each of these 3 studies.	These studies are discussed by comparator, as noted in that section,
Reviewer #11	Methods	Key Question 3, Effect of nitrous oxide on the route of birth, pp. 50-51: Combine all three kinds of operative births to compare N2O to the other method re spontaneous vag. births vs. all operative births!!!	Assisted vaginal births and cesarean births are not equivalent, thus we report them separately.
Reviewer #11	Methods	Key Question 4. Adverse effects of nitrous oxide for labor pain Management, Key Points, p. 52: Re lines 13-15, page 52, provide more than the range to describe findings from the studies re each of the 1st 3 outcomes.	The key points are meant to summarize each section. The detailed synthesis describes the findings more fully.
Reviewer #11	Methods	Key Question 4. Adverse effects of nitrous oxide for labor pain Management, Key Points, p. 52: Re lines 16-19, page 51, give readers some idea of sample size when summarizing data re significance of Apgar score results.	The key points are meant to summarize each section. The detailed synthesis describes the findings more fully.
Reviewer #3	Results	Detail is appropriate. Studies included are reasonably described. Most do not report race/ethnicity. Outside of the USA it is either illegal or highly ethically discouraged to record the race of patients.	Thank you.
Reviewer #5	Results	The results for each key question are comprehensively presented	Thank you.
Reviewer #5	Results	Page 48, Key Question 2. The word 'effectiveness' does not seem quite right for the description of the question. Consider rewording (here and elsewhere) to 'effect of nitrous oxide on women's satisfaction'.	This heading is consistent with the key question.

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Reviewer #5	Results	Page 53, Key Points: In this overall summary of key question 4, I would suggest adding a key point to address the findings related to occupational exposure.	Thank you. This key point has been added.
Reviewer #5	Results	Page 54, paragraph 4: Inactivation of methionine synthase is not a clinical finding; the sentence should be re-worded.	Thank you. This sentence has been reworded.
Reviewer #5	Results	Page 59, 'other maternal side effects': In paragraph 3, the authors describe findings related to tingling/pins and needles. In the last paragraph of that section they talk about other findings related to numbness and paresthesias. These three outcomes (numbness, paresthesias and tingling) are essentially a single outcome and should be dealt with as such.	Thank you. The discussion of these outcomes has been combined.
Reviewer #5	Results	Page 67, paragraph 1: The authors present the percent of newborns scoring 35-40 on the NACS, but it is not clear from the description what that score generally means. The authors should either explain the score or omit the number and just indicate all infants scored the same.	Thank you. These results have been clarified.
Reviewer #5	Results	Page 67-68, occupational exposure: It would be helpful to have this section more clearly framed in terms of the relevance of these studies to current conditions in labor and delivery suites. In particular, the last sentence of that section describes a study in a newer hospital; it would be helpful to have more specific information about the results of that study. The authors note that no one was exposed to more than 100 ppm, but do not relate the findings to the much lower standard in the US.	Thank you. We have added the findings for the standard in the US.
Reviewer #6	Results	The results are presented well in a clear, concise fashion. By separating the studies into the sections under key questions, this facilitates the flow of information. The characteristics of the studies are clearly described in the evidence tables. It might be helpful to have the key points of the studies in the results tables, such as method of administration of N2O. Otherwise all the relevant information is present in the various figures, tables etc.	Thank you.
Reviewer #6	Results	I refer the authors to the following chapter for cross-referencing of studies: Chapter 5 Is nitrous oxide and effective analgesic for labor? A qualitative systematic review. Evidence-based Obstetric Anesthesia. Editors: Stephen H. Halpern, M. Joanna Douglas. BMJ Books, Blackwell Publishing	Thank you.

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Commentator & Affiliation	Section	Comment	Response
Reviewer #6	Results	Under occupational exposure- Page 48, Line 35, there is no reference to environmental impact, which has been a hot topic for some time. I could find little literature on this but it does merit a mention to show the audience that this has been considered. See the following articles: Ratcliff A, Burs C, Gwinnutt CG. The contribution of medical nitrous oxide to the greenhouse effect. Health Trends 1991; 23:119–120. Ek M, Tjus K. Decreased emission of nitrous oxide from delivery wards: case study in Sweden. Mitig Adapt Strateg Glob Change 2008; 13:809–818.	The environmental impact of nitrous oxide is outside the scope of this report.
Reviewer #7	Results	Wonder if the non-English studies discussed during TEP call would have added value.	Our search excluded studies not published in English.
Reviewer #8	Results	The “Detailed Synthesis” section would benefit from additional information to assist the reader in assessing the veracity of findings and conclusions. Some of this additional detail could be added to the tables. Table 3 would benefit from an additional column to summarize study findings (as is the case in Table 6 , p.27).	The purpose of Table 3 is to summarize the interventions and comparators. Findings are presented by key question.
Reviewer #8	Results	Please note in Table 6, to be consistent the country within which the study was conducted should be included in column 1.	This change has been made.
Reviewer #8	Results	The study by Carstoniu, (1994) is cited as the only study for which a placebo is compared to nitrous oxide. The n=26 in the text is not consistent with the n=29 in Table 3.	Thank you. This has been corrected.
Reviewer #8	Results	In reference to the synthesis of other inhalational anesthetic gases it should be noted whether all ‘other’ gases are actually relevant and currently being used, particularly given that some studies were conducted in the 1960s and one would presume under very different conditions when compared to current standards of clinical practice. This would also be the case for the comparators, including epidural. It is not clear which epidural preparation was used at the time of the study. This may have a significant effect on the applicability of studies and should be discussed.	The current use of other inhalational gases is described in Table 1.
Reviewer #8	Results	On page 31 (Key Question 3) the point is made that “the strength of evidence is insufficient to determine the effect of nitrous oxide on the route of birth”. Is the strength of evidence adequate to state that route of birth was associated with method of analgesia?	There is insufficient evidence to make this claim.
Reviewer #8	Results	On page 54 and also on page 201 (Table 1), page 202 (Table 2) and page 204 (Table 3), the note is made that “All of the studies were conducted in hospitals” and that in terms of outcomes of interest, studies for birth centers and home settings have not been reported. Was this an additional exclusion criteria or the direct result of studies being excluded for other reasons? This statement needs to be clarified as the meaning is currently ambiguous.	Thank you. This has been clarified.

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Reviewer #8	Results	On page 35 the terminology changes from "adverse effects" to "maternal harms". The term "adverse effects" is probably the more appropriate term. Maternal and neonatal adverse events should be categorized into minor and major in terms of impact on women and their infants. For example an experience of transient dizziness would be a minor effect, while spinal headache or persistent backache may be considered more severe. The question arises about the impact of the most serious "adverse effects" of nitrous oxide when compared to the most serious "adverse effects" of other methods of pain relief such as epidural, and the likelihood that these will occur. This information is important for women who may trade-off pain relief achieved for lower risk in terms of avoiding permanent or serious adverse effects for herself and her infant and should be discussed in greater detail.	There are many ways adverse effects could be categorized. We have organized this section by related adverse effects. We did not assess adverse effects of other methods of pain management.
Reviewer #8	Results	The format for tables needs to be consistent throughout the report. For example Table 8 needs n(%) as currently only the % appears in each column.	Thank you. Some studies did not provide the N for the specific outcomes presented in this table. We have added a footnote explaining this.
Reviewer #8	Results	Overall the 'Evidence Tables'(pp. 88-109) are not easy to read and interpret. This is due to the extensive use of abbreviations. The table format should be revised to improve readability.	We have used the standard evidence table format for the Vanderbilt EPC.
Reviewer #8	Results	It is not currently possible to understand the criteria used to exclude each study that appears in the list of excluded studies in Appendix E. There are notations such as X-1, X-2 etc. yet this does not correspond to anything in the report regarding exclusion criteria. Without this information it is impossible to verify whether the decisions to exclude evidence contained in specific studies is reasonable or not.	Thank you. The reasons for exclusion have been added.
Reviewer #10	Results	The results are presented clearly, concisely and in the appropriate amount of detail. However, the authors do need to include studies addressing the abuse potential of health care providers who work in / around nitrous oxide.	Thank you. We sought evidence for any health care provider adverse effects. We did not find any studies that address the issue of abuse.
Reviewer #10	Results	Key question 5 does have literature to support it and should be included in this review. Otherwise, it is simply incomplete.	No literature relevant to KQ5 met our inclusion criteria.
Reviewer #10	Results	page 17 -- lines 23-27 -- reference 51 -- the only good study in the section of key question 2 should have its key conclusions included in the summary. The authors state in that paper patients in the epidural group led to "happier mothers as compared to the control group" where the control group was nitrous oxide.	The key points are meant to provide an overall summary, not present individual studies.
Reviewer #10	Results	page 17 -- line 25-26 -- "satisfaction is a more relevant measure of effectiveness than assessment of pain relief" -- I question the choice of the word "relevant" and suggest the word "prevalent" be substituted.	Relevant is the correct word for the intended meaning.
Reviewer #10	Results	page 17 -- lines 40-57 -- the authors should note the study on childhood associated leukemia (reference 31).	This is a summary that cannot include all individual studies.

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Reviewer #10	Results	page 18 -- lines 12-14 & page 22 - lines 20-22 -- what is the current standard for use of room ventilation / scavenging systems for U.S. centers providing nitrous oxide analgesia? Is this equipment a requirement? If so, based on what?	The need for ventilation and scavenging systems is discussed in the introduction which also refers to Appendix F, where more detailed information is provided.
Reviewer #10	Results	page 18 -- lines 18-20 -- Key Question 5 -- The issue of abuse potential among health care workers is a tremendously important question and warrants consideration in this report. Many hospitals have removed nitrous oxide from off-site anesthesia locations, because the nitrous oxide tanks would disappear / be diverted by nitrous abusers. There is much literature on the topic. See Layzer et al Neurology 1978, Krajewski BJA 2007	Thank you. We sought evidence for any health care provider adverse effects, which would include abuse.
Reviewer #11	Results	Overview of the Literature, p. 53: Lines 53-55: EXCELLENT!	Thank you.
Reviewer #11	Results	Detailed Synthesis, Maternal Harms, p. 54: Re. lines 13-15: EXCELLENT!	Thank you.
Reviewer #11	Results	Detailed Synthesis, Maternal Harms, p. 54: Re. lines 17-24, it would be helpful to provide the range of percentages for each "harm" (wrong word!).	The report focuses on the most commonly reported harms. For many of the infrequently reported harms, percentages are not available.
Reviewer #11	Results	Nausea and Vomiting, p. 54: Re. lines 30-32, p. 54: Just giving the range is giving very little info. Give some idea of the average findings. What was the largest study that found 0%? Something more than the range. This applies throughout the paper.	This information is provided in Table 8.
Reviewer #11	Results	Nausea and Vomiting, p. 54: Re. line 50: What is meant by "nitrous oxide with injected analgesics"? N2O inhaled and opioids injected? Be more clear.	Thank you. This has been clarified.
Reviewer #11	Results	Dizziness and Lightheadedness, pp. 54-55: In the studies of dizziness, what was the concentration of N2O, was it being used as now with the woman holding the mask or mouth tube herself, was she using it intermittently or continuous???	This information is presented in Table 8, as supplied by the studies.
Reviewer #11	Results	Unconsciousness, p. 57: Re. line 38, what is meant by "breathing Entonox with analgesics"?	Thank you. This has been clarified.
Reviewer #11	Results	Amnesia and Hazy Memory of Labor, p. 57: Excellent. Very helpful information.	Thank you.
Reviewer #11	Results	Hypoxia, Maternal Oxygen Saturation, and Diffusion Hypoxia, p 58: Lines 13-17 are the following sentence, which refers to reference 72: "Hypoxic episodes exceeding 10 seconds to saturations less than 90 percent occurred at similar rates for all groups in a case series including women using nitrous oxide, nitrous oxide with pethidine," I couldn't access the entire article, but neither the title nor the abstract seem to related to the sentence in lines 13-17. The next citation, #34, does seem to relate to the sentence it is attributed to. The rest of that para seems alright too.	Thank you. This has been updated.
Reviewer #11	Results	Effects on Maternal Circulation, p. 58: Good.	Thank you.

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Reviewer #11	Results	Biochemical Findings, p. 58: Since the main data are re renal dysfunction, "Biochemical Findings" seems like too broad a title for this para.	Multiple outcomes are presented, so this heading seems appropriate.
Reviewer #11	Results	Inactivation of Methionine Synthase, pp. 58-9: This concern is a big deal. I think that it and the concerns about it should be explained.	This has been elaborated on in the text.
Reviewer #11	Results	Restlessness, p. 59: OK	Thank you
Reviewer #11	Results	Dreams, p. 59: Excellent	Thank you
Reviewer #11	Results	Other Maternal Side Effects, p. 59: Re. lines 34 & 35, the study from Iran used 50% N2O and 50% O2 and the patient administered it to herself. There seems to be something wrong with ref. 41; I could not find it through PubMed.	Thank you. This has been updated.
Reviewer #11	Results	Other Maternal Side Effects, p. 59: Excellent, very useful summary! Why are the summaries of some of these more minor effects more useful than the summaries of effectiveness and Women's Satisfaction with Their Birth Experience?? Those summaries should be as enlightening as this one.	The summary of these side effects may seem more useful because there are more data to report than for key questions 1 and 2.
Reviewer #11	Results	Umbilical Arterial and Venous Blood Gases, p. 59: Lines 18-20 describe the only significant finding in Table 9. I suggest that you identify findings with statistically significant differences with asterisks or something like that and do so throughout the report.	We have identified this study in Table 9.
Reviewer #11	Results	Apgar scores, p. 59-66: Lines 7 & 8, p. 61: You should explain why many of the studies that collected Apgar-score data are not included in tables 10 and 11, as you did for table 9. Or else make an overall statement that studies published before 1980 are not included in the studies in the section on fetal and neonatal harms and why.	This is explained on page 42.
Reviewer #11	Results	Apgar scores, p. 59-66: Re line 13, p. 61, "Apgar data were, not was . . . , since "data" is plural.	Thank you. This correction has been made.
Reviewer #11	Results	Apgar scores, p. 59-66: Re. table 11, p. 64: The abstract for Ross et al. makes me think that the last two subsets of data also refer to administration of 50% nitrous oxide in oxygen with 0.25%isoflurane, not N2O by itself. In that case it could be presented as N2O/isoflurane stopped at more than or less than 1 hr. before delivery. I believe that, given larger sample sizes, the differences between the 3 subsets with N2O + isoflurane and narcotics given before the delivery would be statistically significantly different than those without. Some comment should be directed to those differences specifically. They are very different from the others and show the fallacy of relying on significance tests to signal true differences in studies with small numbers.	Thank you. The information in the table is correct, per the article cited.

Commentator & Affiliation	Section	Comment	Response
Reviewer #11	Results	Apgar scores, p. 59-66: Table 11 on page 64 needs a footnote to explain the asterisks next to the findings for the 5th data subset in the study by Ross et al. The footnote under table 10 indicated that asterisks re. data presented in the table meant that “*Some participants used pethidine and/or epidural”. There is no footnote under the parts of table 11 on page 64 or page 65, and the footnote under the last part of table 10 (on page 66) gives a different explanation for the significance of an asterisks. This is not very user friendly!	Tables 10 and 11 have different footnotes. Footnotes are listed at the end of each table.
Reviewer #11	Results	Apgar scores, p. 59-66: In table 11 on page 66, what does “bom” mean by the dates of data collection (I assume), since I don’t know what “bom’ means.	It denotes the year in which participants were born.
Reviewer #11	Results	Apgar scores, p. 59-66: Do you know what percent of Apgar scores <8 at 1 minute are ok for a low-risk group of women? It is bad that two studies only reported 1-minute Apgars and not 5-minute ones for the same group of women.	Apgar scoring is described earlier in the section. We can report only what is included in the studies.
Reviewer #11	Results	Apgar scores, p. 59-66: You should be able to find a way to present all of the data on Apgar scores for each study on one table. Turn the pages sideways to get more rows in. How will the report be published, in print similar to in a journal? Use a smaller font to get all the info about Apgar scores for each study into one table.	We have tried to combine both tables and found that this is the most straightforward way to present the results.
Reviewer #11	Results	Assessment of Neonatal Neurobehavioral Status, p. 67: On line 6 in page 67, all of the studies compared neurobehavioral status of infants using N2O to a control group. Only one compared it to a control group that used TENS but no pharmacologic method of analgesia. With only 110 babies divided into 4 different treatment groups, this could be one of those studies in which small sample sizes affect statistical significance of differences in a way that hides true differences. I don’t have access to the article itself, so I can’t tell. I am suspicious of all this no significant difference results.	We can report only the information the study provides.
Reviewer #11	Results	Assessment of Neonatal Neurobehavioral Status, p. 67: I have the same concerns about the study discussed in lines 12-15 in page 67, which does not have an abstract on PubMed. I really think that you need to address this concern in some way. Consult a statistician. It is one thing to say that the study is too small to have generated statistically significant difference, if you at least give the actual data so that the reader can judge or if you also describe the degree of similarity. Lack of a statistically significant difference is not the same thing as proof of no difference. The way you did it with the study described in the last sentence of this paragraph, lines 15-17, was helpful.	Thank you. A methods expert has been involved throughout the review process and writing of this report. The scores did not differ significantly.

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Reviewer #11	Results	Long-term harms, p. 67: Re. line 29. With use of pure (100%) N2O, the masks would have had to be held to the women's faces by hospital staff, not by the women themselves. This increases the risk of overdosing.	Thank you for this information.
Reviewer #11	Results	Long-term harms, p. 67: Re. the study described in lines 31-33 was exploratory. Data on many possible risk factors were analyzed, and the authors stressed the need for future studies corroborate or relook at the findings presented. The odds ratio found associated with N2O exposure in that study was 1.3, 95% (1.0 to 1.6), which is barely significant, and the study looked at many possible risk factors. Some statistically significant differences are found by chance, and the more associations are looked at, the greater the likelihood that one of them will be found to be significant by chance. I just did a search on PubMed for "childhood leukemia associated with maternal use of nitrous oxide during labor". The study cited in this review is the only one in the literature, even though it was published in Cancer Research 11 years ago, in 1991 and the researchers worked at the Centers for Disease Control. That suggests to me that cancer researchers didn't find the article very convincing, or some follow-up studies may have been conducted but didn't find a relationship. I could be wrong, of course, but it does not seem like a very big risk to me.	This study met our inclusion criteria. The odds ratio with confidence interval is presented so readers can interpret the findings.
Reviewer #11	Results	Occupational Exposure, pp. 67-68: Re. lines 54-56, p. 67 please provide some explanation of N2O concentrations in diffusive air samplers and the significance of the findings from this study in terms of Swedish and US standards for 8-h time-weighted averages. I think it would be worth emphasizing the higher rates of exposure for assistant midwives (does that mean students or the midwifery equivalent of nurses aides?).	Thank you. We have added information about US standards and provided the authors' explanation for the difference in rates of exposure between midwives and assistant midwives.
Reviewer #11	Results	Occupational Exposure, pp. 67-68: Re. lines 57 & 58 on p. 67 and line 3 on p. 68, you should note that this was a recent study, published in 2003, which means that the problem persists in the UK.	The study date is included in the reference.

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Reviewer #11	Results	Occupational Exposure, pp. 67-68: • You should provide some explanation of the authors' suggestion (lines 4-9, p. 68) that the findings of some amount of N2O in the urine of almost half (22 of 46) of the midwives may have resulted from motor vehicle exhaust or other nonwork sources. Although midwives can carry a "body burden" of cellular changes resulting from exposure to N2O while working in a contaminated environment with them when they return to that environment that does not mean that they still have N2O in their blood, although they could possibly have it in their urine, but only if they had very big bladders and returned to work without having urinated between one work shift and another, which is unlikely. Please see the last paragraph on p. 562 of my recent review of the Safety & Risks of N2O labor Analgesia (Rooks JP. Safety and risks of nitrous oxide labor analgesia: a review. J Midwifery Womens Health. 2011 Nov-Dec;56(6):557-65). If the midwives had N2O in their urine during a subsequent shift, had no new exposure to N2O between one shift and another and had emptied their bladders between shifts, then everything we think we know about how N2O is eliminated from the body is wrong. I don't think it is, but this finding is noteworthy and should be examined further.	Thank you. We have clarified the authors' explanation of this phenomenon.
Reviewer #11	Results	Grey literature search results, p. 68: Re line 22, p. 68. You should also refer to the appendix, which is very good	Thank you.
Reviewer #2	Discussion/ Conclusion	The discussion should at least acknowledge that there must be (likely is?) a reason women use nitrous oxide for labor pain, despite lack of good scientific evidence for efficacy. The collective anecdotal evidence suggests some benefit; perhaps we (still) just don't understand the appropriate question to ask to measure and understand that benefit.	We have acknowledged reasons women may choose to use nitrous oxide in both the introduction and discussion sections, as well as challenges of assessing efficacy of this method.
Reviewer #3	Discussion/ Conclusion	The implications, mainly that much research needs to be done on nitrous oxide analgesia are correct. The limitations of prior studies are clearly demarcated The future research section is appropriate and sets out a road map for researchers to follow. I would add, as said above, a content priority of looking for the possibility of acute addiction. This may be a major risk to participants and providers. but may increase parturients satisfaction with its use.	Thank you. This has been added as a content priority for future research.
Reviewer #5	Discussion/ Conclusion	Page 74, methodologic priorities: One priority noted is the design of studies to examine apoptosis. I may have missed it, but I do not recall reading about apoptosis as a concern in the report. If there is literature supporting this, it should be mentioned in the results.	Thank you. This priority has been revised.

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Reviewer #6	Discussion/ Conclusion	The implications of the major findings are clearly stated. The limitations are described adequately. The table of evidence is useful for this. See Results section for omission of literature. The future research section is clear. It will be a challenge to investigate many of the suggested topics but they are all worthwhile and relevant to this subject.	Thank you.
Reviewer #7	Discussion/ Conclusion	Yes, however, I recommend adding epidural and no pain relief or non-pharm pain relief comparators. These are the very real choices for women. Do not discount them. I also recommend adding economic analyses.	Thank you. These are addressed in the future research section.
Reviewer #8	Discussion/ Conclusion	The majority of women in the US are unable to access nitrous oxide as an option for management of labor pain despite the fact that significant proportions of women around the globe are permitted to use nitrous oxide and are supported in doing so . There appears to be no compelling evidence of maternal or neonatal harm associated with the use of nitrous oxide presented in this review. The question that should be answered here, but is not adequately addressed, is whether nitrous oxide is at least as safe as other forms of analgesia (such as epidural) currently used by numerous women in US hospitals. This is important since epidural analgesia is actually associated with higher rates of operative birth when compared to other methods of pain management (p. 32). This is in the context with what appear to be largely transient adverse effects of nitrous oxide such as nausea, dizziness, drowsiness noted as "adverse effects". Operative birth has significant impact on women in the postnatal period and in future pregnancies and this imbalance in severity of risks versus benefits should be more specifically addressed in the discussion. In addition, according to common measures of neonatal condition at birth, such as Apgar scores, nitrous oxide appears to have no effect. There was no difference in Apgar scores for infants whose mothers used nitrous oxide in labor when compared to other pain management methods or no analgesia at all (p. 42) and the key adverse effects noted on page 34 were essentially transient and minor in nature. Although it is important for future research to address limitations in evidence, a stronger conclusion is needed to guide women and policy makers who will rely on this review for guidance.	The comparative safety of nitrous oxide with other labor pain management methods is outside the scope of this review. We have tried to emphasize in the conclusion that the adverse effects of nitrous oxide that were identified indeed appear to be minor and transient.

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Reviewer #8	Discussion/ Conclusion	Future research will need to address the potential challenges associated with the introduction of nitrous oxide into environments where epidural is currently an integral and major part of labor management in the US. In addition to equipment, clinicians will need to be trained in the most effective use of this method and in coaching women who choose to use nitrous oxide in labor. In addition, the impact of providing nitrous oxide as an alternative to epidural services in institutions where it is an important part of anesthetic workload, and may impact on revenue, should be addressed in research regarding impact on healthcare services in the US. Workload for labor nurses may also change and this should be analyzed as part of future research about US childbirth culture.	Thank you. This has been added to the future research section.
Reviewer #10	Discussion/ Conclusion	page 72 -- line 25-26 -- "satisfaction is a more relevant measure of effectiveness than assessment of pain relief" -- I question the choice of the word "relevant" and suggest the word "prevalent" be substituted.	Relevant is the correct word for the intended meaning.
Reviewer #10	Discussion/ Conclusion	page 72 -- key question 4 -- I would include summary data from the leukemia study (ref 31) in the summary on page 72.	This section is intended to summarize the overall literature and not individual studies.
Reviewer #10	Discussion/ Conclusion	The future research section is clear and delineates the key studies and questions that need to be addressed on this topic.	Thank you.
Reviewer #11	Discussion/ Conclusion	State of the Literature, p. 70: Good	Thank you.
Reviewer #11	Discussion/ Conclusion	Strength of Evidence, p. 70-71: Re line 19: I disagree that we know that the strength of evidence about health system factors is insufficient. You didn't look for it. That would have required an entirely different kind of search for papers, which could not be limited to comparative studies. There is evidence, but not the kind you are used to looking for.	Thos refers to the strength of evidence for this review of these key questions, which did include health system factors.
Reviewer #11	Discussion/ Conclusion	Strength of Evidence, p. 70-71: Regarding "study designs with high-risk of bias", in line 22: Please explain what you mean by bias. Do you just mean any study in which subjects are not assigned to study groups randomly? If so, say so. Then explain how difficult is to conduct RCTs of labor pain management methods, because most women enter labor with some idea about what kind of labor analgesia they want to use. Studies that are able to randomize subjects end up with subjects who are unlike most women, thus the findings are not applicable.	Please refer to the methods chapter for a description of SOE terminology, including bias. We have added a footnote to Table 12 referencing the AHRQ methods guide, which details each domain pertaining to the strength of the evidence.

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Reviewer #11	Discussion/ Conclusion	Strength of Evidence, p. 70-71: In addition many women who end up using N2O labor analgesia are given it for a reason that neither the pregnant woman or her care-givers can anticipate—she comes to the hospital in full-blown second-stage labor and there is no time to place an epidural and epidurals that are placed late in second stage have a high rate of failure; she uses N2O because she can't have an epidural when she wants one and that allows the epidural to be placed later in labor and thus to have less negative efforts on her labor or she decides to stick with the N2O, even that isn't what she had been planning to use, etc. Better comparative studies might be to compare what happens re specified outcomes before and after N2O is introduced into use in a hospital that has not used it before. Vanderbilt began using N2O very recently. It might be possible to compare aspects of labor care there before and after. Many more hospitals are planning to start using it as soon as new equipment becomes available, including Mayo, a major teaching hospital in Pittsburgh, and many more. Now would be the time for people interested in it to plan studies.	We agree. These are good questions for future research, which is sorely needed.
Reviewer #11	Discussion/ Conclusion	Strength of Evidence, p. 70-71: Re table 12 on p. 71: Please explain somewhere what you mean by “consistency”, “directness” and “precision”.	Please refer to the methods chapter for a description of SOE terminology.
Reviewer #11	Discussion/ Conclusion	Future Research, State of the Science pp. 74-75: Re line17, what do you mean by the “timing” of administration—stage of labor?	Yes, this refers to the stage of labor.
Reviewer #11	Discussion/ Conclusion	Future Research, State of the Science pp. 74-75: The 3rd bullet, “Developing outcome measures that assess effectiveness as defined by women choosing nitrous oxide” and is excellent!	Thank you.
Reviewer #11	Discussion/ Conclusion	Future Research, State of the Science pp. 74-75: Focus groups of women who have tried and used or tried and decided not to use N2O labor analgesia would be a good source of insight for developing methods to assess both effectiveness of pain relief and satisfaction with labor.	Thank you. We have noted the need for qualitative research.
Reviewer #11	Discussion/ Conclusion	Future Research, State of the Science pp. 74-75: The 8th bullet, “Building consensus about critical maternal, fetal, neonatal, childhood, and occupational exposure outcomes, developing a minimal core data set for future research.” Midwives from the UK, Scandinavia, and the Netherlands would be helpful too and would be glad to help.	Thank you.
Reviewer #11	Discussion/ Conclusion	Future Research, State of the Science pp. 74-75: The 9th bullet, re human studies that examine apoptosis is being taken care of, I believe, but only in relationship to children exposed to N2O and anesthetics during surgery. Physicians and midwives with expertise in N2O labor analgesia should become involved in the planning of these studies, many of which are already underway.	Thank you.

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Reviewer #11	Discussion/Conclusion	Future Research, State of the Science pp. 74-75: Conduct studies that collect cord blood from babies whose mothers used N2O labor analgesia and test their blood for the presence of N2O. Collect blood samples again when the infant is discharged also for determination of the presence of N2O.	Thank you. This has been added as a content priority for future research.
Reviewer #11	Discussion/Conclusion	Future Research, State of the Science pp. 74-75: Conduct better studies to compare the neuro-integration, including newborn/maternal bonding behavior and breastfeeding of newborns grouped by the kind(s) of pain management that was used.	Thank you. This has been added as a content priority for future research.
Reviewer #11	Discussion/Conclusion	Future Research, State of the Science pp. 74-75: This section is excellent and very important!	Thank you.
Reviewer #11	Discussion/Conclusion	Conclusions, p. 75: Excellent overall.	Thank you.
Reviewer #11	Discussion/Conclusion	Conclusions, p. 75: Re. line 25: The word "addressed" should be deleted because health system factors affecting use was not really addressed.	Thank you. This sentence has been revised to reflect this point.
Reviewer #2	Clarity and Usability	This systematic review represents an impressive amount of work, resulting in an overall well-conceived and executed analysis of the clinical scientific literature about the efficacy of nitrous oxide analgesia for labor analgesia. There are no doubts about the overall conclusions expressed on page 56 given the disappointing quality of the available literature.	Thank you.
Reviewer #3	Clarity and Usability	The report is clear and logical. The imitations of past studies are listed. The main points set out are carefully presented. The conclusions are valid though perhaps raise more questions rather than enable policy and practice decisions.	Thank you.
Reviewer #5	Clarity and Usability	The report is well suited for the audiences intended. The results are most useful for future research than policy, since data are very sparse.	Thank you.
Reviewer #6	Clarity and Usability	This a lengthy report but well structured and organized. The main points are clearly stated.	Thank you.
Reviewer #6	Clarity and Usability	I would be reluctant to use this report to facilitate decision making about different labor pain management modalities as there is insufficient information about the other analgesic options for anyone to make a truly informed decision. It is, however, extremely useful to facilitate decisions about using nitrous oxide itself.	Thank you.
Reviewer #7	Clarity and Usability	Yes, the report is very clear, well-organized, and easy to read.	Thank you.
Reviewer #8	Clarity and Usability	The report is not easy to follow at times and the tables in particular need to be revised to improve readability and consistency. A systematic process has clearly been followed however the information in the report does not flow well. There is heavy reliance upon the tables which do not contain complete and consistent information.	Thank you. We hope our revisions have addressed your concerns.

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Commentator & Affiliation	Section	Comment	Response
Reviewer #8	Clarity and Usability	The conclusions are limited by the questions being asked, the inclusion and exclusion criteria and the limited evidence explored within the review. Therefore in its current draft, the conclusions of this report are unlikely to be able to inform policy and practice decisions.	Thank you.
Reviewer #10	Clarity and Usability	The report is very well written and organized -- just a little biased. The main points are clearly presented. I believe if the authors address the concerns raised above, the report will be complete and able to impact decisions in an objective manner.	Thank you. We hope our revisions have addressed your concerns.
Reviewer #11	Clarity and Usability	p. 34: In line 12 on p. 34, you refer to applicability to IP care in the US. I hope that this document will be helpful to people in many countries. Does he AHRQ require you to do that? If so, does it require you to say it? If not, I think it would be better to say in countries with advanced health care systems—oops, that would exclude us. How about in countries that spend a lot of money on health care??? Something more inclusive than just the US would be better.	Yes, we are required to focus on care in the United States.
ASA	General Comments	As the summary reports, based on current evidence and published research, there is insufficient data to recommend widespread adoption or endorsement of nitrous oxide as a labor analgesic. Further research into both the analgesic efficacy and the effects of nitrous oxide on both laboring women and their infants is warranted, as well as research into the environmental safety of nitrous oxide when used for labor analgesia. The American Society of Anesthesiologists Committee on Obstetrical Anesthesia enthusiastically agrees with the need for further well-designed investigation of such safety and efficacy topics, and is willing to work with the AHRQ on addressing these needs.	Thank you for these comments. The purpose of this report is not to make clinical recommendations or provide endorsements.
Reviewer #1	General Comments	My main problem with this manuscript is related to the observation that nitrous is used in virtually every labor unit in the UK, almost without exception, while used in only a handful of centers in USA. Use is also widespread in other countries, such as Canada and Australia, and others. This disparity is remarkable. Thus, there is widespread, ample, robust clinical experience with this mode of labor analgesia. However, the authors of this review have relied almost exclusively on “studies” to arrive at the conclusion. Not surprisingly, there are very few good methodologically sound studies, and hence the conclusion is that much more research needs to be done.	The purpose of this review is to assess the existing evidence.

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Reviewer #1	General Comments	The suggestion of this reviewer is that the authors should spend a week or so in the UK talking to clinicians who actually use this drug. Most clinicians in the UK would laugh out loud at a review like this, as their vast clinical experience will tell you exactly how nitrous works, how it fits in with other modes of labor analgesia, and how women tolerate it. I understand that this is relying on anecdotal evidence, rather than high-quality clinical trials. However, when you have a drug that is used in virtually 100% of the labor units in a particular country (UK), and has been so for decades, that must account for something. To put it another way, Americans are very unfamiliar with nitrous, hence we seek “studies” to document its effectiveness, and etc....Meanwhile, clinicians in the UK can tell you exactly all the answers, no need for RCTs.	Thank you for the suggestion; however, the purpose of this review is to assess the existing evidence.
Reviewer #2	General Comments	In essence, this review was prompted by recent interest in nitrous oxide for labor analgesia in the United States, given its more extensive use in other countries, yet (surprisingly) data for its efficacy is deficient. However, this is not the first review of this literature. As the author of a systematic review of this topic a decade ago, it is interesting to me that this report never references previous attempts to synthesize the literature about use of nitrous oxide for labor analgesia. The background section of this review should provide the reader with a critique of previous reviews and outline how they inform the present effort.	The existing review is cited in the introduction and background of this review. The purpose of this review is to conduct a new assessment of the literature using AHRQ comparative effectiveness methodology.
Reviewer #2	General Comments	The background and results sections of the structured abstract contain conclusive remarks intertwined in the text, some that appear to reflect subtle bias in the presentation. Both sections, Background and Results should be further edited and the summary conclusions of this report should be restricted to the appropriate Conclusion section.	Thank you. We hope our revisions have addressed your concerns.
Reviewer #3	General Comments	It is certainly interesting and if the use of nitrous oxide is increasing in US obstetrical practice then the report is definitely useful and meaningful. The target population and audience are well defined. I would add another part to Key question number 2: Nitrous oxide has been implicated as an amnestic agent in general anesthesia (see PONV meta-analyses). Is that its mechanism in labor pain; does it permit forgetting how absolutely painful the experience was? Or is it the preemptive analgesic effects (see Anesthesiology approx 4 years ago)	Unfortunately, we cannot change the key questions at this point. The mechanism of nitrous oxide in labor pain management is not completely understood.
Reviewer #5	General Comments	This systematic review presents a comprehensive picture of the state of our knowledge related to the use of nitrous oxide for pain relief in labor. Key questions are explicit and appropriate to the topic. It is overall a very well done piece of work and my comments are largely of a minor nature.	Thank you.

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Reviewer #6	General Comments	This a good report given the small number of good quality papers on the subject. The authors have not sugar-coated the limited conclusions and have used the explicitly stated key questions to bring the relevant information to the fore.	Thank you.
Reviewer #6	General Comments	The target audience is well defined. See comments on uses of this report below (Page 6).	Thank you
Reviewer #7	General Comments	Yes, very nicely done. Very clear language. For specific questions and suggestions, please see attachment.	Thank you.
Reviewer #8	General Comments	The topic is important and this report has the potential to be clinically meaningful. The target population and audience are well defined and the key questions are mostly appropriate, although there is some inconsistency within the report regarding whether there are 4 or 5 questions being answered.	There are 5 questions, but there was no literature to address Key Question 5.
Reviewer #10	General Comments	The report is a thorough review of the subject: Nitrous Oxide for Management of Labor Pain. The authors unfortunately are challenged primarily by a lack of high quality studies that can definitively answer the key questions. The target population and audience are explicitly defined and the key questions are appropriate.	Thank you.
Reviewer #10	General Comments	The authors do present a bias towards the use of nitrous oxide for management of labor pain throughout their introduction and summary which is unfounded and needs to be corrected however.	We hope our revisions have addressed your concerns.

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