2017

Nitrous Oxide: Revival of an antiquated pain modality helps to empower women

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NITROUS OXIDE: REVIVAL OF AN ANTIQUATED PAIN MODALITY HELPS TO EMPOWER WOMEN

A MASTER'S PROJECT SUBMITTED TO THE GRADUATE FACULTY

OF THE GRADUATE SCHOOL

BETHEL UNIVERSITY

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SCIENCE IN NURSING

APRIL 2017

BETHEL UNIVERSITY

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May 2017

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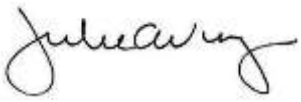
Second Reader Signature: 

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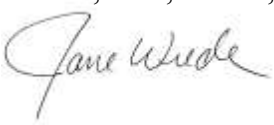
Director of Graduate Nursing Program Signature: 

Abstract

Background: Options for pharmacological pain management in labor are limited. The use of nitrous oxide during labor and gynecological procedures is supported by the American College of Nurse-Midwives (2016); they group suggested that different forms of coping with labor and pain should be made available for women.

Purpose: The purpose of this critical review of the literature is to examine the factors contributing to availability, efficacy, safety, and patient outcomes of nitrous oxide when used during labor and gynecological procedures.

Results: Twenty-four articles were selected for review and were appraised using the John Hopkins Research Evidence Appraisal Tool (Dearholt & Dang, 2012). The major findings of the reviewed literature on the use of nitrous oxide during labor and gynecological procedures reveal that nitrous oxide is a safe and effective form of pain control with minimal side effects. It is cost effective, easy to implement, and has a high rate of patient and provider satisfaction.

Conclusions: Nitrous oxide should be offered as a form of pain management for women during labor and for gynecological procedures.

Implications for Research and Practice: Although there is room for further research on the use of nitrous oxide during labor and for procedures, there is enough current research to support offering it as an effective analgesic during labor and for gynecological procedures.

Keywords: *nitrous oxide, analgesia in labor, Entonox, inhaled analgesic, labor pain management*

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Chapter One: Introduction

Since the beginning of time, the act of giving birth has been associated with some degree of pain for all women. There are two views in regard to dealing with the pain of labor. The first is the pain relief paradigm where it is thought that women in modern society should not have to endure pain during labor. It is believed there are effective analgesics available and the benefits of using these medications outweigh the risks they present to the mother or baby (Jones, 2013). The contrasting view is described as the working with pain paradigm. This side of the paradigm believes "pain plays an important role in the physiology of this process" (Leap, 2010, p. 22). It argues that experiencing pain during labor releases a woman's own endorphins that can help women deal with the pain.

The idea of relieving pain in labor has been surrounded with controversy for hundreds of years. The church and a predominately male medical profession felt that pain was a necessary component of childbirth. Opium was the first known form of pain relief dating back to 3400 B.C., and derivatives of it, such as morphine, are still used in medicine today (Koyyalamudi et al., 2016; Skowronski, 2015). Ether and chloroform came on the scene for labor pain relief around 1847. Their use gained popularity with women even though medical professionals were leery of dangerous side effects. Ether vapors are very explosive and chloroform has cardiac toxicity. Queen Victoria, in the mid- 1800s, was reported to use chloroform during childbirth and this increased its demand for use by women of high society. Twilight sleep, a combination of morphine and scopolamine, was first used in Germany for pain relief and quickly became popular in the United States around 1914. Again, it was women from the upper class that

demanded and popularized this form of pain relief in labor despite doctors' unease. Eventually twilight sleep fell out of favor when one of its feminist advocates died in childbirth with its use (Eley, Callaway, & van Zundert, 2015; Skowronski, 2015). A Spanish military surgeon by the name of Fidel Pages discovered epidurals in 1921. The American anesthesiologist John Bonica popularized their use in America in 1940 (Skowronski, 2015). Epidural use has continued to increase; Koyyalamudi et al. (2016) reported that 61% of women in the United States using this form of pain relief in labor.

Perhaps it is the popularity of epidurals that never allowed the use of nitrous oxide in childbirth to take off in the United States. Nitrous oxide was first discovered by Joseph Priestley an English clergyman and scientist, in 1772. An American dentist named Horace Wells began using it in 1844 and it gained popularity for labor use by the early 1900s. It is still widely used in many European countries (Skowronski, 2015). According to Likis et al. (2014), nitrous oxide use by women in the United Kingdom was between 50-75% and in Finland 60% of laboring women used it. The availability of nitrous oxide in the United States is limited with few centers offering it. At the time of writing, Collins (2014) reported that in the United States 38 hospitals and 28 birth centers had plans to implement the use of nitrous oxide or were already offering it. Interest in its use has been on the rise and, according to a Listening to Women Survey conducted in 2006, more women are desiring less invasive means of coping with childbirth pain than what has been offered in recent history (Collins, Starr, Bishop, & Baysinger, 2012).

Statement of Purpose

The purpose of this paper is to examine the factors contributing to availability, efficacy, safety, and patient outcomes of nitrous oxide for use during labor and

gynecological procedures. Areas to be considered include safety, ease and cost effectiveness of use, and patient satisfaction. The significance to nurse-midwifery will be described and Bandura's theory of self-efficacy will be used as a framework.

Evidence Demonstrating Need for Critical Review

Epidurals are the gold standard of pain relief in the United States and are the most frequently used form of anesthetic (Dammer et al., 2014). However, for some women who do not desire complete pain relief and who ascribe to the working with pain theory, or who want freedom of movement and less interventions, epidurals are not the answer. There are many forms of non-pharmacological pain relief methods used in labor, but with varying effectiveness. Other pharmacological methods, such as short-term IV opioids, are frequently used, but they to are not without side effects for mother and infant and they have temporary effectiveness. Nitrous oxide is being revisited for labor analgesia recently and has been used in dental procedures for many years in the United States. It is widely used in many European countries and has been for hundreds of years: furthermore, it is the predominant form of labor pain relief in some European countries (Collins, 2014; Dammer et al., 2014).

A study by Squires and Anderson (2015) reported that the price per capita for healthcare in the United States was $9,086 in 2013, and 17.1% of the country's gross domestic product (GDP) went toward health care. Of the 13 countries studied, this was almost 50% more than the next highest country, and almost double the spending on healthcare in the U.K. The infant mortality rate was also highest in the United States, as compared to the other 13 countries reviewed. As a well-developed nation, the United States spends more on health care than other developed nations with less favorable

statistics in maternal and infant health. Nitrous oxide, which is safe, cost effective, self-administered, and less invasive than epidurals or intravenous opioids, is not an option for most laboring women in this country.

Nitrous oxide is an odorless, nonflammable gas. It does not effect uterine contractions and has minimal effects on the cardiovascular system (Rosen, 2002). Side effects include dizziness, nausea, vomiting, and feelings of euphoria, but they are reported to be mild and tolerable (Berlit et al., 2013; Dammer et al., 2014). Used as an analgesic in a concentration of 50% nitrous oxide and 50% oxygen, it is a quick, safe, and effective form of pain relief and presents no risk to the mother or infant (Dammer et al., 2014; Mobarki, Yousefian, Seifi, & Sakaki, 2016; Pita et al., 2012). Its use in reducing anxiety in dental and other procedures is widely accepted (Collins, 2014; Onody, Gil & Hennequin, 2006; Singh et al., 2016). An anxiolytic benefit of nitrous oxide in laboring women has also been reported (Collins, 2014; Manouchehrian & Bakhshaei, 2014). In European countries it is available in premixed cylinders and branded as Entonox. A blender apparatus manufactured under the name of Nitronox can be used in either separate cylinder form or via hospital pipeline supply for administration. Nitronox has an on-demand valve that prevents off gassing by way of a negative pressure system and provides scavenging of exhaled gas. The patient self administers the blend by facemask and a closed breathing circuit (Rosen, 2002).

Although the exact mechanism of action of nitrous oxide is not fully understood, the accepted theory is that it works by release of endogenous endorphins, dopamine, and opioids in the brain, and stimulates neuromodulators in the spinal cord. It has also been found to increase prolactin levels and decrease cortisol levels, thereby reducing the

response to stress (Collins, 2014; Rooks, 2011; Rosen, 2002). Nitrous oxide is metabolized in the lungs and greater than 99% is exhaled unchanged. Its half-life is less than five minutes and has a rapid onset of action, within one minute, and offset of within a few breaths (Brucker & King, 2017; Collins, 2014; Pita et al., 2012).

Significance to Nurse Midwifery

In a joint position statement, the American College of Obstetricians and Gynecologist (ACOG) and the American Society of Anesthesiologist (ASA) regarding pain relief in labor noted that women in labor experience extreme pain and that under no other medical circumstance is it acceptable to allow a patient to experience such pain (American College of Obstetricians and Gynecologist, 2004). The groups went on to state that a women's request for pain relief, if not contraindicated, should be met. Insufficient staffing resources, training, refusal to pay for such services by insurance, or the patient's inability to pay for such services, should not prohibit the patient from receiving pain relief.

The American College of Nurse-Midwives (ACNM), in a statement specific to nitrous oxide for labor analgesia, recognized that women experience and deal with the pain of labor in many different ways. It is for this reason that different forms of coping with labor should be made available to them. The ACNM stated that nitrous oxide is a safe, easily used, and inexpensive form of analgesia. The organization reported that it is not without side effects and may not meet the needs of all women. They supported the use of nitrous oxide, the training of midwives in its use, as well as the education of women regarding it as a very reliable option for pain relief (American College of Nurse-Midwives, 2010).

Two Cochrane Reviews relevant to this topic have been completed since the Agency for Healthcare Research Quality (AHRQ) developed their executive summary in 2012, which developed five key questions regarding nitrous oxide's use in managing labor pain. These questions stated that more research was required in areas of effectiveness, patient's satisfaction, route of birth, harms, and factors related to health systems use of nitrous oxide (Agency for Healthcare Research and Quality, 2012). One Cochrane Review looked specifically at the use of inhaled analgesics in labor and found that it may be valuable for some women who want a form of pharmacological relief without invasive methods. They recommended further research addressing specific outcomes of sense of control, satisfaction rates, and women's experiences with breastfeeding and inhaled analgesia use (Klomp et al., 2012). Jones et al. (2013) reviewed both non-pharmacological and pharmacological methods of pain management in labor. They stated that most methods of non-pharmacological methods appear to be safe, but that the effectiveness of these methods is ambiguous. Epidurals, while being the most effective, come with increased interventions and the increased risk of instrumental birth (RR 1.42, 95% CI 1.28 to 1.57, 23 trials, 7,935 women), maternal hypotension (RR 18.23, 95% CI 5.09 to 65.35, eight trials, 2789), maternal fever (RR 3.34, 95% CI 2.63 to 4.23, six trials, 2741 women), urinary retention (RR 17.05, 95% CI 4.82 to 60.39, three trials, 283), and caesarean section for fetal distress (RR 1.43, 95% CI 1.03 to 1.97, 11 trials, 4816 women), Jones et al. (2013). They also recognized that pain management is important to consumers and that healthcare organizations should take this into consideration.

Women are the center of midwifery care. Within the very fiber of the philosophy of midwifery care is the desire to enable women to have ownership of their health care. There are several hallmarks of care that characterize and set the midwifery model apart. One of these hallmarks is to promote the "empowerment of women as partners in health care," and another is "advocacy for informed choice, shared decision making, and the right to self determination" (American College of Nurse-Midwives, 2012, n.p.). The more choices a woman can be given in dealing with pain in labor, the more likely she is to feel in control and actively involved in her experience. The more in control a woman feels, the better she is able to cope, persevere, and have a positive perception of childbirth (Drummond & Rickwood, 1997; Sinclair & O'Boyle, 1999). The use of nitrous oxide in labor offers a choice that helps women to cope with the pain and anxiety that often accompanies childbirth. Furthermore, the use of nitrous oxide may help women reflect on their birth with a positive and empowered trajectory of strength from within that will prepare them to better meet the challenges that lie ahead in motherhood.

Theoretical Framework

The theory of self-efficacy has been applied to many disciplines because it deals with human behavior (Broussard & Weber-Breaux, 1994). It is thought to be an appropriately applied framework for childbirth as it relates to coping. Women anticipate childbirth with mixed emotions; excitement, fear, anxiety, and stress are common. A satisfying birth experience is one where a woman feels that she was able to cope with the pain and stress of the birth while remaining in control (Sinclair & O'Boyle, 1999).

Bandura developed the theory of self-efficacy in 1977, which stated that people using their own cognitive abilities could control how they respond to

situations. How people adapt their behaviors to certain stressors has the ability to influence the outcome of the situation. If people remain in control of their emotions they can cope with the given stressor (Bandura, 1997b; Drummond & Rickwood, 1997; Salomonsson, Gullberg, Alehagen, & Wijma, 2013; Sinclair, & O'Boyle, 1999). In short self-efficacy is the confidence a person has in his or her own abilities to cope with a given circumstance.

Bandura noted that simply having the skills or knowhow to complete a task does not mean that someone will be successful in achieving it. For example, reading about how to ice skate does not mean a person will be able to ice skate. Bandura identified these differences as efficacy expectations and outcome expectations. Outcome expectancy is the belief that a particular behavior will bring about the preferred result. Efficacy expectation is the belief in one's ability to perform the skill needed to achieve the desired outcome (Drummond & Rickwood, 1997; Salomonsson et al., 2013; Sinclair & O'Boyle, 1999).

Four main factors or tools have been identified that can be implemented to increase self-efficacy. Applying self-efficacy tools in stressful situations such as labor or during procedures can help women better cope with the situation. The first, which is thought to be the best indicator of self-efficacy, is performance accomplishments, which are previous successes in accomplishing a given act. Just as skillful marathoners know that they can run the race, multiparous women are more confident that they can successfully give birth because they have done it before and know what to expect. The next most influential aspect of self-efficacy is vicarious experience what a person has knowledge of through another individual or societal influence. Women enter pregnancy

and birth influenced by the birth stories of those who have gone before them. Verbal persuasion is the third factor to increase self efficacy and it is the encouragement people get both emotionally and verbally from their support network. Some women enter pregnancy well supported while others may be completely lacking a support network and find themselves doubting their abilities to be mothers or give birth naturally. The use of nitrous oxide in the birth process is a tool to aid women to successfully complete the task. The final factor is the physiological response to self-efficacy, which involves the emotional response to achieving the accomplishment. Stress and anxiety can have either a positive or negative affect on self-efficacy depending on how it is handled (Bandura, 1997a; Broussard & Weber-Breaux, 1994; Drummond & Rickwood, 1997). Fear and anxiety release catecholamine in the body, which causes a stress response. This can heighten the perception of pain (Herres et al., 2016). Catecholomines can reduce the effectiveness of contractions and slow labor, and can cause maternal exhaustion and fetal distress (Rooks, 2012). The use of nitrous oxide is believed to have the opposite effect on the body by releasing endorphins that increase pleasure and a sense of euphoria, thereby allowing the woman to work with the pain and feel in control (Rosen, 2002).

Summary

Midwives can help women cope with labor pain by offering pharmacologic and non-pharmacologic analgesic options in labor. In addition, self-administered nitrous oxide can allow women to manage their experience when they feel they are losing control. This can empower women to have the self-determination to overcome the challenges that childbirth brings. The implementation of Bandura's self efficacy theory (Bandura, 1997b; Drummond & Rickwood, 1997; Salomonsson,

Gullberg, Alehagen, & Wijma, 2013; Sinclair, & O'Boyle, 1999) enables midwives to identify women's self-efficacy strengths and preferences, thereby helping women believe in their own abilities to successfully achieve the birth experience they desire.

Chapter two will describe the methods used to explore scholarly literature addressing the factors contributing to availability, efficacy, safety, and patient outcomes of nitrous oxide for use during labor and gynecological procedures. Chapter three will provide a synthesis of the literature, discusses major findings, and reviews strengths and weaknesses of the studies. Chapter four concludes with a synthesis of the literature answering the research question, implications for midwifery practice, and recommendations for further research.

Chapter II: Methods

This chapter discusses the methods used to identify and appraise scholarly literature in order to examine the factors contributing to the use of nitrous oxide during labor and gynecological procedures. Utilizing multiple databases and search terms, 72 articles were selected and assessed for their pertinence to this review. The final 24 articles were selected once inclusion and exclusion criteria were met.

Search Strategies Used to Identify Research Studies

The review of literature included studies that were dated between 2002 and 2016. Recent literature of good quality, as of this writing, is limited on the topic of nitrous oxide. It is for this reason that it became necessary to expand the search timeframe to 15 years. Five articles between the years of 2002 and 2011 were incorporated in order to include relevant quality studies. The following databases were accessed: CINAHL, Scopus, Science Direct, PubMed, and the search engine Google Scholar. Single search terms and a combination of search words were used including: nitrous oxide, analgesia in labor, Entonox, inhaled nitrous oxide for labor, pharmacological pain management in labor, epidural use in labor, patient satisfaction with nitrous oxide, labor pain management, and, inhaled analgesic. Research articles were also gathered from the reference lists of articles found during the search process and by related and cited articles in Scopus and Science Direct.

Criteria for Inclusion and Exclusion

It was difficult to find recent articles of good quality. Articles prior to 2006 were numerous but often of poor quality. Articles of good quality that were included focused on the safety and satisfaction with the use of nitrous oxide during labor and pain relief

during procedures. International studies were included due to the widely accepted and long history of use of nitrous oxide. Comparison of nitrous oxide and other pain relieving interventions studies were included. Articles were selected based on quality of research and age of the study. Many of these types of articles recognized the need for current higher quality research.

Several factors led to the exclusion of articles. There were many literature reviews and editorials written on the use of nitrous oxide in labor, primarily reflecting on its use in Europe. These were excluded based on lack of scientific method. Two articles of high quality were found but excluded because of not being available in English. Articles comparing nitrous oxide to other forms of inhaled anesthetic gases were excluded. Studies conducting reviews of the literature, expert opinions, and meta-analysis on nitrous oxide use were included in the initial review so that references could be reviewed in a search for additional original research studies. These studies were not included in the final version of the matrix with the exception of one literature review that included a case study and another one that was often cited in other studies on nitrous oxide. Additional exclusion criteria included quality and age of the article.

Summary of Selected Studies

The review of the literature found 24 research articles that met the inclusion criteria. The articles included in this review consisted of nine randomized controlled trials, five prospective studies, three retrospective non-experimental or case studies, two observational studies, one experimental impact study, one cohort study, and one

systematic review. The research took place in the United States, Iran, Germany, Spain, United Kingdom, China, Sweden, France, Ecuador, and the Netherlands.

Evaluation Criteria

The John Hopkins Research Evidence Appraisal Tool was utilized to evaluate the strengths and quality of the articles selected for review (Dearholt & Dang, 2012). The strength and overall quality of the research was determined for each individual article according to the John Hopkins method. Individual articles were given a rating of level I, II, III, IV, or V. Articles assigned a level I ranking were experimental study, randomized controlled trial, or systematic review of randomized controlled trials with or without meta-analysis. Level II evidence consisted of quasi-experimental studies, systematic reviews of a combination of randomized controlled trials and quasi-experimental studies, or quasi-experimental studies only with or without meta-analysis. Level III articles consisted of non-experimental studies, systematic review of a combination of randomized controlled trials, quasi-experimental and non-experimental studies, or non-experimental studies only with or without meta-analysis and qualitative study, or systematic review with or without a meta-synthesis. Level IV articles consisted of an opinion of respected authorities and/or nationally recognized expert committees or consensus panels based on scientific evidence. Level V articles consisted of evidence obtained from literature reviews, quality improvement, program evaluation, financial evaluation, or case reports.

Quality of articles was assigned after level of evidence was determined. Classifications for quality included high, good, or low, based on several factors in levels I, II, and III. High quality included consistent generalizable results with sufficient sample size for the study and design. High quality level also included adequate controls,

definitive conclusions, and recommendations based on literature reviews that included thorough reference to scientific evidence. Good quality articles were those that included reasonably consistent results, sufficient sample size for study, and some control. They also consisted of fairly definitive conclusions and reasonably consistent recommendations based on a fairly comprehensive literature review that included some reference to scientific evidence. Low quality or those with major flaws had little evidence and were with inconsistent results. They had insufficient sample size for the study design and clear conclusions could not be determined. Level IV and V had alternative criteria however they were still classified as high, good, or low quality.

The 24 articles reviewed consisted of 11 level I studies, five level II studies, five level III studies, and three were of level V evidence. Four studies were high quality, 18 were considered good quality, and two were of low quality.

Summary

Bethel University Library databases were searched along with Google Scholar to identify suitable research articles for review. After obtaining and reviewing the articles, 24 articles met inclusion and exclusion criteria for final review and evaluation. Using the John Hopkins Research Evidence Appraisal Tool (Dearholt & Dang, 2012) each article was analyzed to determine the level of evidence and classification of quality. Chapter three will provide a synthesis of the literature, including a description of the major factors associated with the use of nitrous oxide, barriers to its use, conflicting research, and strengths and weaknesses of the studies.

Chapter III: Literature Review and Analysis

Chapter three synthesizes the major findings of the literature as it pertains to the use of nitrous oxide in labor and during gynecological procedures. The major findings of the reviewed literature on the use of nitrous oxide during labor and gynecological procedures revealed that nitrous oxide was a safe, effective form of pain control with minimal side effects. It was cost effective and easy to implement and had a high rate of patient satisfaction. It also contributed to a woman's sense of self efficacy and it empowered her in the birth process. Barriers to the use of nitrous oxide were found in the literature and will be discussed. Conflicting research on the use of nitrous oxide will also be reviewed, followed by a discussion of strengths and weaknesses of the available research on the use of nitrous oxide in labor and during gynecological procedures.

Synthesis of Matrix

The matrix includes one experimental impact study, one epidemiological prospective survey, one prospective longitudinal study, one observational study, one cohort study, one literature review with a case study, one systematic review, one retrospective non experimental survey study, one retrospective review, one prospective comparative study, one randomized prospective study, one prospective observational pilot study, one prospective observational study, two prospective observational interventional studies, and nine randomized controlled studies. Each article was reviewed and the purpose, sample, design, measurement, results/conclusions, recommendations, and level and quality were determined and documented on the matrix. Subject size ranged from one case study of one individual to an epidemiological prospective survey of 35,828 N2O administrations. The matrix is included in Appendix A.

Major Findings

Safety. Evaluating the safety of any intervention should be a priority. This review overwhelmingly supported the safety and use of nitrous oxide in labor and gynecological procedures. Fourteen articles reviewed the safe use of nitrous oxide. Areas looked at specifically included maternal, neonatal, and occupational safety. Studies representing individuals who were not female or pregnant were included in the synthesis in order to provide background and additional support for the safe use of nitrous oxide in a variety of settings.

Maternal Safety. Talebi, Nourozi, Jamilian, Baharfar, and Eghtesadi-Araghi (2009) investigated the effects of nitrous oxide on maternal SpO2 (N=523) and found that values were significantly higher in the control group (oxygen only) with the first three measurements, but the remaining measurements were not significantly different. Agah, Baghani, Safiabadi Tali, and Tabarraei (2014), in a randomized controlled trial (RCT), found that there were no significant differences in maternal SpO2 levels, duration, or second stage of labor, uterine atony, or need for Pitocin when comparing the safety of continuous use nitrous oxide to that of intermittent nitrous oxide use in laboring women (N=100). A double blinded RCT looked at the use of nitrous oxide in women (N=56) undergoing cesareans to reduce anxiety and found there was no significant difference in SpO2 rates in women receiving N2O as compared to O2 alone (Manouchehrian & Bakhshaei, 2014).

A cohort study (N=6,192) by Rosenstein et al. (2014) found a significant reduction in the use of epidurals in women that used nitrous oxide in labor ($p<0.001$). There were also no significant differences in the rate of cesarean deliveries or postpartum

hemorrhage. Women who used nitrous oxide in this study were less likely to receive oxytocin ($p<0.001$), deliver via cesarean ($p<0.001$), or develop chorioamnionitis ($p<0.001$). In a prospective observational pilot study ($n=126$) where 50.8% of subjects were adolescents in a low income, high volume setting, Pita et al. (2012) found that 96.9% of subjects who had used nitrous oxide in labor delivered vaginally when previous facility cesarean rates had been reported at 50%.

When comparing the effects of nitrous oxide when used in an external cephalic version in a prospective comparative study, Burgos et al. (2013) found that there were no significant differences in the rate of complications ($p=0.91$), and there were no severe complications secondary to nitrous oxide. The cesarean rate was also not significant ($p<0.05$) between the two groups ($N=300$) (Burgos et al., 2013).

Onody, Gil, and Henequin (2006) looked at the safety of nitrous oxide when used in a variety of clinical indications by using an epidemiological prospective survey. They found that a concomitant drug significantly increased the rate of adverse events ($p<0.001$). Anxiolytics were the most common forms of other medications used when these events occurred. Longer durations of inhalation were also associated with higher proportion of adverse events ($p<0.01$). Of the 27 serious adverse events, only nine could be attributed to nitrous oxide.

Bleeding disorders can limit the available options in pain management for women in labor. Chi et al. (2009) reviewed the use of analgesia and anesthesia in laboring women with inherited bleeding disorders and their complications. In their retrospective review of 63 women, Chi et al. found that Entonox was used in 61% of labors and there

were no complications noted. Rosentstein et al. (2014) also noted that nitrous oxide could provide an effective form of pain relief for women when an epidural was contraindicated.

Infant Safety. Apgar scores, which are a determination of an infant's condition, are taken at one and five minutes of life. In six of the reviewed studies, there were no significant differences in the nitrous oxide group's infant Apgar scores at one and five minutes compared to the control groups (Agah et al. 2014; Khadem et al., 2013; Manouchehrian & Bakhshaei, 2014; Mobarki, Yousefian, Seifi, & Sakaki, 2016; Rosenstein et al., 2014; Talebi et al., 2009). Pita et al. (2012), in their prospective observational pilot study (N=126), reported no neonatal complications or neonatal intensive care unit admissions when nitrous oxide was used. All five-minute Apgars in this study were equal or greater than seven. When comparing the effects of intravenous injection of Pethidine (a narcotic opioid comparable to Demerol) and the use of nitrous oxide in labor, Teimoori, Sakhavar, Mirteimoori, and Narouie (2011) found that there were no significant differences noted in infant complications between the two groups.

Occupational Safety. Concerns with occupational exposure to nitrous oxide exist and chronic unsafe levels have been linked with reproductive risk, hematological, and nervous system adverse effects (Messeri et al., 2016; Rosen, 2002; Van Der Kooy et al., 2012). Occupational exposure limits and regulation of equipment varies by country. Time weighted averages (TWA) and short term exposure limits (STEL) are the generally accepted measurements of nitrous oxide exposure. Acceptable TWA of 25 ppm and STEL of 200 ppm were used in the Italian study by Messeri et al. (2016). The 25 ppm is the standard used in the United States. This is an arbitrary setting established in the

1970s. Other countries may use a limit of 100 ppm as the upper limit of exposure (Klomp et al., 2012).

A recent prospective observational interventional study by Messeri et al. (2016) found that mean and median values of TWA and STEL were lower than recommended values in 45 procedures when a double face mask (DFM) (10.8, 11.6 ppm TWA, 13.9, 11.0 ppm STEL) and double face mask with demand valve (DFM-DV) (2.3, 2.8 ppm TWA and 4.4, 3.5 ppm STEL) compared to a conventional anesthesia face mask or anesthesia face mask with DV were used. The DFM and DFM-DV used a portable aspiration scavenging system and the FM and FM-DV were connected to the hospital central scavenging system. This study also tested the N2O urine exposure rates of the staff members (n=2) and found that the DFM-DV urine concentration of N2O was lower than the DFM, with a mean difference of 9.56 ppm. The breathing zone sampling and environmental data of the FM and FM-DV always exceeded the TWA and STEL values established by the National Institute of Occupational Safety (Messeri et al., 2016). The researchers concluded that, for healthcare workers, the use of a double facemask with a demand valve used with a portable aspiration scavenging system was the safest form of nitrous oxide dispensing unit to use.

Another prospective observational intervention study at a birth center in the Netherlands looked at the effectiveness of a nitrous oxide scavenging system by measuring TWA from diffusion samplers worn by midwives (N=15) (Van Der Kooy et al., 2012). They found that in the 19 hour study period the eight hour TWA was not exceeded. The 15 minute TWA was exceeded but this was due to the patients not wearing the chinstrap correctly. The 16 hour exposure sample showed that the 15 minute and

eight hour TWA levels were not exceeded. Acceptable eight hour TWA in this study were 152 mg/m3 and 15 min TWA was set at 304 mg/m3 (Van Der Kooy et al., 2012). The use of a scavenging system when used with nitrous oxide was found to keep midwives' exposure levels well within the safe zone (Van Der Kooy et al., 2012).

Effectiveness of Nitrous Oxide. Sixteen articles were reviewed that looked at the effectiveness of nitrous oxide. Two of these also took into consideration the anxiolytic effects of nitrous oxide. The majority of the findings within the research revealed that nitrous oxide was effective at reducing labor and gynecological procedure pain.

Pain. Nitrous oxide is not the most powerful analgesic, but it provides significant pain relief for 50% of its users when used in laboring women and is comparable to a paracervical block and superior to opioids for pain relief, according to Rosen (2002) in a systematic review of 19 studies.

A RCT of N=100 women compared the effects of nitrous oxide to that of Pethidine during labor. Subjects receiving nitrous oxide had significantly lower visual analog pain scores ($p=0.0001$) and shorter first and second stages of labor ($p<0.05$) than those who received Pethidine via intravenous injection, according to Teimoori et al. (2011). Another study comparing the effectiveness of IM Pethidine to nitrous oxide in a RCT of women in labor (N=100) by Mobaraki et al. (2016) reported that pain scores at 30 minutes after administration were significantly lower in the N2O group ($p=0.001$) compared to the Pethidine group, however, not at the 60 minute interval ($p=0.592$), with $p<0.05$ considered statistically significant.

Pain during labor in a RCT using a single blinded placebo controlled method conducted by Talebi et al. (2009) found that subjects (N=523) who received nitrous oxide

had significant pain relief, as reported on visual analog scales, compared to those who received only oxygen. In another RCT of pregnant women in labor (N=98) using a Likert criterion scale, Pasha et al. (2012) noted that there was a significant decrease in labor pain ($p=0.004$) in the nitrous oxide group compared to the control group who did not receive nitrous oxide, with $p<0.05$ being considered statistically significant.

A prospective observational pilot study conducted by Pita et al. (2012) in a low income, high volume setting in Ecuador assessed the benefits and effectiveness of nitrous oxide during childbirth (N=126) using a visual analog scale They found that the rate of pain of labor was significantly reduced with the use of nitrous oxide ($p=0.001$). In an observational study conducted in Germany, Dammer et al. (2014) looked at both midwife and patient satisfaction with the use of nitrous oxide in labor; the pain intensity level after administration of nitrous oxide was significantly reduced ($p<0.0001$). The midwives recorded this data using a numerical pain rating scale before and after initiation of nitrous oxide (Dammer et al., 2014).

One RCT double blinded placebo study (Singh et al., 2016) looked at the effectiveness of nitrous oxide in providing pain relief for women (n=40) during intrauterine device insertion compared to a control group (n=40) that received only oxygen. Pain was measured using a visual analog scale before the procedure and at discharge. Researchers found that mean pain scores were similar in the two groups ($p=0.86$). In a prospective randomized study examining the effectiveness of nitrous oxide compared to locally injected anesthetic on subjects (N=100) undergoing postpartum perineal repair, Berlit et al. (2013) found that there was no statistically significant difference ($p=0.467$) in pain experienced between the two groups. A prospective

comparative study by Burgos et al. (2013) analyzed the use of nitrous oxide during external cephalic version and its effects on perceived pain in subjects (N=300) compared to those who received no analgesic. Researchers found that the median level of pain was statistically lower in women given nitrous oxide ($p< 0.01$) compared to the control group. Severe pain was 49% less in the nitrous oxide group, which was statistically significant ($p<0.01$).

Herres, Chudnofsky, Manur, Damiron, and Deitch (2016) conducted an evaluation of the effectiveness of nitrous oxide on reducing the pain in ED patients (N=85) presenting with a moderate to severe painful condition. Mean pain scores showed statistically significant reduction in pain at 20 and 60 minute periods using a visual analog scale.

Anxiety. Nitrous oxide has been used in dental and emergency rooms for many years and its beneficial property of being an anxiolytic is well documented, according to Collins (2015). In this review, two articles were examined that looked at this useful aspect of nitrous oxide in labor. Tension and anxiety slow the birth process. The literature review and case study by Collins (2015) provided scientific rationale that nitrous oxide was a good option for analgesic and anxiolytic effects in labor. In a double blind RCT by Manouchehrian and Bakhshaei (2014), nitrous oxide was used to reduce anxiety on subjects (N=56) undergoing cesarean section while receiving spinal anesthesia, and found the results to be statistically significant ($p=0.003$).

Richardson, Lopez, Baysinger, Shotwell and Chesnut (2016), in a retrospective non-experimental survey study, found that labor pain management scores were higher ($p<0.001$) in subjects (n=6,242) that used neuraxial analgesia compared to nitrous oxide

either alone, or who started with nitrous oxide and then converted to an epidural. Also, a RCT conducted in China (Feng et al., 2016) found that patient controlled epidural analgesia is superior to nitrous oxide in controlling labor pain (98% compared to 50%).

Satisfaction. Even when pain scores were similar or higher with the control group, satisfaction scores with the use of nitrous oxide were significantly higher. This was the case in Richardson et al. (2016) when comparing epidurals to nitrous oxide ($p=0.002$). Satisfaction scores with nitrous oxide during intrauterine device insertion were significant ($p=0.04$), although pain scores were similar to that of the control, which was oxygen alone (Sing et al., 2016).

When comparing the effects of Pethidine to nitrous oxide in labor, Teimoori et al. (2011) found in their RCT that women (N=100) using nitrous oxide had significantly higher satisfaction scores ($p=0.01$) when asked to use a verbal rating scale. In a RCT evaluating women's desired and actual use of nitrous oxide, pregnant women (n=98) reported a high rate of satisfaction and positive expectations ($p=0.01$) after use. Their awareness and understanding towards nitrous oxide increased after use ($p=0.02$) as well.

When determining the methods of pain relief women preferred in labor, nitrous oxide was the method chosen most often (79%) by questionnaires in a prospective longitudinal study of 936 Swedish women. Epidurals were chosen in 33% of labors. Women reported having a less positive birth experience when epidurals were used (Lindholm & Hildingsson, 2015). In another prospective observational pilot study assessing the benefits of nitrous oxide in labor, 96% of users (N=126) reported they would recommend it and graded it as good/excellent (92.9%) (Pita et al., 2012). Both midwives and laboring women (N=66) in an observational study in Germany reported

high satisfaction ratings when using nitrous oxide and would chose it again (p=0.0129), both during bearing down (p=0.0008) and expulsion phases (p=0.0003) (Dammer et al., 2014). Patients (N=85) in a prospective observational study presenting to the ED in moderate to severe pain reported they would use nitrous oxide again (82%). Satisfaction of nurses and physicians with its use was 82% as well (Herres et al., 2016).

Side Effects/Tolerance. Side effects with the use of nitrous oxide in laboring women (N=98) in one RCT (Pasha et al., 2012) with the control group not receiving any analgesic reported mild adverse side effects (p=0.001). While another RCT comparing women (N=523) in labor and the use of nitrous to that of those given oxygen found that side effects in the nitrous oxide group were significantly higher for all side effects (p=0.001), except for vomiting which was p=0.030 (Talebi et al., 2009). When Mobaraki et al. (2016) compared nitrous oxide during labor to the use of Pethidine in a RCT of 100 women, they reported no significant difference in side effects between the two groups with the exception of mouth dryness, which was greater in the nitrous oxide group (p=0.044). Manouchehrian and Bakhshaei (2104), in a double blind RCT of women undergoing cesarean section and using nitrous oxide as an adjunct, found no significant difference in nausea and vomiting between the nitrous oxide and control group who received only oxygen as an adjunct to spinal anesthesia.

In one observational study of 66 laboring women, nitrous oxide was well tolerated in 82% of cases. Side effects were minimal with 65% of women reporting none (Dammer et al., 2014). In another prospective observational pilot study (Pita et al., 2012) using nitrous oxide in childbirth, subjects (N=126) reported the main adverse effect as dizziness (43.7%) and reported it to be mild and tolerable. Berlit et al. (2013), in a prospective

study with subjects (N=100) randomized into a nitrous or infiltrative aesthesia group for perineal repairs, found that there were no side effects from nitrous oxide in 21 subjects. Nausea (two), vertigo (17), euphoria (15) and dizziness (19) were reported in the others. Onody et al. (2006), in an epidemiological prospective survey where nitrous oxide was used in a wide variety of clinical indications (N=35,828), reported adverse events in 4.4% of administrations, most of which were gastrointestinal and neuropsychiatric (86%). Herres et al. (2016), when evaluating nitrous oxide in a prospective observational study (N=85) in the ED, found that 38 subjects experienced minor adverse events and only three required interventions.

Ease of Use/Cost Effectiveness. A benefit of nitrous oxides is its ease of use and while many studies did not report this outcome, several mentioned it in their discussion or conclusion (Agah et al., 2104; Berlit et al., 2013; Dammer et al., 2014; Onody et al., 2006; Talebi et al., 2009). Other reported benefits include that it is inexpensive and easy to administer in many settings, especially those with limited organizational and or staff resources (Collins, 2015; Pita et al., 2012; Rosen, 2002). Herres et al. (2016), in a prospective observational study, noted that 97% of nurses in the ED found that nitrous oxide was easy to set up and operate and 73% of these nurses felt that nitrous oxide improved their ability to care for their patients.

Barriers to Use of Nitrous Oxide

The two biggest barriers to the use of nitrous oxide are availability and education. Although it has been used in the dental industry and by laboring women in European countries for hundreds of years, its use in the United States and other countries is limited. This may be in part to limited access to delivery systems until 2012 when the Nitronox

system became available again after previously production had been discontinued. Education of providers and nursing staff on nitrous oxide's effectiveness and ease of use could also be a roadblock to offering it to patients as Herres et al. (2016) found.

Conflicting Research

When comparing the efficacy of epidural versus Entonox for labor analgesia in nulliparous women, Khadem et al. (2103) in their RCT found that there was no statistical difference between length of labor ($p=0.89$) or cesarean rate ($p=1$) between the two groups. Pain scores were lower in all stages with the epidural group than with Entonox. This is not surprising because epidurals have proven to be the gold standard for complete pain relief during labor. Satisfaction rates were also higher in the epidural group in the study by Khadem et al. (2013). Feng et al. (2016) in a RCT conducted in China also reported better pain relief when comparing nitrous oxide and patient controlled epidural analgesia.

Satisfaction in two RCT was higher with epidural use than with nitrous oxide use in labor pain (Feng et al., 2016; Khadem et al., 2013). Feng et al. (2016) compared the use of patient controlled epidural analgesia to nitrous oxide and found that patient and family satisfaction rates were hugely significant in the epidural groups.

An experimental impact study by Bobb, Farber, McGovern, and Camann (2016) found that the availability of nitrous oxide does not influence the use of epidural analgesia in laboring women. They suggest that choice of pain control in labor is multifactorial.

Strengths and Weaknesses

The quality of the evidence reviewed was overall rated as good with four research studies being of high quality, based on the John Hopkins Research Appraisal Tool. Strengths of the review included nine randomized controlled studies and the majority of the studies reviewed had large sample sizes. The purpose, sample, design, measurements, results/conclusions and recommendations were all easily extracted from all but two of the articles included within the matrix.

Limitations of the existing research on nitrous oxide in labor and for gynecological procedure use included availability of high quality current research, small sample sizes in some studies, challenges with measuring pain and satisfaction rates, and lack of standard assessment tools. Cultural views of coping with pain may vary and affect results as well as limited external generalizability.

Summary

The matrix consists of 24 research studies that assessed the use of nitrous oxide during labor and gynecological procedures. Through the use of the John Hopkins Research Appraisal Tool each article was assessed and reviewed and a quality and evidence level were then assigned. A good quality rating was given to 16 of the articles and a high quality rating was assigned to four of them. The evidence revealed that nitrous oxide was a safe and effective method of pain control for women during labor, neonates, and gynecological procedures and had the ability to reduce or eliminate pain and anxiety. It was safe for healthcare workers when proper equipment was used. Nitrous oxide was associated with high patient and provider satisfaction, had minimal and manageable side effects, and was cost effective and easy to implement in many settings.

Chapter four will close with a synthesis of the literature answering the research question. It will also address implications for midwifery practice and identify recommendations for further research.

Chapter IV: Discussions, Implications and Conclusions

Synthesis of the Literature

The original research question stated: *What factors contribute to availability of nitrous oxide for use during labor and gynecological procedures?* The John Hopkins Research Evidence Appraisal Tool (Dearholt & Dang, 2012) was used to analyze 24 pertinent articles on this topic. The findings were then synthesized to evaluate trends and gaps in the literature and to identify implications for nurse-midwives as well as future research needs. Integration of Bandura's theory of self-efficacy was applied to the use of nitrous oxide during labor and gynecological procedures to provide a framework for how patients respond to labor, and other stressful and painful situations, by remaining in control of their emotions and actions to help cope with the given stressor.

Implications for Nurse-Midwifery Practice

Nurse-midwives advocate for non-intervention in normal physiological processes, such as birth. They also strive to empower women by encouraging informed choice, and the right to autonomy. This is accomplished through patient education based on scientific evidence and through shared decision making. The use of nitrous oxide in birth and other gynecological procedures allows women to be in control through self-administration and it is a respected tool for coping with the pain and distress of such situations. The evaluation of the literature in this review supported midwives' advocacy for and implementation of nitrous oxide for their patients. Current evidence on nitrous oxide use is adequate to promote it, although further studies are recommended to add to the existing understanding.

Nurse-midwives should encourage the use of nitrous oxide as an option with unique properties. It is safe for both mother and infant, and has a rapid onset, and when discontinued it is quickly reversible. It allows freedom of movement, and requires less intervention and monitoring, which aids the physiological birth process and the descent of the infant. It has been shown not to effect uterine contractions, slow the birth progress or rate of vaginal births, and may shorten first and second stages of labor (Teimoori, Sakhavar, Miteimoori, & Narouie, 2011). Rosentstein et al. (2014) reported that women who used nitrous oxide in labor were less likely to require oxytocin, deliver by cesarean, or develop chorioamnionitis.

Fear of birth and anxiety are not uncommon in laboring women and those undergoing gynecological procedures. This can slow the birth process or increase the perception of pain. Nitrous oxide has been shown to have anxiolytic effects as well (Collins, 2015; Manouchehrian and Bakhshaei, 2014). It has been found to be safe for women who have bleeding disorders and for whom other methods of pain relief would be contraindicated (Chi et al., 2009). Nurse-midwives should inform their patients of these properties and benefits.

Pain management options should be discussed with patients prior to labor or implementing them. Nurse-midwives can educate patients in regard to their options in advance and help them in the informed decision making process. This can be initiated at prenatal visits and during prenatal parenting classes. Awareness, understanding, and expectations towards nitrous oxide increased after its use (Pasha et al., 2012). This would support the need to educate patients on its benefits prenatally. One study conducted in Sweden by Lindholm and Hildingsson (2015) focused on preferred methods of pain relief

in labor and showed that nitrous oxide was the most often requested pain relief method (79%). This supports the need to increase its availability as an option for women.

Anesthesia staff is not required to administer nitrous oxide. The literature suggested and promoted the belief that nurse-midwives and nurses can be trained on how to safely administer nitrous oxide. It is cost effective, easy to use, and can be implemented quickly in a variety of settings (American College of Nurse-Midwives, 2016; Collins, 2015; Herres et al., 2016). Nurse-midwives are well positioned to promote and educate health care organizations, other providers, and nurses on the benefits and use of nitrous oxide. It is associated with high satisfaction rates by both patients and providers (Agency for Healthcare Research and Quality, 2012; American College of Nurse-Midwives, 2016; Herres et al., 2016). As health care becomes more consumer driven and patient satisfaction based, offering this service will benefit both organizations and patients alike.

Recommendations for Future Research

Although the safety and effectiveness of using nitrous oxide for labor is well documented in European countries, recent articles continue to prove its safety. Further research can help to expand on existing knowledge, including studies on a continuous use method, efficacy of more precise timing of administration, and research without confounding factors, as suggested by Agah et al. (2014) and Rosen (2002). The effects of nitrous oxide on breastfeeding have not been established and this is an area that needs to be investigated. There are mixed reports whether or not the use of nitrous oxide affects the route of birth or if it has an effect on the rate of cesarean births. Singh et al. (2016)

suggested that further study is needed to determine if nitrous oxide is appropriate for pain management in gynecological office based procedures.

This review recognized the recurrent theme of patient satisfaction with the use of nitrous oxide in several settings, including childbirth, gynecological procedures, and emergency room use. Another area to be explored would be the effect of nitrous oxide on reducing fear and anxiety in childbirth and its connection to the psychosocial aspects and correlation to protracted labor, as suggested by Collins (2015).

The Agency for Healthcare Research and Quality (2012) suggested five key questions for further investigation regarding the use of nitrous oxide in labor. Most of these key questions have been investigated at least in part. One area that needs to be further explored is the factors affecting nitrous oxides use within health systems. This should include provider preferences, availability, setting resources, and utilization. This would then also identify barriers to implementation that could be addressed.

Chi et al. (2009) looked at the use of analgesia and anesthesia in women with several inherited bleeding disorders and found that nitrous oxide was safe. Studies that specifically examined the effects of nitrous oxide on women with low platelet levels would be beneficial as this study was outdated and had a relatively small sample size.

Sing et al. (2016), while evaluating nitrous oxides use in IUD insertion, suggested that the results of the study could have been affected by the high altitude location of the study. Effects of altitude on the use and effectiveness are an area needing further research.

It would be interesting to compare the timing of when use of epidurals began and the increased rate of cesarean sections in the United States and compare this data to use in

other countries. This data, correlated with nitrous oxide use in countries of high use compared to their epidural and cesarean rates, is an area that should be further evaluated.

Integration and Application of Theoretical Framework

Bandura's theory of self-efficacy (1997b) is a framework that can be used to support the use of nitrous oxide. A satisfying birth experience is one where a woman feels she is able to cope with the pain and stress of the birth while remaining in control (Boylan as cited in Sinclair, & O'Boyle, 1999). Bandura's self-efficacy theory is applicable to women in childbirth because it deals with people's ability to control how they respond to a situation.

Everyone responds to pain and stress differently and this is also true of women's individual responses to childbirth. Women need to believe that they have the ability to accomplish the task of labor. The current pharmacological approaches to managing the pain of labor take away a woman's ability to control how she responds to the stress of labor. Intravenous opioids dull the perception of pain and also lessen the ability to interact with one's surroundings. Neuraxial analgesic decreases or eliminates the ability to be in control of one's own physical body. Self-administered nitrous oxide increases a woman's self-efficacy by allowing her to control the amount and duration of analgesic while maintaining complete physical freedom. Although it does not completely eliminate pain, it provides a sufficient form of relief that allows her to work and cope with the experience of childbirth.

The use of nitrous oxide by women can be applied to each of Bandura's four factors of self-efficacy (1997b). Childbirth can be a transformative time in a woman's life with her ability to build on previous accomplishments and increase her belief in her

capabilities to perform difficult tasks in the future. Nitrous oxide is an effective tool in the childbirth process that can increase a woman's chance of having a positive birth experience. Having another form of medication that she can self administer increases her choices, decision making, and adds to the outward sense of control, while the nitrous oxide helps her to gain control over internal factors, such as anxiety and other emotions, as well as pain. All of this adds to her performance and accomplishment and gives her a stronger sense of success.

Society forms its feelings and sense of what is normal based on individual experiences. Women love to share their birth stories and this helps to form what other women feel they should expect in childbirth. This is what Bandura (1997b) refers to as vicarious experience. For many women, drama adds to a well told story. People tend to base their experiences by comparing them to others. This can increase other women's fears of childbirth. Nitrous oxide could help improve women's self efficacy by increasing the number of positive birth stories and it could have the potential to help normalize birth in our society.

Midwives spend a lot of effort encouraging women. How they go about this is important. If midwives falsely praise people for their efforts, they will begin to see through it. Motivating individuals to understand they have the capabilities to complete a task brings about better performance. This is what Bandura (1997b) referred to as the verbal persuasion factor of self-efficacy. The use of nitrous oxide provides a worthy tool to help them remain in control of the situation so that they can take in the outward verbal persuasion of others, and in turn use it to strengthen their own inward self persuasion. Self affirming beliefs are a motivating force that leads to accomplishment.

It is interesting that some women cope with pain or distress through outward distractions and others become very inwardly focused on what is going on with their bodies. Bandura's fourth self-efficacy (1997b) factor deals with the physiological response a person has when dealing with a situation. Some levels of stress can be motivating, but when discomfort or pain becomes to great it causes a stress reaction that releases catecholamines, and this affects the body's response. This physiological response can lessen an individual's coping abilities. Nitrous oxide is thought to release endogenous endorphins, dopamine, and opioids, and decreases the body's stress response.

The more choices a woman can be given in labor, the more likely she will feel in control and actively involved in her birth. The more in control a woman feels, the better she is able to cope, persevere, and have a positive perception of childbirth (Drummond & Rickwood, 1997; Sinclair & O'Boyle, 1999). The use of nitrous oxide in labor offers a choice that helps her cope with the pain and anxiety that can accompany childbirth. Being able to have control in the birth experience increases self-efficacy and can be a very empowering force. Having a positive birth experience increases self-confidence and positions women to believe in their ability to perform in their new roles of motherhood.

Conclusion

The significant findings of this literature review were that the use of nitrous oxide in childbirth and gynecological procedures helps women cope with the pain, stress, and anxiety that often accompany these situations. It was found to be beneficial and safe for both women and neonates and, with proper delivery equipment, unsafe occupational exposure can be avoided. It was shown to be effective, have minimal side effects, and be cost effective and easy to use and implement in a variety of care settings. Use of nitrous

oxide was found to be associated with high rates of patient satisfaction and, if made more widely available, it could increase the number of positive birth experiences. Application of Bandura's self-efficacy theory can provide the theoretical framework for nurse-midwives to assist women in coping with the challenges of birth and other stressful situations. Midwives can play an integral role in educating patients, other providers, and the public on the many benefits of this effective, pain reducing modality.

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Van Der Kooy, J., De Graaf, J. P., Kolder, Z. M., Witters, K. D., Fitzpatrick, E., Duvekot, J. J., . . . Bonsel, G. J. (2012). A newly developed scavenging system for administration of nitrous oxide during labour: Safe occupational use. *Acta Anaesthesiologica Scandinavica, 56*(7), 920-925. doi:10.1111/j.1399-6576.2012.02668

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Agah, J., Baghani, R., Safiabadi Tali, S. H., & Tabarraei, Y. (2014). Effects of continuous use of Entonox in comparison with intermittent method on obstetric outcomes: A randomized clinical trial. *Journal of Pregnancy, 2014*, 245907. doi:10.1155/2014/245907	To compare the safety of continuous use nitrous oxide to that of intermittent use nitrous oxide in labor.	Included 100 women admitted for vaginal deliveries with singleton pregnancies in cephalic presentation at term. Study took place in Iran in 2013 at Sabzevar Mobini Hospital.	Randomized control trial	Rates of labor progression, maternal SpO2, vacuum assisted births, perineal lacerations, and uterine atony were recorded and compared. Fetal Apgar scores at one and five minutes were assessed. An unbiased observing midwife using a prepared scale recorded rate of maternal pushing. Maternal satisfaction was measured. P value < 0.05 was considered statistically significant.	Researchers found no significant difference in maternal SpO2 levels (P>0.05), duration of second stage of labor (p= 0.3), and fetal Apgar scores (p=0.3). Vacuum assisted delivery rate was higher in the intermittent use group, but not statistically significant (p=0.4). There was no statistically significant difference in uterine atony between the two groups (p=0.2). Maternal collaboration in pushing was greater in the continuous group (p=0.03). Intermittent group had higher rate of perineal lacerations (p= 0.04). Need for Pitocin was not statistically significant (p=0.2). Maternal satisfaction scores were significantly higher in the continuous use group (p= 0.0001).	Continuous use of nitrous oxide during labor is safe. Researchers found that the continuous use group had fewer perineal lacerations and that this may be related to a greater rate of maternal cooperation.	Level I High quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Berlit, S., Tuschy, B., Brade, J., Mayer, J., Kehl, S., & Sütterlin, M. (2013). Effectiveness of nitrous oxide for postpartum perineal repair: A randomized controlled trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 170*(2). Doi: http://dx.doi.org.ezproxy.bethel.edu/10.1016/j.ejogrb.2013.06.025	To examine the effectiveness of nitrous oxide compared to locally injected anesthetic during postpartum perineal repairs.	Included 100 women 18 years old or greater with singleton vaginal deliveries requiring perineal repair with less than a 4th degree injury. None of the subjects had received an epidural. Deliveries occurred between November 2012 and February 2013 at a university hospital in Mannheim, Germany.	Prospective study with subjects randomized into either self-administered nitrous oxide mixture or infiltrative anesthesia during repair.	Maternal characteristic data was collected for statistical analysis. McGill Pain Questionnaire was filled out immediately after repair was completed. Comparisons between the two groups were made using univariate test. P value < 0.05 was considered statistically significant.	There were no statistically significant demographic or labor characteristic differences between the two groups. No statistically significance differences in pain experienced between the two groups was found (p=0.467). Satisfaction between the two groups was not statistically significant (p=0.0699). Additional injected anesthetic was required in the study group (p=0.0001). There were no side effects from using nitrous oxide in 21 women. Those reporting side effects noted nausea in two subjects, vertigo in 17, and 15 experienced euphoria, and 19 experienced dizziness.	Nitrous oxide should be considered an effective and satisfactory alternative method for pain control during perineal repair. Further research with larger sample sizes is recommended.	Level I Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Bobb, L. E., Farber, M. K., McGovern, C., & Camann, W. (2016). Does nitrous oxide labor analgesia influence the pattern of neuraxial analgesia usage? An impact study at an academic medical center. *Journal of Clinical Anesthesia, 35*. doi:10.1016/j.jclinane.2016.07.019	To determine if the use of nitrous oxide in labor influences the rate of epidural use.	Data on epidural use for labor both 8 months prior (4315 births) and 8 months after (4224 births) introduction of nitrous oxide was introduced was gathered from the nursing and anesthesia department databases at Brigham & Women's Hospital in Boston.	Experimental impact study	Chi-square statistics were used to analyze the data.	Analysis of the month-to-month births showed no change in the use of neuraxial analgesia (p=0.24). Researchers suggest that neuraxial analgesia use is not influenced by the availability of nitrous oxide for pain relief in labor.	Researchers recognized that there are many factors contributing to a woman's choice of pain control in labor and suggested further studies to determine the overall effect of nitrous oxide on patient satisfaction and its role in pain management in labor.	Level II Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Burgos, J., Cobos, P., Osuna, C., de Mar Centeno, M., Fernández-Llebrez, L., Astorquiza, T. M., & Melchor, J. C. (2013). Nitrous oxide for analgesia in external cephalic version at term: Prospective comparative study. *Journal of Perinatal Medicine*, *41*(6), 719-723. http://dx.doi.org/10.1515/jpm-2013-0046	To analyze the use of nitrous oxide during external cephalic version and its effect on the procedure, pain, and obstetric and perinatal outcomes.	Correlation rate of 2:1 was used to determine the sample size. It included 300 women with singleton pregnancy in breech presentation at term undergoing an ECV who used nitrous oxide and 150 women in the control that had no analgesia during ECV.	Prospective comparative study The control group received (n=150) no analgesia during the ECV while the study group (n=300) received Nitrous Oxide in a 50:50 mix with oxygen administered via a face mask three minutes before beginning the ECV and continuous through the procedure for two to four minutes.	A gynecologist who was not involved in the procedure assessed the degree of pain using a numeric pain scale 30 minutes after the procedure. Other factors analyzed included success rate of the procedure, complication rates, and emergency cesarean rates. P value <0.05 was considered statistically significant. SPSS was used in comparative analysis and Chi-square statistics were used to analyze the data.	The success rate was 52.3% in the nitrous oxide group and 52.7 in the control group. This was not found to be statistically significant (p=0.94). The median level of pain was statistically lower in women given nitrous (p<0.01) compared to the control group. Severe pain was statistically significant between the two groups with the N2O group having a 49% less severe pain (p<0.01). There were no significant differences in rate of complications (p=0.91) and there were no severe complications secondary to Nitrous Oxide inhalation. The cesarean rate was also not significant between the two groups (p=0.87).	Further studies are needed which eliminate the bias in the use of consecutive cohort groups, as opposed to a randomized trial. A study with a larger sample would also be helpful in eliminating errors due to a beta error.	Level II Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Chi, C., Lee, C. A., England, A., Hingorani, J., Paintsil, J., & Kadir, R. A. (2009). Obstetric analgesia and anaesthesia in women with inherited bleeding disorders. *Thromb Haemost*, *101*(6), 1104-1111. http://dx.doi.org/10.1160/th08-10-0694	To review the use of obstetric analgesia and anesthesia in women with inherited bleeding disorders and their associated complications.	Consisted of 63 women with inherited bleeding disorders who had 80 pregnancies between January 1 2000 and December 31 2005. Women delivered at Royal Free Hospital in London.	Retrospective review based on case notes of women with inherited bleeding disorders.	Clinical data was collected including type of bleeding disorder, labor and delivery data, method of pain relief, and any complications attributable to the anesthesia.	In 67 of the pregnancies where the woman labored, Entonox was used in 61% of the labors and no complications were noted. Researchers suggest that regional blocks can be offered to women with bleeding disorders if their coagulation disorders during pregnancy are within normal levels or if they have received haemostatic agent that provides adequate coverage.	Each case must be assessed individually. The type of pain relief used is determined by the patient's preference, and collaboration with obstetrics, anesthesia, and based on her haemostatic risk. Entonox is safe for women with inherited bleeding disorders, as opposed to other methods which may be contraindicated.	Level V Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Collins, M. (2015). A case report on the anxiolytic properties of nitrous oxide during labor. *JOGNN: Journal of Obstetric, Gynecologic & Neonatal Nursing, 44*(1). doi:10.1111/1552-6909.12522	To examine the anxiolytic effects of nitrous oxide in labor and reflect on a woman's experience of its use during labor to reduce her fear and anxiety.	Literature review of 30 articles on nitrous oxide in labor, dental procedures, IV cannulation, and fear in childbirth as well as one case study on a 30 year old, G3P2002 woman who experienced stalled labor r/t anxiety in labor.	Literature review and case study	Literature review used to provide scientific rationale and case study offers logical conclusion.	Nitrous oxide appears to be a good option for analgesia in labor with potential anxiolytic effects.	Further research into the anxiolytic effects of nitrous oxide in labor is needed.	Level V Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Dammer, U., Weiss, C., Raabe, E., Heimrich, J., Koch, M. C., Winkler, M., . . . Kehl, S. (2014). Introduction of inhaled nitrous oxide and oxygen for pain management during labour: Evaluation of patients' and midwives' satisfaction. *Geburtshilfe Und Frauenheilkunde, 74*(7). doi:10.1055/s-0034-1368606	To determine both midwive's and patient's satisfaction in Germany with the use of nitrous oxide in labor.	66 women with singleton term pregnancies at the University Hospital Erlangen, Germany, and their midwives.	Observational study	Subjective patient data was recorded by the midwife and included a numerical pain rating scale before and after initiation of inhalation of nitrous oxide, statements of tolerance, side effects, and if the patient would choose this method again. The midwife's own satisfaction with the inhaled analgesic was recorded. P value < 0.05 was considered statistically significant.	The pain intensity level after administration of nitrous oxide was significantly reduced ($p<0.0001$). The nitrous oxide was reported as being well tolerated in 82% of cases. Of these satisfied women 68% reported that they were very likely to use inhaled analgesia again ($p=0.0129$). Subjects who used N2O during expulsion or bearing down reported that they would very likely use it again ($p=0.0003$ and $p=0.0008$, respectively). Side effects were minimal with 65% of women reporting none and no statistically significance between the two groups ($p=0.7053$). The midwives also reported satisfaction with the use of nitrous oxide.	Nitrous oxide is a safe and effective form of pain relief during labor.	Level III Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Feng, X., Yang, J., Cao, S., Yi, J., Ji, S., Bai, Y., & Cao, W. (2016). Patient-controlled epidural analgesia is superior to nitrous oxide inhalation in controlling childbirth pain. *International Journal of Clinical and Experimental Medicine, 9*(7). Retrieved from http://www.ijcem.com/files/ijcem0022018.pdf	To determine which method was most effective at controlling labor pain in a comparison of nitrous oxide and patient controlled epidural analgesia (PCEA).	Vaginal deliveries of 400 women ages 21-42 years old with gestational age of 34-42 weeks. There were no significant demographical differences between the two groups.	Random controlled trial of 400 women was randomly divided into two groups of 200 cases each. One group used N2O and the other patient controlled epidural analgesia. Subjects in both groups were also given a pudendal block.	Visual analogue pain scale and a patient and family satisfaction survey after delivery were used. Chi-square statistics were used to analyze the data. Results were reported in percentages with no P values given.	When compared with N2O, PCEA was associated with better pain relief and greater patient and family satisfaction rates and reported as being hugely significant. Satisfaction rate of 50% in nitrous oxide group and 99% in the PCEA group.	Researchers suggested that PCEA used with pudendal block achieve the goal of minimizing pain during childbirth.	Level I High quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Herres, J., Chudnofsky, C. R., Manur, R., Damiron, K., & Deitch, K. (2016). The use of inhaled nitrous oxide for analgesia in adult ED patients: A pilot study. *American Journal of Emergency Medicine, 34*(2), 269-273. doi:10.1016/j.ajem.2015.10.038	To evaluate the analgesic effectiveness of nitrous oxide in the ED in patients presenting with a painful condition. To determine patient and staff satisfaction with portable NO device.	Consisted of 85 patients 18 year old and older with moderate to severe pain.	Prospective observational study.	Pain reduction from baseline using a VAS at 20, 40, and 60 minutes. Secondary measurement was patient, nurse, and physician satisfaction reported on a brief questionnaire.	Clinically and statistically significant reduction in mean pain scores from baseline to 20 minutes (29.5 mm) and sustained through 60-minute period (37.7 mm) with a 95% CI. 93% of subjects were satisfied with ease of use, 82% reported they would use N2O again. Satisfaction of nurses and physicians was 82%, and 73% of nurses' felt that N2O improved their ability to care for their patients. 97% of nurses felt that N2O was easy to set up and operate. Thirty-eight subjects experienced minor adverse events and only three required interventions. Results suggest that N2O is an effective adjunct analgesic for ED patients.	This was a pilot study and lacked convenience sample, a control group, and lack of patient and staff blinding. Reluctance of the nurses to initiate N2O suggests that a comprehensive educational program of staff is indicated.	Level I Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Khadem, N., Zirak, N., Soltani, G., Sahebdelfar, N., Sepehri Shamloo, A., & Ebrahimzadeh, S. (2013). Comparison of epidural versus Entonox for labor analgesia in nulliparous women. نشریه جراحی ونترومز, 5-1 ,)1(*1*. Retrieved from http://www.ijs.ir/	To compare the efficacy of epidural versus Entonox methods for labor analgesia in nulliparous women.	Consisted of 84 nulliparous women with gestational age at or >37 weeks with singleton, cephalic pregnancies admitted to Imam Reza Hospital	Randomized controlled trial Subjects were randomly divided into two groups. 42 women used Entonox in the active phase of labor at the beginning of each contraction and 42 women received an epidural.	The subjects rated pain using a verbal report scale of 0 to 10. Data was analyzed using SPSS software. Confidence coefficient was 95% and $p<0.05$ was considered statistically significant.	Pain score was lower in all stages with epidural than with Entonox ($p=0.00$). There was no statistical difference between length of labor ($p=0.89$), cesarean rate ($p=1$), and Apgar scores ($p=0.87$, $p=0.75$). Complete satisfaction rate was higher in the epidural group ($p=0.002$).	Epidurals recommended for painless delivery but Entonox is safe and may be considered when regional analgesia is not performed. Researchers suggested that more studies with higher population and more studied groups be included to be sure of results.	Level I Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Lindholm, A., & Hildingsson, I. (2015). Women's preferences and received pain relief in childbirth: A prospective longitudinal study in a northern region of Sweden. *Sexual & Reproductive Healthcare: Official Journal of the Swedish Association of Midwives, 6*(2). doi:10.1016/j.srhc.2014.10.001 [doi]	To determine what types of pain relief methods women preferred in labor when asked in late pregnancy.	Pregnant Swedish speaking women (n=936) at 17-18 weeks gestation	Prospective longitudinal study using three separate questionnaires. Likert scales were used to determine fear of birth and to rate birth experience.	Descriptive statistics along with logistical regression modeling and statistical analyses using social science software were implemented.	Patient's preference and primiparity were the strongest factors for choosing type of pain relief during labor. The pain relief chosen most often was nitrous oxide (79%), followed by bathing (39%), breathing techniques (36%), epidural (33%), and massage (13%). Women reported a less positive birth experience when epidural was used. Women with fear of childbirth and preference for caesarean section were more likely to prefer an epidural.	Researchers suggested that positive birth experiences may be associated with pain relief methods where the patient feels a sense of control or being in charge. Pain relief methods and preferences should be explored and discussed with women.	Level II Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Manouchehrian, N., & Bakhshaei, M. H. (2014). Nitrous oxide effect on relieving anxiety and pain in parturients under spinal anesthesia for caesarean section. *Anesthesiology and Pain Medicine, 4*(2). doi:10.5812/aapm.16662	Determine the effectiveness on N2O versus O2 on reducing pain and anxiety on patients undergoing cesarean section while receiving spinal anesthesia.	Subjects (n=56) were primigravida patients with an uncomplicated pregnancy with a mean age of 23.15 years undergoing elective caesarean section. Sample size was determined with a 95% confidence interval.	Double blind random control trial Subjects in the intervention group received 50/50 blend of N2O/O2 three minutes prior to receiving the spinal and was continued until delivery. The control group received only oxygen.	VAS scales were used to determine both anxiety and pain. Recordings were obtained at six stages before, during, and in recovery from procedure. Chi-square test was used to compare the categorical variables and t-test for the continuous variables. Pearson's correlation coefficient test was used to examine the correlation between variables. A P value of equal or < 0.05 was considered statistically significant.	Pain (p=0.042) and anxiety (p=0.003) levels were significantly reduced when N2O and O2 were given in a 50/50 blend compared to oxygen alone during caesarean section in subjects who received spinal anesthesia. No significant differences were found between the two groups in regard to SpO2, Apgar scores, ephedrine use, operation time, delivery time, nausea, and vomiting.	The use of nitrous oxide is beneficial to decrease the amount of anxiety a patient experiences while having a caesarean section.	Level I High quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Messeri, A., Amore, E., Dugheri, S., Bonari, A., Pompilio, I., Arcangeli, G., & Rizzo, G. (2016). Occupational exposure to nitrous oxide during procedural pain control in children: A comparison of different inhalation techniques and scavenging systems. *Paediatric Anaesthesia, 26*(9), 919-925. doi:10.1111/pan.12966	To determine occupational exposure to N2O when administered to children using different inhalation delivery devices and two different scavenging systems.	Two Staff members involved in administration of N2O during 45 procedures. Samples were taken during procedures using standard anesthesia face mask (FM) (n=10), standard anesthesia face mask connected to a demand valve (DV) (n=10), closed circuit of a double face mask (DFM) using a portable aspiration scavenging system (N=12), and a group using a DFM with a DV connected to the portable aspiration scavenging system (n=13).	Prospective observational interventional study	Consisted of environmental sampling by time weighted average (TWA) measurements and short-time exposure levels (STEL) of N2O during 45 procedures and urine N2O concentrations in staff at the end of the procedure. Number of patients was sufficient to give a difference of 9.56 ppm with an alpha of (0.05) and a power of 87%. Statistical analysis and t-testing was performed. A P value of 0.05 was considered statistically significant. There was normal distribution between groups with no statistically significant difference.	Mean and median values of TWA and STEL were lower than recommended values in the DFM (10.8, 11.6 ppm TWA, 13.9, 11.0 ppm for STEL) and DFM-DV (2.3, 2.8 ppm TWA and 4.4, 3.5 ppm for STEL). The N2O urine exposure in DFM-DV was lower than the DFM group with a mean difference of 9.56 ppm. The breathing zone sampling and environmental data of the FM and FM-DV always exceeded the TWA and STEL values established by NIOSH.	Occupational exposure of N2O when administered as 50% N2O/O2 were reduced to safe levels when DFM or DFM-DV and portable scavenging system were used. Higher compliance may have been achieved due to the presence of a health safety environmental specialist. Small number of patients may also present a limitation of this study.	Level II Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Mobaraki, N., Yousefian, M., Seifi, S., & Sakaki, M. (2016). A randomized controlled trial comparing use of Enthonox with pethidine for pain relief in primigravid women during the active phase of labor. *Anesthesiology and Pain Medicine, 6*(4) doi:10.5812/aapm.37420	To compare the effectiveness and safety of intramuscular Pethidine to inhaled 50% N2O during labor.	Women (n=100) in spontaneous labor with uncomplicated pregnancies expected to have a vaginal delivery. Sample size confidence level of 95%. Mean age of subjects was 26.2 years for the Entonox group and 27.2 years for the Pethidine group.	Random control trial Subjects were randomly allocated into either a group using Entonox or a group receiving 0.5 mg of IM injection of pethidine	Demographic data was collected by a questionnaire. Pain was determined by a VAS before receiving analgesia and at 30 and 60 minute after receiving the intervention. A questionnaire was completed at 30 and 60 minutes also. Continuous variables were compared using t-test and Chi-squared analysis for categorical variables. Statistical analyses were performed using SPSS software. A p value equal or < 0.05 was considered statistically significant.	Pain scores at 30 minutes after intervention were significantly lower in the N2O group (p=0.001) but not at the 60-minute interval (p=0.592). Apgar scores were satisfactory with no significant difference between the two groups (p> 0.05). There were no significant differences in side effects between the two groups with the exception of mouth dryness, which was greater in the nitrous oxide group (p=0.044).	N2O is more effective in short-term use in labor pain management than pethidine	Level I Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Onody, P., Gil, P., & Hennequin, M. (2006). Safety of inhalation of a 50% nitrous oxide/oxygen premix. *Drug Safety*, *29*(7), 633-640. http://dx.doi.org/10.2165/00002018-200629070-00008	To determine the safety of premixed N2O and O2 in a 50:50 mix when used in a wide variety of clinical indications based on factors of tolerance and occurrence rates of adverse events.	Data sheets collected from 191 French hospitals pediatric and adult units totaling 35,828 administrations of premixed N2O.	Four-year epidemiological prospective survey In order to maintain temporary licensed use of the single canister use of N2O the manufacturer supplied and required the completion of a data sheet with each administration. These were required to be completed even in the absence of an adverse event.	Types of adverse events were described and factors affecting the adverse events were analyzed by chi-squared statistics. Patient demographics, description of the premix including brand, route, starting date and time, indications for use, description of any concomitant drugs, and full details of each adverse event, including body site and severity, duration, correlation of disappearance, and recurrence of the reaction with stopping and reintroducing the drug, recovery, and sequelae conditions.	A total of 1581 (4.4%) adverse events were reported, which were mostly gastrointestinal and neuropsychiatric disorders. Three main factors were associated with adverse events: 1) age, which was found to be statistically significant ($p<0.001$) with the most adverse events occurring in 5.6% in 11-18 year olds and 4.2% in 5-10 year olds; 2) class of concomitant drug significantly affected the rate of adverse events ($P<0.001$) with anxiolytics being most frequent cause; 3) longer duration of inhalation was associated with significant higher proportion of adverse events ($P<0.01$). There were 27 reported serious adverse events, though only nine of them could possibly be attributed to the nitrous oxide.	The survey confirms the pharmacological safety of a 50% premix nitrous oxide and oxygen in a wide variety of clinical indications. There is a need for rational training of medical personnel in its administration.	Level III Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Pasha, H., Basirat, Z., Hajahmadi, M., Bakhtiari, A., Faramarzi, M., & Salmalian, H. (2012). Maternal expectations and experiences of labor analgesia with nitrous oxide. *Iranian Red Crescent Medical Journal, 14*(12). doi:10.5812/ircmj.3470 [doi]	To evaluate women's desired and actual use of nitrous oxide when used during childbirth.	Pregnant women (n=98) in active phase of labor (4 cm or>) were randomized into two groups of 49. All subjects were G2 or > and had non-complicated term pregnancies with cephalic presentations. The intervention group received Entonox and the control group did not.	Randomized controlled trial	SPSS software analyzed the data using descriptive analytical statistics. Chi square, t-test, ANOVA, and Mc Nemar test were used to analyze all other data. A P value < 0.05 was considered significantly significant.	The study suggested that the use of N2O in labor decreases labor pain (p=0.004). Patients using N20 reported a having an increase in positive expectations after use (p=0.01) and high rate of maternal satisfaction (p=0.001) with mild adverse side effects (p=0.001). Awareness, understanding (p=0.02), and positive expectations r/t N2O increased after its use.	Researchers recommend that more information on the methods of labor analgesic, including N2O, be provided to pregnant women through development of a disseminating system as a way of promoting natural childbearing while decreasing labor pain.	Level I High quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Pita, C., Pazmiño, S., Vallejo, M., Salazar-Pousada, D., Hidalgo, L., Pérez-López, F., & Chedraui, P. (2012). Inhaled intrapartum analgesia using a 50-50% mixture of nitrous oxide-oxygen in a low-income hospital setting. *Archives of Gynecology & Obstetrics, 286*(3). doi:10.1007/s00404-012-2359-6	To assess the benefits and effectiveness of nitrous oxide during childbirth in a low-income, high-volume setting.	Subjects (n=126) included in the study were 50.8% adolescents and had uncomplicated singleton pregnancies in cephalic position. Births occurred at a low-income, high-output hospital in Guayquil, Ecuador.	Prospective observational pilot study	Pain was measured using a 10-point visual analog scale at baseline and one hour after using N2O. A minimum sample size was determined to be adequate with a 95% confidence level. Statistical analysis was performed using SPSS software and Kolmogorov-Smirnov test to determine distribution pattern of data. Chi-square statistics and t-test were used to analyze the data. A P value of <0.05 was considered statistically significant. With a confidence interval of 95%.	N2O was found to be a safe, desirable, and effective method of labor pain management at a facility with limited organizational and staffing resources. Rate of pain was reduced significantly with the use of nitrous oxide (p=0.001). Main adverse effect was dizziness (43.7%) and reported to be mild and tolerable. Positive neonatal outcomes were noted with Apgars at five minutes were all ≥ 7. Of interest was the finding that 96.9% of subjects delivered vaginally. Previous facility cesarean rates of adolescents had been reported at 50%.	Researchers acknowledged the lack of a control group and randomization. They suggested a need for high-quality studies in low-resource settings and further studies to determine the effect of N2O on rate of cesarean sections.	Level II Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Richardson, M. G., Lopez, B. M., Baysinger, C. L., Shotwell, M. S., & Chestnut, D. H. (2016). Nitrous oxide during labor: Maternal satisfaction does not depend exclusively on analgesic effectiveness. *Anesthesia and Analgesia,* doi:10.1213/ANE.0000000000001680	To compare the effectiveness and satisfaction of labor pain relief methods when either epidural, nitrous oxide, or both forms of analgesia are used in vaginal deliveries.	Sample consisted of data collected postpartum via standardized survey over a 34-month period, which included 6242 subjects from 2011-2014 who received labor anesthetic care at Vanderbilt University Medical Center in Tennessee.	Retrospective non-experimental survey study	Statistical analysis was performed by logistical regression of the three analgesic groups (nitrous oxide alone, neuraxial, or nitrous followed by neuraxial) and the scores of analgesic effectiveness and patient satisfaction with chosen analgesic. A P value of 0.05 was considered statistically significant.	Although labor pain management scores were not as high in the nitrous oxide group as those that used neuraxial analgesia ($p<0.001$), satisfaction scores of nitrous oxide alone ($p= 0.002$) were higher than those who received epidurals alone ($p=0.005$) or those that converted to epidurals after nitrous oxide ($p=0.003$). This finding suggested that analgesia is not the only factor to determine overall maternal satisfaction of method of pain relief chosen.	The relationship between patient satisfaction with anesthesia care in labor and effectiveness of method needs further study.	Level III Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Rosen, M. A. (2002). Nitrous oxide for relief of labor pain: A systematic review. *American Journal of Obstetrics and Gynecology, 186*(5 Suppl Nature), S110-26. doi:a121259 [pii]	To review and evaluate the effectiveness and safety of nitrous oxide during labor.	Consisted of 19 studies, which included laboring women using nitrous oxide. Important factors in determining article selection included: randomization, appropriate control group, and assessment of effectiveness of analgesia in a timely fashion after delivery, reported by laboring patient.	Systematic review	Data was analyzed in a qualitative fashion to determine efficacy, side effects, and adverse outcomes of nitrous oxide. No analysis of power was completed.	Nitrous oxide was not the most powerful analgesic, but provided significant pain relief for 50% of its users. Its benefits included self-administration, ease of use in many settings, safe and inexpensive with rapid onset and illumination. Analgesic effects were comparable to paracervical block and superior to opioids.	Continued research on the use of N2O is needed in many forms. Suggested areas of further research include: efficacy of precise timing of administration, studies without confusing factors, if N2O co-administered with opioids is safe, use at different stages of labor, safety with breastfeeding, and safety of administration with different levels of supervision.	Level V High quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Rosenstein, M., Flood, P., Thiet, M. P., Nakagawa, S., Bishop, J., & Cheng, Y. (2014). 598: The use of nitrous oxide analgesia during labor at a single institution in the United States. *American Journal of Obstetrics and Gynecology*, *1*(210), S294-S295. http://dx.doi.org/10.1016/j.ajog.2013.10.631	To describe the neonatal and maternal outcomes associated with the use of nitrous oxide during labor at a single U.S. hospital.	The sample included 6,192 laboring women with singleton non-anomalous gestations in cephalic presentation from a single U.S. hospital between 2007-2012. 14% of them used nitrous oxide and of that group 42% also used an epidural.	Cohort study Of the sample 14% used N2O during labor (n=868) and of those women 42% also used an epidural. Of the sample, 76% (n=4,705) of the women did not use N2O (P<0.001).	Neonatal admission to the intensive care unit was the primary outcome. Secondary outcomes included maternal and neonatal outcomes. Logistical regression was used to control the confounding factors influencing N2O use. A propensity score based logistical regression model was used to determine significant differences of the odds of the outcomes.	The number of women who used nitrous oxide and ended up with an epidural compared to those who did not use nitrous oxide and got an epidural is statistically significant (p<0.001). There were no significant differences in the odds of NICU admission (CI 95%), academia (CI 95%), five- minute Apgar score <7 (CI 95%), cesarean delivery (CI 95%) or postpartum hemorrhage (CI 95%) in the group that used nitrous oxide. Nitrous oxide users were more likely to be nulliparous and less likely to receive oxytocin, deliver via C-section, or develop chorioamnionitis.	Nitrous oxide as a labor analgesic is safe for the neonate and is not associated with adverse maternal outcomes.	Level III Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Singh, R. H., Thaxton, L., Carr, S., Leeman, L., Schneider, E., & Espey, E. (2016). A randomized controlled trial of nitrous oxide for intrauterine device insertion in nulliparous women. *International Journal of Gynecology & Obstetrics, 135*(2), 145-148. doi: http://dx.doi.org.ezproxy.bethel.edu/10.1016/j.ijgo.2016.04.014	To determine the effectiveness of N2O in pain management of nulliparous women undergoing IUD insertion.	Consisted of 80 English-speaking women age 13-45 years. Sample size was determined based on 15 mm difference in pain scores on a VAS determined by previous studies.	A randomized double blinded, placebo controlled trial. Forty women were computer allocated into one of two groups. One group received 50/50 mix of N2O and O2 or the control group, which only received O2 during IUD insertion.	Subjects completed a demographic and medical history questionnaire prior to the procedure. A VAS was used to assess pain before during and at discharge from the clinic. Primary outcome was maximum pain assessed two minutes post procedure. A Likert scale was used to determine satisfaction with pain management. Physicians documented difficulty of insertion and also asked to guess which patients had received N2O. Data software analysis was used. *T*-est and analysis of variance were used to compare continuous variables. Non-normal distribution variables were compared by non-parametric Wilcoxon rank	Mean insertion pain scores were similar (P=0.86). Satisfaction with pain management was similar between the two groups (P=0.14); however, significantly more women in the N2O reported satisfaction on the Likert scale (P=0.04). Most women reported that they would chose an IUD again, recommend it to a friend, and chose N2O during insertion. The 63% reported that they would be willing to pay an additional fee to use N2O for pain management. Although their pain was not reduced, their overall satisfaction was greater with the use of N2O.	The use of N2O may improve the experience of IUD insertion by increasing satisfaction with pain management. Researchers suggest that a higher ratio of N2O could help to reduce pain. They also noted that the use of N2O is cost effective after initial investment is achieved. They noted limitations of external generalizability and that the high altitude (1600 m above sea level) may have contributed to the lack effectiveness of N2O.	Level I Good quality

sum test. Fisher exact test compared categorical variables. A $P<0.05$ was considered statistically significant.

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Talebi, H., Nourozi, A., Jamilian, M., Baharfar, N., & Eghtesadi-Araghi, P. (2009). Entonox for labor pain: A randomized placebo controlled trial. *Pakistan Journal of Biological Sciences: PJBS, 12*(17). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19943458	To explore the efficacy of nitrous oxide in labor and its effect on pain and maternal SpO2 levels.	Subjects included 523-term primigravid or second gravid women in active labor with mean age of 25.5 years.	Randomized controlled trial using a single blinded placebo-controlled method. Subjects were placed into either a 50% nitrous oxide or 50% oxygen group.	VAS was used to assess rate pain. Continuous SpO2 monitoring with blood pressure and fetal heart rate at the onset of the active phase and every hour thereafter. Side effects were reported at the end of the study. Apgar's at one and five minutes were recorded. Statistical calculations were performed using SPSS software. Chi-square statistics and t-test were used to analyze the data. A P value was considered statistically significant if <0.05.	The use of nitrous oxide at a concentration of 50% is associated with few side effects, provides significant pain relief and is safe for the infant. VAS scores were significantly lower in the N2O group (p value not reported). The SpO2 values were significantly higher in the control group in the first three measurements but not significantly different in the measurements after the initial three (no p value reported). The first and fifth Apgar scores showed no significant difference between the two groups (p=0.760 and p=0.860, respectively). Side effects were significantly higher in the N2O group with p values of 0.001 for all side effects except vomiting which reported a p= 0.030.	Researchers suggest that studies should be completed that consider the evaluation of pain during delivery, and at 36 and 48 hours after delivery. Instruction on the timing of self-administration should occur before the use of nitrous oxide to improve individual's technique.	Level I Poor quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Teimoori, B., Sakhavar, N., Mirteimoori, M., & Narouie, B. (2011). Nitrous oxide versus pethidine with promethasine for reducing labor pain. *African Journal of Pharmacy and Pharmacology, 5*(17). doi:10.5897/AJPP11.490	To compare the effects and side effects of nitrous oxide and injection of Pethidine used during labor.	Subjects consisted of 100 term women with cephalic presentations expected to have normal vaginal deliveries in active labor with mean ages of 26.2 and 27.2 years in the Entonox and Pethidine groups, respectively.	Randomized controlled trial with one group receiving 50% self-administered nitrous oxide and the other group receiving 1 mg Pethidine combined with 25 mg promethazine intravenous injection.	Labor pain was measured using a VAS score once prior to administration and after each contraction. A verbal rating scale was used to measure the patient's satisfaction with the analgesia. A nurse evaluated patient's somnolence and sedation using the Ramsey Score. Descriptive statistics was used to report demographic data and SPSS software used for analysis. Chi-square statistics and t-test were used to analyze the data.	Patients receiving nitrous oxide had significantly lower VAS pain scores ($p=0.0001$), shorter first and second stages of labor ($p<0.05$), and significantly higher satisfaction scores ($p=0.01$) compared to the Pethidine group. There were no significant differences noted in infant complications. Nitrous oxide, although not a potent analgesic, was found to be more beneficial than pethidine in reducing labor pain.	Nitrous oxide has more beneficial effects than Pethidine and is easy to administer and suggested to be safe for both mother and infant.	Level I Good quality

Citation	Purpose	Sample	Design	Measurement	Results/Conclusions	Recommendations	Level & Quality
Van Der Kooy, J., De Graaf, J. P., Kolder, Z. M., Witters, K. D., Fitzpatrick, E., Duvekot, J. J., . . . Bonsel, G. J. (2012). A newly developed scavenging system for administration of nitrous oxide during labour: Safe occupational use. *Acta Anaesthesiologica Scandinavica, 56*(7). doi:10.1111/j.1399-6576.2012.02668.x	To determine the effectiveness of a nitrous oxide scavenging system.	Midwives (n=15) working at a birth center in the Netherlands.	Prospective observational intervention study	Readings of Time weighted averages (TWA) were taken from N2O diffusion sampler worn by the midwives after 15-minute and eight-hour intervals. Exposure to N2O was taken in two samples after 19 hours and 16 hours of exposure.	In the 19-hour study period the eight-hour TWA was not exceeded. The 15-minute TWA was exceeded but this was due to the patient not wearing the chinstrap correctly. The 16-hour exposure sample showed that the 15-minute and the eight-hour TWA level was not exceeded.	Limitations noted by researchers include small number of participants and that the system was tested in the continuous presence of a safety and environmental specialist.	Level III Low quality