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Neonatal Abstinence Syndrome: Assessment and Management

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NEONATAL ABSTINENCE SYNDROME: ASSESSEMENT AND MANAGEMENT

by

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Abstract

Opiate addiction is a problem for many women, posing a particular challenge during pregnancy. Fetal exposure to opiates results in a set of withdrawal symptoms known as Neonatal Abstinence Syndrome (NAS), along with other short and long term consequences. The purpose of this independent study was to address the question: When is it most appropriate to start abstinence scoring on neonates with known exposure to methadone or buprenorphine and what is the most effective course of treatment to better manage withdrawal symptoms? Evidence-based literature was utilized to address the following concerns: NAS symptoms, scoring tools, non-pharmacologic management, and pharmacologic management. According to the evidence, NAS should be managed from birth by assessing NAS scores every four hours, provide non-pharmacologic nursing interventions as first line treatment, followed by medically managed pharmacologic treatment for more severe NAS. It is vitally important that Family Nurse Practitioner's understand the short- and long-term effects of NAS for the child in order to successfully manage the health care across the lifespan for the infant and their family. Following an exhaustive literature review, a policy, procedure, and set of standing orders was developed for use by neonatal nurses and advanced practice nurses to standardize the care of opiate-exposed neonates.

Neonatal Abstinence Syndrome: Assessment and Management

Neonatal abstinence syndrome (NAS) affects 50-94% of infants exposed to opiates in utero (Agthe et al., 2009; D'Apolito, 2009). Many opiate-addicted women seek treatment for their addictions during pregnancy, with methadone and buprenorphine as the two treatment programs available to pregnant women. Methadone is currently the only drug approved by the Food and Drug Administration (FDA) for the treatment of opiate-dependency during pregnancy (Batki, Kauffman, Marion, Parrino, & Woody, 2005). However, the incidence of NAS from maternal methadone ingestion has been demonstrated to be more severe and last longer than NAS from other opiates, including heroin (Lall, 2008). Buprenorphine has been shown to elicit NAS that is less severe and shorter in duration than methadone; however, the most current statement from the FDA recommends that, because no adequate and well controlled studies are available, buprenorphine is only be used in pregnant women if the potential benefit justifies the potential risks to the fetus (Food and Drug Administration, n.d.).

The concerns with assessment of the neonate born to an opiate-addicted mother include (a) how soon after birth the NAS assessments should be initiated, (b) how often assessments should be done, and (c) what assessment tool is best to use. Non-pharmacologic management concerns for NAS include nursing interventions and breastfeeding safety. Pharmacologic management concerns for NAS include (a) determining the minimum score for initiating pharmacologic treatment, (b) discerning what medications are safe and effective for treatment, and (c) weaning the neonate from the medication safely.

The increasing incidence of methadone and buprenorphine use in pregnant women has elicited many studies on the effects of these medications on the fetus, the incidence of NAS symptoms in neonates exposed to these medications, and the differences in treatment options

available for NAS. This independent study addressed the evidence-based literature that focused on the assessment and non-pharmacologic management of NAS in neonates exposed to opiates, primarily methadone and buprenorphine, in utero. It also identified the safest and most effective pharmacologic treatment of NAS in neonates, as evidenced in current literature.

Purpose

The following clinical question will be addressed by this independent study: When is it most appropriate to start abstinence scoring on neonates with known exposure to methadone or buprenorphine and what is the most effective course of treatment to better manage withdrawal symptoms? The purpose of this question was to identify the most current evidence-based literature in developing a policy, procedure, and set of standing orders for nurses to utilize in the acute care newborn nursery setting. The location of this setting was a rural, regional hospital that is qualified to care for level one and level two neonates; level three neonates are transferred to a Neonatal Intensive Care Unit (NICU) at a larger facility for more specialized care. Currently, the facility does not provide standardized care for neonates experiencing NAS. As a Family Nurse Practitioner (FNP) it will be necessary to understand the short- and long-term effects of NAS for the child in order to successfully manage the health care across the lifespan for the infant and their family.

Significance

Opiate addiction is a significant problem in the population that is cared for at the facility described above; this includes the use of illicit and prescription opiates along with the controlled use of methadone and buprenorphine. The effects on the fetus are remarkable, with both short- and long-term effects being noted in the literature. Lall (2008) discussed the short-term effects of opiates on the fetus including (a) an increased risk of fetal distress, (b) meconium stained

amniotic fluid, (c) low birth weight, and (d) an increased incidence of sudden infant death syndrome. Also discussed were risks to the mother including an increased risk of placental abruption and antepartum hemorrhage. Long-term effects of opiates on the fetus include (a) an increase in cerebral palsy, (b) lower intelligence quotients, (c) lack of spontaneous vocalization, (d) increase in delinquent and aggressive behavior, (e) slow adaptation to new situations, and (f) vision problems (Lall).

The high priority of this project is demonstrated by the lack of standardized, evidenced-based care for neonates suffering from NAS in this facility. By using evidence-based literature to develop a policy, procedure, and set of standing orders, the care provided for these infants will improve, along with the many benefits to nurses and providers. The ambiguous nature of the current scoring tool, along with a lack of guidelines on when to use the scoring tool, when to notify providers, and how to treat these infants are all factors that increase the legal liability of the nurses and providers caring for these infants.

Definitions

Several definitions informed this Independent Study. Fetus implies the period of time prior to birth; while neonate implies the period of time immediately following birth through four weeks of age. Neonatal abstinence syndrome refers to a set of symptoms, to be discussed, experienced by a drug exposed neonate. The term "level one" refers to neonates that require only routine care with no additional support measures by the nursing staff, these neonates are allowed to room in with their mothers. "Level two" neonates require some nursing support including cardio-respiratory and oxygen saturation monitoring, peripheral intravenous access, umbilical vein or artery access, antibiotic therapy, intravenous fluids for blood glucose control, phototherapy, or are unable to room-in with their mothers for some other reason. Finally, "level

three" neonates are those that need a high level of nursing support, such as neonates who require the use of a ventilator for respiratory support.

Methods

An extensive search for evidence-based literature was performed, including consultation from an experienced, professional librarian. In the beginning of the literature search, the keywords "Neonatal Abstinence Syndrome" were used and this turned out 750 results on PubMed and 233 results from the Cumulative Index to Nursing and Allied Health Literature (CINAHL). To limit the evidence-based literature to a practical amount, the search was narrowed to include only methadone and buprenorphine exposed neonates. Therefore, the next keywords that were searched included "methadone neonatal abstinence" (248 PubMed and 88 CINAHL results) and "buprenorphine neonatal abstinence" (60 PubMed and 23 CINAHL results). Following this search, the keywords "management of neonatal abstinence syndrome" (131 PubMed and 36 CINAHL results) were used in order to retrieve more articles focusing on the care of these drug-exposed neonates.

The literature search began using CINAHL and many pertinent articles were found that were recently published. Using CINAHL in the initial search during the formulation of the clinical question ensured that there was enough research out there to continue on this topic for the independent project. Next, the search of the Cochrane Database revealed two reviews that had already been located in CINAHL. Later in the search, PubMed was utilized and many of the initial articles that were found were the same as those from CINAHL and the Cochrane Database, until trying new keywords suggested by PubMed, which identified a few new articles that were utilized. Finally, the National Guideline Clearinghouse was searched. This search did not uncover any references solely based on the neonatal experience of NAS; however, it did

reveal one guideline for pregnant women on opiate-maintenance programs and within this guideline were guidelines for the care of the neonate exposed to opiates.

The process of implementing a policy, procedure, and set of standing orders for NAS in this facility began by discussing the topic with the Family Care Center Director of Nursing (DON). The topic was well received by the DON who has started a similar project but has been unable to complete it due to time constraints. The DON felt a good starting point to introduce the topic would be to present the evidence-based literature at a Pediatrician Team meeting consisting of pediatricians, the DON, the pediatric resource nurse, and a pharmacist. Once the necessary staff was involved and interested, the process of creating a policy, procedure, and set of standing orders began. Once the policy, procedure, and set of standing orders were developed, the author presented the materials to key physicians and hospital staff for revision suggestions. Once revisions were made, the author presented the materials at a nurse staff meeting. Following this presentation to the unit nursing staff, the materials were submitted to the DON for implementation into practice. As an FNP, it is important to be cognizant of the procedures that surround the birth of an opiate-exposed infant to provide the best possible health care for the infant and their family.

Review of Literature

Appendix A provides a description of each study utilized in this discussion. The table includes the type of study, conclusions, credibility, significance, and applicability of each study. The author utilized Brown (2009) to assist with the compilation of this table. Appendix B provides a description of literature, other than studies, that were utilized in this independent study.

Symptoms and Surveillance of NAS

Symptoms of NAS vary according to the body systems involved which can include the autonomic nervous system, central nervous system, and gastrointestinal system. Symptoms of autonomic nervous system over-reactivity include yawning, sneezing, mottling, and fever (Oei & Lui, 2007). Cerebral involvement of the central nervous system includes symptoms of irritability, high pitched cry, tremors, hypertonicity, and seizures (Oei & Lui). Gastrointestinal symptoms can include vomiting, diarrhea, poor feeding, and failure to thrive (Oei & Lui). Other symptoms that can affect drug-exposed neonates include tachypnea, nasal stuffiness, excessive sucking, sleeplessness, hyperactive Moro reflex, sweating, and excoriation of skin (Finnegan, Kron, Connaughton, & Emich, 1975). There are multiple screening tools that can assist in the detection and management of NAS including the Lipsitz scoring tool, the Finnegan scoring tool, and the Neonatal Narcotic Withdrawal Index (NNWI).

The Lipsitz scoring tool was developed in 1975. It provides a scale from 0-20 with the symptoms of (a) tremors and irritability each given a score from 0-3; (b) hyper-reflexia, stools, increased muscle tone, tachypnea, and skin abrasions each given a score from 0-2; and (c) sneezing, yawning, vomiting, and fever each given a score from 0-1 (Lipsitz, 1975). The Lipsitz scoring tool was found to have a 77 percent success rate in identifying newborns of narcotic-addicted mothers by two pediatric residents who used the tool to evaluate a series of newborn infants (Lipsitz). However, in this initial study, the author does not delineate the score at which a neonate is considered to be experiencing NAS, nor does the author discuss the point at which treatment should be initiated or discontinued. Other studies have identified a score of greater than 9 on the Lipsitz as severe NAS and the point at which pharmacologic treatment should begin (Lejeune, Simmat-Durand, Gourarier, & Aubisson, 2006).

The Finnegan scoring tool, also developed in 1975, is the most widely accepted scoring tool for use in research and clinical practice. The Finnegan scoring tool is the most comprehensive tool available as it includes the greatest number of symptoms and is accompanied by guidelines for pharmacologic management (D'Apolito, 2009). The Finnegan scoring tool, in the original study, had an inter-rater reliability coefficient mean of 0.82 (Finnegan et al., 1975). The Finnegan scoring tool is comprised of a list of symptoms, each with its own score; if present the score is recorded, if not present, the score is zero. The list of symptoms (including the score) for the original Finnegan tool include: high pitched cry (2), continuous high pitched cry (3), sleeps less than 1 hour after feeding (3), sleeps less than 2 hours after feeding (2), sleeps less than 3 hours after feeding (1), hyperactive Moro reflex (2), markedly hyperactive Moro reflex (3), mild tremors when disturbed (1), marked tremors when disturbed (2), mild tremors when undisturbed (3), marked tremors when undisturbed (4), increased muscle tone (2), generalized convulsion (5), frantic sucking of fists (1), poor feeding (2), regurgitation (2), projectile vomiting (3), loose stools (2), watery stools (3), dehydration (2), frequent yawning (1), sneezing (1), nasal stuffiness (1), sweating (1), mottling (1), fever less than 101° (1), fever greater than 101° (2), respiratory rate over 60/minute (1), respiratory rate over 60/minute with retractions (2), excoriation of nose (1), excoriation of knees (1), and excoriation of toes (1) (Finnegan et al.). If the total score is greater than or equal to 8 on three consecutive scorings or greater than or equal to 12 for two consecutive scorings, treatment should be initiated within 2-4 hours (D'Apolito).

The NNWI was developed in 1981 to encourage the use of a standardized system by simplifying the process of scoring NAS. Green and Suffet (1981) had found that the previously developed Lipsitz and Finnegan scoring tools were being underutilized. Upon further investigation, they found that users of the aforementioned tools found both to be time consuming

and complex (Green & Suffet). Therefore, Green and Suffet developed the NNWI, which provides a scale of 0-2 for the following six symptom categories: respiratory rate, crying, tremors, muscle tone, axillary temperature, and vomiting. A seventh category, titled "other" symptoms, includes sneezing, diarrhea, sweating, skin abrasions, generalized seizures, localized seizures, poor suck, salivation, yawning, stuffy nose, and weight loss. If the neonate is experiencing any of the other symptoms, the examiner circles the symptoms that are present and a score of zero is given for 0-1 other symptoms; one for 2-4 other symptoms; and two for 5 and over other symptoms (Green & Suffet). A score of 5 or greater on at least two occasions in a 24 hour period results in pharmacologic treatment (Green & Suffet). In this initial study, Green and Suffet found the inter-rater reliability coefficient mean to be 0.771.

The National Guideline Clearinghouse published a guideline developed by Batki et al. (2005) to standardize medication-assisted treatment, including after-birth care, for opiate-addicted pregnant women. This guideline recommends that all neonates with known exposure to opiates in utero should receive abstinence scoring every four hours starting from birth to assess the onset, progression, and diminution of symptoms (Batki et al.). They also recommend that other conditions such as hypoglycemia, hypocalcemia, sepsis, and neurological illnesses be ruled out by performing a complete blood cell count with differential, electrolyte and calcium levels, comprehensive neurological consultation, and head ultrasound if indicated (Batki et al.).

Effects of Maternal Methadone Use on Neonates

Conflicting evidence has been found regarding the maternal dose of methadone and the effects on the neonate. In a retrospective cohort study on 444 neonates born to women in a methadone treatment program, a positive correlation was found between the maternal methadone dose and the development of NAS (Dryden, Young, Hepburn, & Mactier, 2009). The

recommendations of this study are to provide the lowest possible dose of methadone to pregnant women and to encourage and support breastfeeding (Dryden et al., 2009). Another retrospective cohort study of 66 neonates found similar conclusions that higher doses of methadone prior to delivery are associated not only with increased incidence of treatment for NAS, but also with longer duration of NAS, indicating a more severe neonatal withdrawal (Lim, Prasad, Samuels, Gardner, & Cordero, 2009). Alternatively, a separate retrospective cohort study of 204 neonates exposed to methadone found that more severe NAS was identified only in those of later gestational age and concomitant exposure to benzodiazepines, not in those infants of mothers on higher doses of methadone. This study advises that a higher dose of methadone should be considered if necessary to prevent poly-substance abuse and that benzodiazepine use should be avoided in methadone-maintained pregnant women (Seligman et al., 2008).

Dysart, Hsieh, Kaltenbach, and Greenspan (2007) performed a retrospective cohort study to determine the difference in the effects of methadone on preterm versus term neonates. Their study involved 53 preterm neonates, defined as a gestational age less than 37 weeks; and 66 term neonates, defined as gestational age greater than 37 weeks. They found that the preterm neonates, with a mean age of 34.2 weeks gestation and a mean birth weight of 2226 grams, had a mean stay of 28.4 days and a mean length of treatment of 19.8 days, the mean maximum dose of neonatal opium solution for the preterm group was 0.43 mg/kg/day. Meanwhile, the term neonates, with a mean age of 38.7 weeks gestation and mean birth weight of 2995 grams, had a mean length of stay of 37.8 days and a mean length of treatment of 31.8 days, the mean maximum dose of neonatal opium solution for the term group was 0.62 mg/kg/day. Their findings, all statistically significant, indicated better outcomes for preterm infants as they required less neonatal opium solution to control symptoms, shorter duration of therapy, and

shorter hospitalization for NAS (Dysart et al.). In agreement with this study, Seligman et al. (2008) also found a statistically significant shorter duration of treatment in neonates born at less than 37 weeks gestation. In their retrospective cohort study of 204 neonates born to methadone exposed mothers, the mean length of treatment for neonates with a (a) gestational age of 23-32 weeks was 11.9 days; (b) gestational age of 33-36 weeks was 26.2 days; and (c) gestational age of 37-42 weeks was 38.1 days (Seligman et al.).

Effects of Methadone versus Buprenorphine on Neonates

In a retrospective study of 259 pregnant women and 260 neonates (one set of twins), the effects of methadone and buprenorphine on neonates were compared; 100 women in the study were methadone-maintained, and 159 women were buprenorphine-maintained. This retrospective study did not find any statistically significant differences in the severity of NAS or the treatment duration between the two groups (Lejeune et al., 2006). The only significant difference between the methadone and buprenorphine groups was the mean onset of NAS, 45 hours and 37.5 hours respectively; and the mean age at maximum Lipsitz score, 80 hours and 66 hours respectively (Lejeune et al.).

In contrast, Ebner et al. (2007) found a significant difference in favor of neonates born to buprenorphine-maintained mothers as compared to methadone-maintained mothers. Of the 53 neonates in this study, 21 neonates had no or mild NAS that did not require treatment. Seven of these neonates were born to methadone treated women (32 percent of the total methadone-exposed neonates); three were born to slow-release morphine treated women (18 percent of the total morphine-exposed neonates); and eleven were born to buprenorphine treated women (79 percent of the total buprenorphine exposed neonates). The remaining 32 neonates in the study

required treatment for NAS, with 68 percent of the methadone-exposed neonates versus only 21 percent of the buprenorphine-exposed neonates requiring treatment (Ebner et al.).

Non-Pharmacologic Management of NAS

Encourage breastfeeding.

Many studies have concluded that breastfeeding during methadone or buprenorphine opiate treatment is beneficial to the neonate (Jansson et al., 2008; Lall, 2008; Lim et al., 2009; Oei & Lui, 2007). Jansson et al., in a non-randomized control trial, measured the maternal breast milk and neonatal plasma concentrations of methadone of eight breast feeding and eight bottle feeding subjects. Findings indicated low neonatal plasma concentrations of methadone in the breastfeeding group that had no significant correlation to the maternal dose of methadone ($r = 0.25$; $P = 0.37$) (Jansson et al.). They also found no neurobehavioral differences between the groups of infants; furthermore, NAS scores and pharmacotherapy for NAS were not related to infant plasma methadone concentrations (Jansson et al). The conclusions of this study indicated that the benefits of breast feeding outweigh the risks of small concentrations of methadone in breast milk.

Encourage small frequent feedings.

Small frequent feedings are recommended to aid in digestion, prevent regurgitation, and provide adequate calories for neonates experiencing NAS (Beauman, 2005). Many neonates with NAS lose a significant caloric intake due to regurgitation, by feeding smaller amounts more frequently, the neonate is able to better tolerate feedings and reduce regurgitation. Gavage feedings may be necessary for neonates with a disorganized suck, which is often seen in neonates with NAS and is shown as an inadequate ability to coordinate the necessary suck and swallow

for proper feeding. Neonates with poor weight gain may also benefit from gavage feedings or intravenous infusions which will also prevent hypoglycemia and hypocalcemia (Beauman).

Other interventions.

Neonates with excessive irritability may benefit from swaddling to decrease sensory stimulation (Beauman, 2005; AAP 1998). Observation of sleep habits will assist caregivers in altering the environment to promote normal newborn sleep-wake cycles. Interventions that alter the neonate's environment include providing a dark, quiet environment, as well as ensuring temperature stability (Beauman; AAP). Altering the environment along with pacifier use can also assist the neonate with self-calming behaviors (Beauman; AAP).

Pharmacologic Management of NAS

In a 1998 Policy Statement, the American Academy of Pediatrics (AAP) recommended that pharmacologic therapy be initiated for neonates with confirmed drug exposure when the following symptoms are present: seizures, poor feeding, diarrhea and vomiting resulting in excessive weight loss and dehydration, inability to sleep, and fever unrelated to infection. The recommendation also stated that the use of a screening tool can be helpful to document manifestations of withdrawal, provide objective criteria for assessing neonates, and determining treatment; however, the validity of the screening tools available have not been proven. Finally, the AAP recommended the use of oral tincture of opium as the preferred pharmacologic treatment for opiate withdrawal and oral phenobarbitone as the preferred pharmacologic treatment for sedative-hypnotic withdrawal (American Academy of Pediatrics [AAP], 1998). Since the publication of the AAP recommendations, D'Apolito (2009) discusses the use of oral morphine as being superior to oral tincture of opium due to the reduced alcohol content of oral morphine, 10 percent, versus that of tincture of opium, 17 to 21 percent.

In a review of the literature, D'Apolito (2009) discussed the pharmacologic management options for the treatment of NAS. Oral clonidine is the first medication discussed and is not recommended for use in neonates because of the risk of over sedation and no current supportive evidence for the use of this drug, as a first-choice treatment option, for NAS (D'Apolito). The next classification of drugs discussed were sedatives, including phenobarbital, chlorpromazine, and diazepam. D'Apolito did not support the use of oral phenobarbital as a first-choice medication for the treatment of narcotic withdrawal given that (a) no therapeutic blood level has been identified, (b) large doses may depress the central nervous system, and (c) phenobarbital does not resolve gastrointestinal symptoms (D'Apolito). Neither oral chlorpromazine nor oral diazepam are recommended due to their long half-life, making titration difficult. Moreover, late-onset seizures have been reported with the use of diazepam (D'Apolito). Paregoric, an oral morphine solution which had been the pharmacologic treatment of choice for NAS in the past, is no longer recommended due to the additives in the solution including 44-46% alcohol, camphor, anis oil, benzoic acid, and glycerine (D'Apolito).

A very limited number of studies have been performed using oral methadone as the first-choice drug; however, it has been found to have results similar to those for oral morphine. Finally, oral morphine has been recommended as the first-choice treatment for NAS for reasons including decreased treatment length, decreased length of hospital stay, short half-life of the medication, and its effectiveness for the treatment of gastrointestinal symptoms (D'Apolito).

Agthe et al. (2009) performed a randomized, controlled trial to determine the effectiveness of oral clonidine as an adjunct to oral opioid therapy for the management of NAS. The trial involved 80 neonates, 40 of which were randomly assigned to the diluted tincture of opium (DTO) and clonidine group, and 40 of which were randomly assigned to the DTO and

placebo group. The primary outcomes of the study indicated that the length of treatment was 27% shorter for the DTO and clonidine group versus the control group (Agthe et al.). Secondary outcomes found no statistically significant difference between the groups related to maximum weight loss, with the DTO and clonidine group losing 6.91 percent of birth weight and the control group losing 7.79 percent of birth weight (Agthe et al.). To date, this is the largest prospective double-blind, randomized trial of neonates experiencing NAS; therefore, further studies are necessary to assess for the long-term safety of oral clonidine use in neonates.

In a pilot study, Kraft et al. (2008) trialed the use of buprenorphine for the treatment of NAS. The buprenorphine was administered to neonates sublingually at an initial dose of 13.2 μg/kg per day in three divided doses. The trial was open-label and neonates were randomly assigned to participate in either the buprenorphine group or the neonatal opium solution group, with 13 subjects in each group. The findings conclude that the use of buprenorphine for NAS is effective with a mean of 22 days for length of treatment in the buprenorphine group and 32 days with the NOS group; likewise the buprenorphine group had a mean length of stay of 27 days whereas the NOS group had a mean of 38 days (Kraft et al.). It was noted that phenobarbital for adjunct therapy was required for three neonates in the buprenorphine group and one neonate in the NOS group after maximum daily doses where reached and NAS symptoms were still present (Kraft et al.).

The AAP discussed appropriate dosing of medications used for withdrawal symptoms in their 1998 policy statement. The AAP has not established updated recommendations to date, however, given the updated literature reviewed in this independent study, it is noted that these recommendations are still valid, and new medication therapies have not undergone adequate studies to be put into practice. The recommendations are the same for all oral morphine

solutions, including tincture of opium, paregoric, and oral morphine. A dilution of 0.4 mg/ml is recommended with a starting dose of 0.1 ml/kg with feedings every four hours (AAP, 1998). This dose may be increased by 0.1 ml/kg every three to four hours until symptoms are controlled; however, no daily limit is recommended (AAP). Finally, the AAP recommended that once symptoms have been controlled, determined by every four hour abstinence scoring, at a steady dose for three to five days, the dosage should be tapered by gradually decreasing the dose, not by increasing dosing intervals.

The AAP recommendations are lacking in specificity with regards to the frequency of dose reduction and the amount of reduction per time. Cloherty, Eichenwald, and Stark (2004) provide more specific guidelines for oral morphine administration for the treatment of NAS. The initial starting dose is dependent on the NAS scores and varies between 0.32 mg/kg/day orally to 0.8 mg/kg/day orally; the dose is divided into four hour increments; with three consecutive scores above 8, recommendations are to increase the dose by 0.16 mg/kg/day orally to the maximum dose, divided into 6 doses; when three consecutive scores are below 8, recommendations are to wean by 10% of the maximum daily dose; finally, if the neonate is weaned too quickly, return to the previous effective dose (Cloherty, Eichenwald, & Stark).

Osborn et al. (2005a, 2005b) performed two Cochrane Reviews to evaluate the most current research on the pharmacologic treatment of opiate-withdrawal NAS. Their findings concurred with the previous AAP recommendations, stating that opiates are the most acceptable first-line pharmacologic treatment for opiate withdrawal; likewise, phenobarbital is the most appropriate pharmacologic treatment for sedative withdrawal (Osborn et al., 2005b). Osborn et al. (2005b) also found that phenobarbital can be used as an adjunct to opiates for neonates with severe withdrawal symptoms which has also been recommended by other studies (Coyle,

Ferguson, Lagasse, Liu, & Lester, 2005; Coyle, Ferguson, Lagasse, Oh, & Lester, 2002). They were unable to find sufficient evidence to support the use of chlorpromazine or clonidine for NAS (Osborn et al., 2005b). Ebner et al. (2007) also found that the treatment outcome for opiate withdrawal with oral morphine is superior when compared to oral phenobarbital, with treatment lasting a mean of 10 and 18 days, respectively. Ebner et al. also signifies the importance of a standardized procedure in the treatment of NAS with three positive outcomes noted: shorter treatment duration; shorter period of separation from mother, thus improving mother-child bonding; and lower financial costs.

Batki et al. (2005) does not recommend a specific abstinence score for the initiation of pharmacologic therapy; however, they do state that an abstinence score of less than 8 in a neonate with rhythmic feeding and sleep cycles and adequate weight gain is considered to be under control. If pharmacologic management is indicated according to the scoring system being utilized, the Batki et al. recommends that the dosage of medication at which the neonate is under control of symptoms be continued for 72 hours prior to weaning. When weaning occurs, Batki et al. recommends decreasing the dose by 10% daily or as tolerated. A minimum 5 day hospitalization is also indicated to adequately evaluate the neonate for signs and symptoms of NAS (Oei & Lui, 2007; Pritham, Troese, & Stetson, 2007).

Results

The formal presentation of the policy, procedure, and standing orders to the Pediatrician's Team occurred at Sanford Medical Center of Bemidji on December 15, 2010. As mentioned previously, the Pediatrician's Team audience consisted of the four pediatricians, the DON, the pediatric resource nurse, and a pharmacist. Copies of the policy and procedure (see Appendix

C), and standing orders (see Appendix D) were dispersed at the beginning of the meeting, this was the first review of the documents for all present except the author.

Suggestions for revision came from the pediatricians and included eliminating the minimum hospital stay requirement and replacing it with a statement of consideration to prolong hospital stay, thus allowing physicians to determine appropriate length of hospital stay on an individual basis. Another pediatrician recommended revision of the oral morphine guidelines based on the guidelines in her previous practice at a children's hospital, changing the starting dose of 0.32 mg/kg/day to 0.05 mg/kg/dose, the dose increase from 0.16 mg/kg/day to 0.025 mg/kg/dose, and the maximum dose from 0.8 mg/kg/day to 0.1 mg/kg/dose. The change in dosing guidelines simplifies the dosing calculations to help prevent errors and does not result in a significantly different dose, for example the starting dose with the pediatrician recommended guidelines would be 0.05 mg/kg/dose versus 0.0533 mg/kg/dose after dividing the literature recommended 0.32 mg/kg/day into six doses. The pediatricians also suggested to include in the policy and procedure to use the birth weight of the child until the child is 7 days old and then use the current daily weight of the child from day 8 until completion of therapy, this is again to help prevent dosing errors as neonatal weight changes significantly over the first week of life. Finally, it was recommended that the author consult with other major hospitals to compare and contrast the author's policy, procedure, and order set with those of other major hospitals.

In accordance with the feedback obtained, the author revised the policy and procedure (Appendix E) and standing orders (Appendix F) to include the pediatrician recommended revisions. The author then consulted the Neonatal Outreach Nurse at Children's Hospitals and Clinics of Minnesota (CHCM). The Neonatal Outreach Nurse shared the policy and procedure as well as the standing orders used for NAS at the facilities affiliated with CHCM. The author

compared both sets of policies and procedures and both sets of standing orders and found no revisions that needed to be made. The references utilized by both the author and CHCM were also consistent.

Discussion

The intent of this evidence search was to formulate a policy, procedure, and order set for nurses, advanced practice nurses, and physicians to follow in caring for neonates exposed to opiates in utero. As a result of evidence-based policy implementation, level one and level two neonates exposed to opiates who are born at this facility will receive documented NAS scoring, using a modified Finnegan scoring tool, every four hours starting within two hours of birth. The modified Finnegan scoring tool will provide a method of scoring that will offer consistency across examiners to monitor for symptoms of NAS, progression of the withdrawals, need for treatment, response to treatment, and readiness to be weaned from treatment.

Neonates exposed to opiates in utero will remain in the hospital for a sufficient period of time to monitor for symptoms of NAS. Physicians will be responsible for determining the appropriate number of days on a case by case basis. In determining appropriate length of hospital stay, physicians will take into account the opiate that the neonate was exposed to, the length of in utero exposure, and the pattern of Finnegan scores obtained by the nursing staff.

Non-pharmacologic nursing interventions should be initiated shortly after birth for all infants exposed to opiates in utero and will continue until the neonate is discharged from the hospital. Nursing interventions include swaddling, decreasing environmental stimuli, frequent small feedings, observation of sleep habits, temperature stability, weight monitoring, and monitoring for changes in clinical status that may indicate another disease process. Upon

hospital discharge, nursing staff will educate caregivers on the above interventions to facilitate continued comfort of the neonate.

Nurses will notify physicians of the need for pharmacologic treatment when the neonate receives three consecutive Finnegan scores greater than 8 or two consecutive Finnegan scores greater than 12. Neonates will receive oral morphine at a starting dose of 0.05 mg/kg/dose, every four hours. Dosing may be increased by 0.025 mg/kg/dose, every four hours until NAS scores fall below 8. If unable to control NAS at the maximum morphine dose of 0.1 mg/kg/dose or neonate is presenting with seizures, consider the use of phenobarbital as adjunct therapy or transfer to a level three NICU. Once Finnegan scores are maintained below 8 for 24-48 hours, weaning may begin by decreasing the dose by 10% of the maximum daily dose, divided, every four hours.

Implications for Nursing

Practice

Nursing practice in the care of NAS in this facility will change immensely. Once the policy has been implemented and nursing staff has sufficient knowledge, skill, and ability in the assessment and care of neonates experiencing NAS, they will be held more accountable for the observation and non-pharmacologic treatment of NAS. Nursing staff will be consistent in the practice of contacting providers with elevated NAS scores and will be proficient at providing pharmacologic management as ordered by providers. Advanced practice nurses and physicians will be responsible for providing consistent, evidence-based care in the pharmacologic treatment of NAS. Neonates with prenatal opiate exposure will receive enhanced care and parents/guardians of these neonates will receive thorough education on the signs and symptoms

of NAS, short and long term implications of opiate exposure, and techniques for home care management of NAS.

Research

Advanced practice nurses have many opportunities for research related to NAS, especially in the area of pharmacologic therapy. Further research opportunities include the use buprenorphine for the treatment of NAS; the use of methadone for treatment of NAS; the use of clonidine and phenobarbital as adjunct therapies to morphine in the treatment of NAS. Other prospects for research include long-term effects of the various pharmacologic therapies available on the growth and development of children who were exposed to opiates in utero. Further research would also be beneficial in the area of NAS scoring tools to determine the most reliable and valid tool to use and how to best use it.

Education

Nurses in this facility will be re-educated on the use of the modified Finnegan scoring tool to increase accuracy and consistency of results. Nurses will also be informed of the addition of the policy, procedure, and standing orders for the care of opiate-exposed neonates. With the increase in knowledge, skills, and abilities the nursing staff will be better equipped to care for neonates with NAS. Emphasis for nursing staff will be placed on monitoring for symptoms every four hours, providing non-pharmacologic evidence-based nursing care and contacting physicians when scores are elevated as noted previously.

Advanced practice nurses and physicians will be included in the development of the policy, procedure, and standing orders and be responsible for appropriate use of the standing orders to provide evidence-based pharmacologic therapy for opiate-exposed neonates. Further educational opportunities for advanced practice nurses include correctly identifying symptoms of

NAS, the nursing and medical management of NAS, and the short- and long-term effects of opiate exposure to the growth and development of the child. Finally, the advanced practice nurse must be thoroughly educated in the anticipatory guidance of post-hospitalization care as well as follow up with health care professionals to provide the best possible primary care to the opiate-exposed neonate through the lifespan.

Health Policy

According to the American Nurses Association (1991), the individual nurse has at least three responsibilities in the realm of ethics and human rights. First, to provide nursing care in a way that meets the needs and is consistent with the goals of the individual patient with respect to level of health and quality of life (American Nurses Association [ANA]). Second, social action and reform to facilitate access to health care and availability of nursing care (ANA). Lastly, patient education and advocacy to ensure that informed decisions are made based on knowledge of all available options and consequences (ANA). In accordance with this policy statement, the goal of this project is to ensure that neonates are receiving the best possible care that is evidence-based. Caring for neonates is a challenging specialty, as they are unable to speak for themselves. Nurses must be strong advocates for neonates, ensuring that the care provided is alleviating the suffering that comes with NAS.

Conclusion

This independent study has addressed the evidence-based literature concerning NAS. The significance of this independent study as it relates to practice is to present guidelines that will assist nursing staff, advanced practice nurses, and physicians in providing consistent, evidence-based care for opiate-exposed neonates. Findings include the importance of initiating abstinence scoring, using the Finnegan scoring tool, which is the most comprehensive and

widely used instrument for the identification of NAS, within two hours after birth at intervals of every four hours. Non-pharmacologic nursing management of NAS as first line treatment including swaddling, decreasing environmental stimuli, frequent small feedings, observation of sleep habits, temperature stability, weight monitoring, and monitoring for changes in clinical status that may indicate another disease process. Identification of NAS requiring medically managed pharmacologic treatment with three consecutive Finnegan scores over 8 or two consecutive scores above 12. Finally, evidence indicates the use of morphine as the preferred pharmacologic treatment for symptoms of NAS. The author utilized this evidence to develop a policy and procedure (see Appendix E), and set of standing orders (see Appendix F) to standardize the care of opiate-exposed neonates.

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Appendix A

Summary Table of Study Characteristics

Author(s), Year	Description of Study	Conclusions	Comments
Agthe, A.G., Kim, G.R., Mathias, K.B., Hendrix, C.W., Chavez-Valdez, R., Jansson, L. et al (2009)	Prospective, block-randomized, double blind, placebo-controlled trial. Aim of this study was to determine if oral clonidine, used as an adjunct to diluted tincture of opium (DTO), would reduce the duration of opioid detoxification for NAS. The sample size used was 80 newborn infants, assigned randomly to the placebo group or the clonidine group (40 in each group). The inclusion criteria were infants between 0-14 days of life, prenatal exposure to opioids, and two consecutive Finnegan scores ≥9 requiring pharmacotherapy; infants were excluded for gestational age of <35 weeks, intrauterine growth restriction, congenital anomalies, illness requiring oxygen, IV fluids, or medications, and breast feeding. The primary outcomes measured were the length of pharmacotherapy for the two different groups. The secondary outcomes that were measured included the amount of DTO required to treat the NAS, treatment failure, seizures, weight gain, blood pressure, heart rate, and oxygen saturations.	For the clonidine/DTO group, the length of pharmacotherapy was 27% shorter than for the placebo/DTO group. The clonidine group had an average of 11 days of pharmacotherapy with a range of 4-28 days; while the placebo group had an average of 15 days of pharmacotherapy with a range of 4-100 days. For the secondary outcomes, there were no differences between the groups in maximum weight loss or the time it took to reach their birth weight again; overall the clonidine group required less DTO per day of treatment than the placebo group; five of the 80 infants failed treatment, all from the placebo group; three infants experienced seizures, all from the placebo group; seven infants, all from the clonidine group rebounded; blood pressures and heart rates were statistically lower in the clonidine group. This study found that clonidine, when used in combination with DTO, assisted infants who were experiencing moderate to severe NAS to stabilize and detoxify more rapidly than DTO alone.	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the study subjects were selected using strict inclusion and exclusion criteria, and were randomized into one of two groups; the measuring instruments were valid laboratory tests, vital sign measurements, and the Finnegan scoring tool; extraneous variables were well controlled; this was a double blind study, the investigators, parents, and care takers were blinded to group allocations until the study was completed; the clonidine group had a statistically significant shorter duration of pharmacotherapy than the placebo group; randomization was effective in controlling for confounding factors; interventions were well defined and consistent; confounding variables were taken into consideration when evaluating the results of the study; this is the first study on the use of clonidine as adjunct therapy for NAS; this is a credible study. **Clinical Significance:** This is a pilot study on a moderately sized sample of neonates, the authors discuss the limitations of the study and areas of need for further study; this study is not clinically significant at this time because there is not enough evidence to confirm safety and efficacy. This study is of medium-high quality.
Batki, S. L,	Clinical Practice Guideline.	Other conditions may mimic	**Credibility:** The panel was comprised

Kauffman, J. F., Marion, I., Parrino, M. W., & Woody, G. E. (2005)	Discusses the guidelines for the care of pregnant and postpartum women receiving opioid treatment and the effects on the newborn. This guideline was produced by Batki, Kauffman, Marion, Parrino, and Woody; Center for Substance Abuse Treatment. This guideline was developed in 2005 and updated on May 1, 2009.	NAS, therefore, should be ruled out by obtaining a CBC with diff, electrolyte and calcium levels, a comprehensive neurological consultation, and a head ultrasound if indicated. An abstinence scoring system should be used to monitor the onset, progression, and diminution of symptoms in opioid-exposed neonates. The NAS score is used to determine whether pharmacotherapy is necessary and monitor the optimum response to therapy. This guideline recommends that all infants exposed to opioids should be scored every 4 hours. Control of NAS is achieved when the Finnegan score is less than 8.	of members with the necessary expertise; the guideline did not discuss the search and selection of research, nor are the recommendations followed by supporting evidence; it is also not clear when research evidence was lacking and when expert opinion was being used; it is unclear whether the guidelines are free from bias; the guidelines are current and peer reviewed; it is unclear if this guideline is credible, it is possible that the supporting evidence is available through the one listed bibliographic source, however, I am unable to access this to determine the credibility. **Clinical Significance:** The important decisions that a practitioner would need to make are identified by the guideline; patient concerns and risks are identified; because of the lack of references, it is difficult to say if the recommendations, based on research evidence, would produce good patient outcomes, however, according to the research that I have done myself, yes, the recommendations would produce good outcomes. The recommendations are clinically significant. **Applicability:** The guideline does address our situation; we should use the guideline in part (utilizing the recommendations for neonates); in order to use the recommendations, we will need to implement a policy and procedure and a set of standing orders; we do have the resources to make these changes; we need to get the family practice and pediatrician doctors on board with this project and, once in motion, get the nursing staff involved before the final drafts are in place; I will be doing a chart review of the neonates in the recent past and will do a chart review after the initiation of this change to determine if there is a benefit. Overall, this is a medium

			quality clinical guideline.
D'Apolito, K. (2009)	Integrative Research Review. Aim of this review is to identify signs and symptoms of NAS, assessment tools to monitor the severity of NAS, and options for pharmacologic management. The individual research reports that compare treatments for NAS are listed in a table, this table includes the methods, doses, and sample sizes that each study used. The studies used for the other aspects of the review were included within the text of the review. The author did not disclose how the research articles were chosen for the review. There were 54 references listed and it appears as though 26 of these references were research studies that the author used to compare assessment tools and treatments.	Using the available literature, the author deducted that oral morphine is currently the best option in treating NAS. However, she notes that buprenorphine may be a viable option, but it needs more research. The author notes that the Finnegan scoring tool for NAS is the most frequently used in research and clinical practice, it is the most comprehensive assessment tool available, and is accompanied by guidelines for pharmacologic management.	**Credibility:** The topic was clearly defined; it appears as though the search for research articles was unbiased, however, the author did not disclose the process; the designs and findings of the studies were discussed in detail; there was a synthesis of the findings from each study; the author did explore differences between studies; there was a sufficient number of studies reviewed; the use of morphine for NAS was the most consistently supported intervention; the conclusions of this review are credible. **Clinical Significance:** The use of the Finnegan scoring tool and morphine oral solution for the first-choice treatment of NAS; these findings are clinically significant. **Applicability:** The IRR does address the problem we are facing in our setting; the patients are similar; there is no known reason why the conclusions would not apply to our setting; the barriers to incorporating these recommendations in our setting including recruiting physician support for implementing a policy, procedure, and set of standing orders for the assessment and treatment of NAS, these barriers can be overcome; training would including presenting the new policy, procedure, and set of standing orders to the physicians and nurses that will utilize such information; we will have a consistent treatment plan for NAS in newborns and see a reduction in the NAS withdrawal scores of neonates born to methadone- and buprenorphine-maintained women; we should proceed to design a protocol incorporating all of these conclusions.

Dryden, C., Young, D., Hepburn, M., & Mactier, H. (2009)	Retrospective cohort study. The aim of this study was to investigate factors associated with the development of NAS and the resources available to infants born to drug-misusing women. The sample size was 444 infants and 450 women (there were six stillbirths). The women in this study were on the methadone program, there was no exclusion criteria, so many of the women were poly-substance abusers. The study looked at the maternal characteristics, including age, parity, social deprivation category, tobacco users, alcohol users, hepatitis C serology, history of depression and use of antidepressants, and illicit drug use. The infant characteristics that were reviewed included gestational age at birth, birth weight, head circumference, mode of delivery, and congenital anomalies. The study also looked at the number of infants experiencing, severity of, and treatment of NAS, the factors associated with the development of NAS, the hospital workload, and finally discharge and follow-up of the participants.	This study found that 45.5% of infants received pharmacological treatment for NAS (when Lipsitz scores were ≥5, treatment was then considered). The median age at the start of treatment was 3 days (with a range of 1-13 days of life); this was not related to the pattern of maternal drug use. Duration of oral morphine therapy ranged from 1-44 days with a median of 11 days. This study found that infants who were also exposed to benzodiazepines were significantly more likely to experience NAS requiring treatment. Also, they found a strong correlation between the prescribed methadone dose and poly-substance use (when not enough methadone was being given, the chance of poly-substance increased). This study found that 48.4% of infants were admitted to the NICU for a duration of 1-108 days (with a median of 13 days). The reasons included respiratory distress, prematurity, and social reasons, however, 40% of these admissions were primarily for continuing treatment of NAS in term infants. Hospital stay was longer for infants of poly-substance using women than methadone-only using women.	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the study subjects were selected based on enrollment in the methadone program, with no exclusion criteria; the measuring instrument included the Lipsitz scoring tool and data extracted from chart reviews; extraneous variables were not well controlled; no intervention was tested; this study's results were similar to other studies; this is a credible study. **Clinical Significance:** This is a clinically significant study of the effects of poly-substance versus methadone-only NAS in newborn infants, especially given the larger sample size. However, this study was done in the United Kingdom, so the demographics may not be comparable to that of our hospital. Overall, this is a low-medium quality study.
Dysart, K.,	Retrospective cohort study.	This study found that	**Credibility:** The study was published

Hsieh, H. C., Kaltenbach, K., & Greenspan, J. S. (2007)	The purpose of this study was to determine the effect of preterm delivery on the course of NAS in infants born to mothers participating in a methadone maintenance program. Inclusion criteria for the study were infants born between 1998-2002 to women maintained on methadone; no exclusion criteria were discussed. The sample size included 53 preterm infants and 66 term infants.	preterm infants require lower doses of neonatal opium solution and shorter courses of therapy than do term infants.	in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the study subjects were term and preterm neonates selected based on having mothers enrolled in the methadone program, no exclusion criteria were discussed; the measuring instrument included the Finnegan scale and data extracted from chart reviews; extraneous variables were not well controlled; no intervention was tested; this study's results were similar to other studies; this is a credible study. **Clinical Significance:** This is a clinically significant study of the effects of NAS in newborn infants that were term versus preterm. This study used a small sample size and did not control extraneous variables. Overall, this is a low-medium quality study.
Ebner, N., Rohrmeister, K., Winklbaur, B., Baewert, A., Jagsch, R., Peternell, A., Thau, K. et al (2007)	The aim of this study was to compare the difference in incidence and timing of NAS in newborns of opiate-maintained women and the intensity and duration of NAS on either morphine or Phenobarbital. Inclusion criteria for the study were infants that were born to mothers enrolled in this specific opioid maintenance therapy, with the exclusion of those who were poly-substance users, alcohol users, and twin pregnancies. The final sample size was 53 women and their infants. NAS symptoms were measured every 4 hours using the Finnegan scale and were treated for scores higher than 10 with either Phenobarbital or morphine.	This study found that NAS occurred in 60% of the 53 neonates. Also of note, was that a significant portion (79%) of the neonates of the buprenorphine-maintained women did not require medical treatment of NAS. The onset of clinical NAS symptoms presented most rapidly in the neonates of mothers maintained with slow-release morphine with a mean onset of 33.2 hours (range of 1-134). The mean onset of NAS in infants of mothers maintained on buprenorphine was 34.3 hours (with a range of 25-52). Finally, the infants of mothers maintained on methadone had a mean onset of NAS at 57.5 hours (with a range of 16-161). The treatment duration for infants receiving	**Credibility:** The study was published in a peer reviewed journal; the design was not clearly stated, it is difficult to determine if the infants were randomly selected for each group and also if the parents, caregivers, and/or investigators were blinded to which infant was in which group; the data obtained did answer the study question; the study subjects were selected using strict inclusion and exclusion criteria; the measuring instruments were the Finnegan scoring tool, Apgar scores, and birth weight, length, and head circumference measurements; since it is not clear if this study was randomized or blinded, it is possible that the lack of controls and anonymity could have influenced the findings; the morphine group had a statistically significant shorter duration of treatment than the Phenobarbital group, also the infants exposed to buprenorphine had a shorter duration of NAS than those exposed to methadone in utero; it is not clear if randomization

		Phenobarbital had a mean of 17.7 days with a range of 4-42; while the morphine group had a mean treatment time of 9.9 days with a range of 3-35 days. This study concludes that Phenobarbital should only be recommended for neonates of mothers suffering from poly-substance abuse.	occurred, however inclusion criteria appeared effective in controlling for confounding factors; interventions were well defined and consistent; confounding variables were taken into consideration when evaluating the results of the study; this is a moderately credible study. **Clinical Significance:** This study was performed in Austria with an all-Caucasian cohort, which does not compare to our facility. This study is of low-medium quality.
Finnegan, L. P., Kron, R.E., Connaughton, J.F., Emich, J.P. (1975)	Randomized control trial. The aim of this study was to evaluate the reliability and effectiveness of a scoring tool to assess for NAS in neonates with known exposure to narcotics. The study group consisted of four pairs of nurses on varying shifts that were randomly selected to independently rate the same group of passively addicted infants. The first of the pair assessed the infants approximately 15 minutes before the second nurse in the pair, to reduce the chance of random changes in the infant's level of arousal. The secondary aim of this study was to evaluate the difference in treatment between the infants that were assessed using the scoring tool and the infants that were not assessed with a scoring tool. The measures included the use of the Finnegan scoring tool.	The use of the scoring tool showed an inter-rater reliability coefficient ranging between 0.75-0.96 with a mean of 0.82. The group of infants that were not assessed using the scoring tool had a treatment rate of 60% versus 54% of infants in the group that was assessed using the scoring tool, thereby reducing the number of hospital stays in the group that was assessed using the tool by 25%. The Finnegan tool for NAS is highly reliable and can be used to rate the severity of NAS, regulate the drug dosage levels during therapy, and compare the relative efficacy of various pharmacologic agents in the management of NAS.	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the study subjects were selected using inclusion criteria of being born to mothers with known narcotic use, however, no exclusion criteria were documented; the measuring instrument was the Finnegan scoring tool, which at this time was new and not yet proven; extraneous variables were not controlled; this did not appear to be a blinded study, however, it was not mentioned in the report if the parents knew which group their infant was in; the group of infants that were assessed using the tool had a 25% shorter hospital stay and 6% less treatment rate with pharmacologic therapy; randomization was effective in controlling for confounding factors; interventions were well defined and consistent for the study group, however, there were no defined interventions for the control group, this was the norm at the time, however, and was the reason for testing a tool to create uniformity; confounding variables were taken into consideration when evaluating the results of the study; this is a credible study.

			Clinical Significance: This is a pilot study on a small sample of neonates, the authors discuss the limitations of the study and areas of need for further study; this study is clinically significant, and has sparked many more studies of its kind since. This study is of medium quality.
Green, M., and Suffet, F. (1981)	Non-randomized control trial. The aim of this study was to evaluate the effectiveness of a NAS scoring tool that was simplistic and accurate. At this time, many physicians were not using a scoring tool because of the lengthiness of the available tools, therefore, by creating a shorter, simpler tool, the authors hoped to encourage uniformity of the assessment and treatment of NAS. The sample included 50 full-term infants (11 of which were low birth weight) who were born to methadone-maintained women and 40 full-term healthy infants born to non-addicted mothers. The researchers were not blinded to the group that the infants were in, and the infants of the control group were only scored once on the second day of life, as compared to scoring the NAS group as often as deemed necessary according to the infant's behaviors.	The authors conclude that this is a valid study as it was able to distinguish a significant difference between the control group and the NAS group, thereby identifying infants with NAS. The authors also conclude that the reliability of this tool is high, with an inter-examiner reliability of 0.771.	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question, however, should have been a blinded study design; the data obtained did answer the study question; the study subjects were selected using inclusion criteria and the control group was matched to the experimental group, however, the authors do not give detail as to the quality of the matching between the groups; the measuring instrument was the Neonatal Narcotic Withdrawal Index; extraneous variables were not controlled; this was not a blind study, the physicians, nurses, and parents all knew what group each infant was in, therefore, providing an opportunity for bias; the authors found the tool to be statistically significant in regards to reliability; randomization was not performed; interventions were well defined and consistent; confounding variables were not taken into consideration when evaluating the results of the study; this is not a credible study. **Clinical Significance:** This is a pilot study on a small sample of neonates, the authors do not discuss the limitations of the study and areas of need for further study; this study is not clinically significant at this time because there is not enough evidence to confirm efficacy of the tool. This study is of low quality.
Jansson, L.M., Choo,	Correlational Study. Aim of study is to determine the	Concentrations of methadone in human milk in	**Credibility:** It is in a peer reviewed journal; the design was appropriate to

R., Velez, M.L., Harrow, C., Schroeder, J.R., Shakleya, D.M., & Huestis, M.A. (2008)	concentrations of methadone found in breast milk and plasma of breastfeeding methadone-maintained women, infant outcomes among matched samples of breastfed and formula-fed infants of methadone-maintained mothers, and plasma methadone concentrations among the infants of women in the 2 groups. Sample size is 16 women (8 who chose to breastfeed matched with 8 who chose to formula feed) and 16 infants (8 breastfeeding matched with 8 formula-feeding). Measures: Pre and post feeding breastmilk samples on days 1, 2, 3,4,14, and 30 from the breastfeeding group, along with methadone plasma samples (peak and trough) from both breastfeeding and formula feeding groups of mothers on the same days. Plasma methadone levels from all infants on day 14. NAS scoring using the Finnegan scale on all infants every 3-4 hours during their entire hospitalization and NICU Neonatal Neurobehavioral Scale evaluations of all infants on days 3, 14, and 30.	the first month are low and the amount ingested by infants is also low (<0.2 mg/day at the end of the first month of life). Concentrations of methadone increase over time, particularly in the first 4 days of life, however concentrations of methadone in breastmilk is unrelated to the maternal dose of methadone. The results of this study support the recommendation for breastfeeding, as the benefits of breastfeeding likely outweigh the risks of the small concentrations of methadone found in the breastmilk; however, more studies are needed to determine the effects of the small amount of methadone on infant and child development.	the question; the data and analysis did answer the question; the 16 study participants were found from a group of 2257 pregnant or postpartum women in a methadone treatment program, they first determined 8 women who chose to breastfeed and then matched them with 8 women of similar characteristics who chose to bottle feed; they used laboratory values of breastmilk and plasma and proven screening tools for NAS for their instruments; all important extraneous variables were controlled; the study design did not influence the findings; a difference was found between the groups, however, not statistically significant; random assignment was not done; the interventions were well defined and consistent; the confounding variables (such as infant sex) was taken into consideration; the findings of this study were consistent with 2 previous studies; this is a credible study. **Clinical Significance:** No statistically significant differences were found, this study is not clinically significant, due to the major limitations of group size and short length (one month) of the study as identified by the authors. This study is of medium-high quality.
Kraft, W.K., Gibson, E., Dysart, K., Damle, V.S., LaRusso, J.L., Greenspan, J.S., Moody, D.E. et al. (2008)	Randomized, open-label, active-control study. Aim of study is to demonstrate the feasibility and safety of administering sublingual buprenorphine for the treatment of NAS. Sample size of 26 neonates born to mothers who were methadone-maintained, with 13 infants receiving the standard-of-care dose of morphine (in the form of neonatal opium solution) and	Buprenorphine was associated with a 31% reduction in the length of treatment and a 29% reduction in the length of stay; however, the variance seen in both treatments was large and there was not a statistical difference between the two treatments. This study demonstrated that the use of buprenorphine for the	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the study subjects were selected using strict exclusions, however, the two treatment groups were not matched 'exactly'; the measuring instruments were valid laboratory tests and the Finnegan scoring tool; extraneous variables were well controlled; this was not a blind study, the physicians, nurses, and

	13 receiving sublingual buprenorphine solution. Using the heel-stick method, plasma levels of buprenorphine were measured pre-dose, post-dose, and mid-interval for the infants randomly assigned to the buprenorphine group. Infants were also assessed at regular intervals using the Finnegan scoring tool for NAS.	treatment of NAS is feasible and has an acceptable safety margin, however, this was a pilot study, and more research in this area is needed.	parents all knew what group each infant was in, therefore, providing an opportunity for bias and there was a higher number of boys in the buprenorphine group; no statistically significant differences were found between the two groups, however, length of stay and treatment were shorter in the buprenorphine group; randomization was effective in controlling for confounding factors; interventions were well defined and consistent; confounding variables were taken into consideration when evaluating the results of the study; this is the first study on the use of buprenorphine for NAS; this is a credible study. **Clinical Significance:** This is a pilot study on a small sample of neonates, the authors discuss the limitations of the study and areas of need for further study; this study is not clinically significant at this time because there is not enough evidence to confirm safety and efficacy. This study is of medium-high quality.
Lejeune, C., Simmat-Durand, L., Gourarier, L., & Aubisson, S. (2006)	Prospective, multicenter, observational study. Aim of study is to compare the perinatal morbidity and NAS of infants born to women taking methadone or buprenorphine during their pregnancies. Sample size included 259 women, 100 (39%) were methadone-maintained, and 159 (61%) were buprenorphine-maintained; and 260 infants (one set of twins) that were born to these mothers. Measures utilizing the Lipsitz scoring tool for NAS (interval of screening not indicated).	There were no statistically significance differences in the NAS symptoms of neonates between the methadone-exposed and buprenorphine-exposed groups. A trend was noted, however, of a later onset of NAS in methadone-exposed infants.	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the study subjects were not randomly selected, nor were there exclusion criteria to limit variables, there were poly-substance abusing women in the study, which may skew the results; the measuring instrument was the valid and tested Lipsitz scoring tool; extraneous variables were not well controlled; this was not a blind study; no statistically significant differences were found between the two groups, however, a trend of later onset of NAS was noted in the methadone-exposed group; randomization was not present; interventions were not well defined and

			consistent; confounding variables were not taken into consideration when evaluating the results of the study; this is one of the first studies on the difference in NAS between buprenorphine- and methadone-exposed infants; this is a mildly credible study. **Clinical Significance:** This is a prospective study to compare the NAS outcomes of infants exposed to buprenorphine compared with those exposed to methadone in utero. The results of this study are not impressive enough to be considered for clinical use; however, it is a good starting point. The authors do indicate the limitations of the study and suggestions for further study. This study is of medium-low quality.
Lim, S., Prasad, M.R., Samuels, P., Gardner, D.K., & Cordero, L. (2009)	Retrospective Cohort Study. The aim of this study was to examine high dose methadone in pregnant women and its effect on the duration of NAS. The sample included 68 neonates and their mothers, inclusion criteria was the enrollment in a methadone treatment program and delivery at The Ohio State University Medical Center; exclusion included a lack of documentation of NAS and lack of documentation of a maternal dose of methadone prior to delivery. The researchers placed the women into three different cohorts depending on their methadone treatment dose. The low- dose group consisted of women receiving methadone at 70 mg or less; the medium-dose group received 71-139 mg of methadone; and the high-dose group received 140 mg or more	This study found that higher doses of methadone not only resulted in higher treatment rates, but also longer periods of NAS, suggesting more severe withdrawal. The authors also performed additional linear regression analysis with maternal methadone dosage as the continuous variable and found that for every 1 mg increase in maternal methadone, NAS symptoms were treated for 0.18 more days. In other words, for every 5.5 mg increase in methadone in the mother, the infant experienced 1 more day of treatment for NAS.	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the study subjects were not randomly selected, however strict inclusion and exclusion criteria were utilized; the measuring instrument was the valid and tested Finnegan scoring tool; extraneous variables were not well controlled; this was not a blind study, however the scoring of the infants was solely dependent on their NAS scores, not the methadone dose in the mother; no statistically significant differences were found between the low- and medium-dose methadone groups, however, there was a statistically significant higher rate of treatment in the high-dose compared with the low-dose group; randomization was not present; interventions were well defined and consistent; confounding variables were taken into consideration when evaluating the results of the study; there have been multiple studies on the

	of methadone. The method of data collection was via chart review. The Finnegan scoring tool was used to assess for NAS.		effect of low-dose vs. high-dose methadone with mixed results, either showing no relationship with NAS or an increase in NAS with high-dose methadone; this is a credible study. **Clinical Significance:** This is a retrospective study to compare the NAS outcomes of infants exposed to low, medium, or high dose methadone in utero. The results of this study are impressive in that the researchers studied a broad and evenly distributed range of maternal methadone dosages, along with the use of additional linear regression analysis with maternal methadone as the continuous variable. The authors do indicate the limitations of the study and suggestions for further study. This study is of medium-high quality.
Lipsitz, P. J. (1975)	Non-randomized control study. The aim of this study was to evaluate the use of a screening tool for NAS. The evaluation consisted of two pediatric residents examining a series of newborns twice daily, 90 minutes prior to the next feeding, without being aware of the infants' pertinent histories. After the study was complete, the neonatal histories were examined, and the neonates were classified into 5 groups, 4 of which were neonates of non-addicted mothers and one group of neonates born to narcotic addicted mothers. There were a total of 41 infants in this study.	The results for the first four groups of infants ranged from 0-3 to 0-4 depending on the group, where as the last group of infants (those exposed to narcotics in utero) had scores ranging from 0-9. This was a statistically significant finding. The author suggested a clinical cut-off point for infants not exposed to narcotics to be at 4, as none of the infants in this study who were not exposed scored over 4.	**Credibility:** The study was published in a peer reviewed journal; the design was appropriate to the study question; the data obtained did answer the study question; the author did not discuss inclusion or exclusion criteria for the study participants; the measuring instrument was the Lipsitz scoring tool for NAS; extraneous variables were not controlled; this was a blind study, the residents did not know which infants were born to addicted mothers and which were not, which limited the bias; there was a statistically significant difference in the scores between the non-addicted infants and the addicted infants; randomization was not done; interventions were well defined and consistent; confounding variables were taken into consideration when evaluating the results of the study; this is a credible study. **Clinical Significance:** This is a pilot study on a small sample of neonates; the authors discuss the limitations of the study and areas of need for further

			study. This study is of medium quality.
Seligman, N. S., Salva, N., Hayes, E. J., Dysart, K. C., Pequignot, E. C., & Baxter, J. K. (2008)	Retrospective cohort study. The aim of this study was to identify maternal variables that may help to predict the length of treatment for NAS. The study examined infants from 2000-2006 whose mothers were on methadone maintenance at delivery. The authors used a mixed-effects linear regression to examine the interaction of maternal and neonatal variables with the length of treatment.	Variables that were found to increase the length of treatment included an advanced gestational age and concomitant maternal use of a benzodiazepine.	**Credibility:** The study was presented at the 28th Annual Meeting of the society for Maternal-Fetal Medicine. The authors utilized an appropriate study design for the question posed. The data that was obtained and the analysis that the authors conducted was able to answer the research question. Inclusion criteria allowed only for neonates diagnosed with NAS. Exclusion criteria included if the length of neonatal treatment could not be determined, if the neonate was enrolled in a coinciding NAS study, stillbirths, and deliveries at less than 23 weeks gestation. The measuring tool was the Finnegan scale and the authors utilized charts from neonates diagnosed with NAS. Variables were not controlled, as it was the variables that were being studied to determine what variables increased or decreased length of treatment; this study's results were similar to other studies; this is a credible study. **Clinical Significance:** This is a clinically significant study of the variables that affect the length of treatment for NAS of a moderate sample size. Overall, this is a medium quality study.