Clinical Performance Guideline
Neonatal Resource Services
Neonatal Abstinence Syndrome (NAS)

Medical Necessity Guideline

Purpose: To provide guidelines for the monitoring and management of neonates with intrauterine exposure to illicit substance and for treatment of infants with neonatal abstinence syndrome (NAS).

Target Client Population: This guideline applies to the neonate who exhibits NAS from intrauterine exposure to maternal illicit drug use or prescribed drugs or as a result of sedation and pain management during NICU hospitalization.

Background	Neonatal abstinence syndrome (NAS) has been described as a group of clinical findings associated with infant opioid withdrawal although signs of withdrawal can be also exhibited in infants exposed in utero to other substances such as benzodiazepines, barbiturates and alcohol. (AAP, 2012) NAS occurs more frequently in infants exposed to long-acting and maintenance opioids than in those exposed to short-acting opioids. (Patrick, 2015) The incidence and duration of NAS may be decreased in pregnant women treated with buprenorphine and naloxone compared to methadone. (Nanda, 2015; Wiegand, 2015) The symptoms of NAS vary based on maternal and neonatal factors but may include irritability, lethargy, poor feeding, vomiting or diarrhea, hypertonicity, excessive sucking, nasal stuffiness, tachypnea, sweating, jitteriness, tremors and occasionally seizures. For infants with suspected or known substance exposure, observation and supportive care should be initially provided. Early ongoing engagement with the primary caregiver is preferable. Supportive care could include adjustment of the environment to decrease stimulation, swaddling of the infant, nutritional support and introduction of a pacifier for excessive sucking. Mild NAS symptoms may resolve within a few days without additional intervention. (Ordean, 2015) Pharmacologic treatment may be necessary for infants exhibiting signs of moderate to severe withdrawal symptoms despite supportive care. Failure to provide the appropriate treatment for NAS may result in significant morbidity and mortality for the neonate. Preterm infants have a lesser risk of NAS and withdrawal symptoms than late preterm or term infants. Medical evidence has validated Finnegan scoring for term and late-preterm neonates. The use of Finnegan scoring in preterm infants may result in an inaccurate assessment of neonatal withdrawal status. Universal screening should be applied equally to all women. Punitive measures do not work. Opioid agonist therapy (AKA medication assisted treatment) is safe, effective and associated with improved maternal and infant outcomes. (Patrick, 2017) The management of NAS should be based on the symptoms of the infant and individualized for each neonate. Psychosocial assessment of applicable family members in the hospital followed by appropriate interventions based on that assessment is recommended.
Treatment Criteria	<u>Clinical evidence in the medical literature supports the following:</u> • Postnatal monitoring for withdrawal symptoms is indicated if there is a history of maternal substance use or enrollment in a methadone program, exposure to certain prescribed medications (benzodiazepines, barbiturates, etc.) or as part of a differential diagnosis when the infant has unexplained seizures, irritability

	or encephalopathy.
	• In infants at high-risk for NAS, including those with mothers positive for substance use and those who exhibit signs/symptoms of withdrawal, the first urine and/or meconium specimen should be obtained for drug exposure screening. Urine specimens can detect recent substance exposure while meconium screening can detect substance exposure from the time of gut development. Umbilical cord testing is an additional option. This screening must comply with state laws. (AAP, 2012; Montgomery, 2006)
	• Infants presenting with signs of neonatal opioid withdrawal without history or suspicion of maternal substance abuse should have additional diagnostic testing performed to differentiate NAS from other conditions.
	• Withdrawal symptoms occurring in the first 24 hours of life should prompt for history of maternal nicotine use as this may represent nicotine withdrawal as opposed to opiate withdrawal. (Garcia-Algar, 2008)
	• Neonatal abstinence scoring using a tool such as the Finnegan NAS scoring system should be performed at least 2 hours after birth for infants with known or suspected substance exposure. This scoring includes clinical attributes or signs of withdrawal related to metabolic, gastrointestinal, neurological and respiratory status.
	• Subsequent serial NAS scoring should occur 30-60 minutes after each feeding. It is preferable to use the same reviewer/scorer each shift to minimize inter-rater variability and to give more reliable scores.
	• For clinically stable neonates, a rooming-in policy should always be adopted to enhance mother-infant bonding where possible. (Patrick, 2016)
	• When environmental and supportive measures are not sufficient, pharmacotherapy is necessary to treat NAS. NAS treatment is designed to control mild to severe symptoms and avoid complications such as seizures, weight loss and dehydration. (McQueen, 2016)
	• Infants with Finnegan scores ≤ 7 require only observation and supportive care. The utility of a calm environment and parental engagement is extremely effective in facilitating medication weaning and shortened LOS in infants requiring NAS treatment. (Grossman, 2017) The first approach to NAS is non-pharmacologic, involving environmental measures. All neonates at risk for withdrawal should be kept in a quiet, soothing place that is free of excessive light and noise. Gentle handling, containment and non-nutritive sucking are key elements. (Hudak, 2012) For those infants not warranting treatment:
	  • An inpatient stay of 3 days is appropriate for newborn infants exposed to short-acting opiates and 5 days for newborn infants exposed to opiates with longer half-life (e.g., buprenorphine, methadone). (Hudak, 2012)
	  • For infants exposed to short-acting benzodiazepines (e.g., alprazolam), a 3 day observation period is appropriate with up to 5 days for exposure to longer-acting benzodiazepines (e.g., diazepam).
	  • Infants with known antenatal exposure to both opioids and benzodiazepines can be observed in the hospital for 4 to 7 day duration based on short vs. long half-life of the drug exposure.

	(Hudak, 2012) • Observation and NAS scoring can be performed in the normal newborn nursery or the mother's room. • Pharmacologic management may be initiated for an infant when 3 consecutive Finnegan scores are ≥ 8, when 1 score is ≥ 12 or the average of two scores are ≥ 12. It may also be warranted for infants with seizures, significant feeding intolerance (diarrhea, emesis) and weight loss or failure to gain weight, or unexplained fever and inability to sleep despite supportive measures. (Dow, 2012) It is reasonable to use a sum total of the last three scores to initiate treatment if the sum is >24. • NAS standardized treatment protocol and staff education are effective strategies to reduce hospital LOS. (Asti, 2015; Hall, 2014; Hall, 2015) • Options for pharmacologic treatment of withdrawal symptoms may include morphine, methadone, and phenobarbital or combination therapy. The choice of drug should match the class of drug used by the mother, including the duration of action. The advantage of methadone versus morphine for reducing the length of NAS treatment is inconclusive. (Kraft, 2016) • Morphine may be started at an initial dose of 0.04mg/kg PO administered with feedings every 3-4 hours. The dose may be increased depending on NAS scores by increments of 0.04 mg/kg/dose up to a maximum of 0.2 mg/kg per dose. (AAP, 2012) • Methadone, compared to morphine, has the potential to shorten the length of NAS treatment. (Brown, 2015) Methadone may be started at an initial dose of 0.05-0.1 mg/kg/dose PO administered with feedings every 6-24 hours. The dose may be increased depending on NAS scores by increments of 0.05 mg/kg/dose. (AAP, 2012) • Buprenorphine shows promise as an alternate agent to treat NAS with a shortened LOS. The initial dose is 4-5 mg/kg/dose and is administered sublingually. The maximum dose is 60 mg/kg/day. The dosing frequency is every 8 hours. (Kraft, 2017) • Phenobarbital is a nonspecific central nervous system depressant used as an adjunct in opioid withdrawal in addition to treatment of non-opioid withdrawal. Combination therapy utilizing morphine/phenobarbital may reduce not only the severity/duration of symptoms but also the LOS. • Clonidine (an alpha 2-adrenergic receptor agonist) has been reported as both a first-line and adjunctive agent for NAS. (Agthe, 2009; Kraft, 2008; Broome, 2011; Bada, 2015) • Benzodiazepines are not recommended as first line or adjunct agents. Benzodiazepines have a synergistic effect with opioids and can lead to life threatening respiratory depression/hypotension. The neonate has a limited capacity to metabolize diazepam. • Paregoric is a short-acting opiate that is no longer recommended for managing opiate withdrawal because it contains alcohol benzoic acid camphor, which can be neurotoxic. (Bio 2011) • Tincture of opium is not recommended due to 25-fold higher concentration of

	morphine risking medication errors and morphine overdose. (Hudak, 2012) • The lowest dose to control symptoms should be utilized with regular review for weaning. • Weaning should be initiated when the infant's NAS scores consistently remain < 8 for 1-2 days. The dose should be decreased 10-20% from the highest total daily dose every1-2 days for oral morphine and every 2-4 days for oral methadone based on symptoms. Morphine weaning should be based on dose and not interval due to its short half-life. • Morphine and methadone should be stopped when the dose reaches 10% of the highest dose for 24-48 hours. • Discharge should occur within two days of stopping opiate therapy if all other discharge criteria are met and NAS scores do not meet criteria to reinstitute treatment. Hospital stay should not be extended if subsequent scores following this 48 hour observation period do not meet criteria to restart pharmacologic management. • Select patients with optimal home environment and provider follow-up can successfully complete the NAS weaning process as an outpatient. (Backes, 2012; Smirk, 2014; Kelly, 2014; Hall, 2015; Lee, 2015) • Due to its long half-life, phenobarbital adjuvant therapy can be weaned on an outpatient basis. • For infants weaning from clonidine adjuvant therapy, data is lacking for support of a need to taper the medication over a period more than 48 hours. A reasonable time period to monitor for any cardiovascular changes is up to 48 hours after stopping the medication. (Agthe, 2009) • Infants with NAS are in a hypermetabolic state. Their high caloric needs may warrant high caloric density formula or fortified human milk to prevent excessive weight loss and promote optimal weight gain. • Women who are on methadone or buprenorphine maintenance and not abusing other drugs should be encouraged to breast-feed. Breastfeeding is associated with milder NAS symptomatology and reduced need for pharmacologic intervention; therefore, it should always be promoted when not contraindicated. (McQueen 2011; D'Apolito 2013; Rossen, 2016) • It has been suggested that newborns exposed to selective serotonin reuptake inhibitors (SSRI) antidepressants such as Prozac, Zoloft, Celexa and Paxil may be at risk for developing withdrawal symptoms after delivery. The symptoms usually disappear in 48 hours and do not require medical intervention. (Levinson-Castiel, 2006) • Other studies have suggested that withdrawal from SSRIs may actually be secondary to serotonergic hyperstimulation. (Laine, 2003) • The most commonly observed symptoms from SSRI withdrawal are tremor, increased muscle tone, sleep disruption, gastrointestinal disturbance and high-pitched crying.
Clinical Evidence	**<u>Pharmacotherapy</u>** • A retrospective cohort study by Gibson et al (2016) compared the length of

	pharmacotherapy and hospital stay of opioid-exposed infants at various gestational ages. Study participants included 102 late preterm, 158 early term, 122 full term and 21 late term infants. The requirement for pharmacotherapy in NAS treatment was identified as similar among the cohorts. When medication was administered, the duration was longer in the early and full term infants than the preterm or late term infants. • McQueen & Murphy-Oikonen (2016) estimated 60-80% of infants with NAS do respond to nonpharmacologic treatment and need to progress to management with medications. The purpose of pharmacologic treatment is to reduce any moderate-to-severe symptoms an infant may be experiencing. These symptoms may include weight loss, dehydration, fever or seizures. • Nanda et al (2015) analyzed data from infants admitted to West Virginia University Hospital's NICU due to maternal drug exposure from 2009 to 2011. The number of cases related to buprenorphine exposure increased from one case in 2009 to 25 cases in 2011. The number of infants admitted with methadone exposure did not change significantly over this three-year period. For infants who required pharmacological treatment, morphine was the drug of choice used to treat NAS in both of these cohorts. No significant difference in LOS or length of treatment was identified between infants with buprenorphine versus methadone exposure. The authors noted that although the incidence of infants with buprenorphine exposure increased during the study period, only one-fourth of these infants required pharmacological treatment. • Brown et al (2015) conducted a prospective, double-blind randomized trial comparing the treatment duration of methadone and morphine for NAS. Thirty-one methadone- and buprenorphine-exposed infants met the authors' inclusion criteria after maternal consent. Randomization placed 15 infants in the methadone treatment cohort and 16 in the morphine treatment group. The median length of methadone treatment (14 days) was identified as significantly shorter than that of morphine treatment (21 days). The authors noted the need for a larger multicenter trial to confirm their findings. • A double-blind clinical trial by Kraft et al (2017) evaluated the use of sublingual buprenorphine versus oral morphine for the treatment of NAS. The study included 63 term infants who had been exposed to opioids in utero and were showing signs of NAS. The buprenorphine cohort required a shorter duration of treatment with a shorter inpatient LOS than the morphine cohort. Similar adverse events were found between the two groups. • A single-center prospective study by Bada et al (2015) compared morphine versus clonidine treatment for NAS. Thirty-one infants were randomized to receive morphine or clonidine in eight divided doses. Protocol allowed a 25% dose escalation every 24 hours for continued symptoms and a tapered dose by 10% every other day after control of symptoms. Blinded researchers assessed the infants with the NNNS, Bayley Scales III and Preschool Language Scale IV. Infants treated with clonidine demonstrated a lower height of arousal and excitability with a shorter duration of treatment. Twelve-month motor, cognitive and language scores were similar between the two groups. The authors concluded that clonidine could be considered a favorable single-drug alternative to morphine but additional multicenter randomized trials are needed.

	• A randomized prospective study by Bada et al (2015) compared the effects of clonidine versus morphine treatment for NAS on neurobehavioral performance. Dosing protocols for each were established and following control of symptoms, the dose was tapered by 10% every other day. The duration of morphine treatment was identified as significantly longer than the clonidine treatment. The NICU Network Neurobehavioral Scale (NNNS) was administered at 1 week and again at 2-4 weeks after initiation of treatment. The Bayley Scales II and Preschool Language Scale IV were administered at 1-year adjusted age. At one year of age no significant differences were noted between the two cohorts. However, the NNNS scores improved with clonidine but not with morphine. The authors acknowledge the need for a multicenter randomized trial comparing these two NAS treatments. • In 2012, Kraft and van den Anker provided recommendations on the management of opioid NAS. They indicated morphine is currently the standard opioid replacement although the use of buprenorphine and clonidine is emerging. The authors advised that although there is general lack of high quality clinical trial data to guide optimal NAS therapy, the currently available evidence supports the use of morphine therapy adjusted for symptom control with gradual weaning. Morphine dosing is addressed and the authors acknowledge there is not a generally accepted morphine maximum when treating NAS. This article indicated the use of phenobarbital appears to be particularly effective when used in infants with poly-drug exposure and is often used when maximum opioid replacement therapy is not effective or as an adjunct in combination therapy. Breastfeeding of NAS infants is promoted in women receiving methadone or buprenorphine maintenance. The authors concluded by addressing the need for improved pharmacologic treatment for infants with NAS which would not only result in decreased resource utilization but also improved psychosocial and developmental outcomes in these infants. The transition to outpatient therapy was noted as an emerging trend in NAS treatment. • A prospective randomized clinical trial by Surran et al (2013) assessed the efficacy of adjunctive morphine sulfate treatment with clonidine versus phenobarbital for NAS. The authors found the addition of phenobarbital reduced the number of morphine treatment days as compared to clonidine. Adjunctive phenobarbital, however, resulted in an overall longer treatment time as compared to clonidine. • Broome and Tsz-Yin (2011) discuss the signs and symptoms of NAS, scoring systems used in the assessment of NAS and treatment options for these infants. They focus on the utilization of clonidine and detail the studies that have evaluated its use. Although the authors conclude clonidine may be an alternative option for treatment of NAS, they also acknowledge the evidence is limited with no long-term outcomes available. They indicate additional studies are needed in support of the efficacy and safety of clonidine for treatment of NAS. • Bio et al (2011) provided an update on the pharmacologic management of infants with NAS. After their literature review, the authors concluded that paregoric is no longer recommended, oral morphine solutions appear to be the standard therapy for opiate withdrawal, methadone and buprenorphine are other potential therapies, and phenobarbital and clonidine can potentially be

utilized as adjunctive treatment.

- In 2012 the American Academy of Pediatrics published an updated clinical report on Neonatal Drug Withdrawal. This report provides guidance on the identification and management of infants exposed to intrauterine substances in addition to the management of hospitalized neonates who need weaning from analgesics or sedatives.
- A Cochrane Review by Osborn et al (2010) evaluated the treatment of infants with NAS who were born to opiate dependent mothers. They attempted to evaluate the effectiveness and safety of using a sedative to treat opiate withdrawal symptoms. They concluded that infants with NAS secondary to opiate withdrawal should receive initial treatment with an opiate. They also indicated that in infants treated with an opiate, the addition of phenobarbitone or clonidine may reduce withdrawal severity.

Non-Pharmacologic Management

- Velez and Jansson (2008) discussed the non-pharmacologic management of infants with NAS and emphasized the importance of individualizing this care based on the needs of the infant in order to improve both the short- and long-term outcomes of these neonates. The authors indicate non-pharmacologic management should be the standard of care for all infants at risk for NAS even though it is not meant as a substitute for infants who require pharmacologic management based on their symptomatology.

Monitoring

- A quality improvement project was conducted by Asti et al (2015) with the intent to reduce LOS for infants with NAS. Accurate monitoring of NAS symptoms, use of a standardized treatment protocol, education of hospital personnel and multi-disciplinary collaboration were identified as key drivers. This project successfully reduced hospital days from 36 to 18 days by the end of the study period. No infants were readmitted within 30 days due to NAS symptoms. Standard treatment protocol and staff education on NAS were found to be the two most effective strategies for reducing length of hospitalization.
- Jansson et al (2009) discussed commonly used tools to assess NAS in addition to NAS management. They describe in detail how to use the most commonly referenced tool, the Finnegan Neonatal Abstinence Scoring System, including scoring, timing and management based on the severity of symptoms. The authors conclude a symptom-based treatment algorithm for affected NAS infants could result in less medication administration than a weight-based protocol. They also acknowledge additional research is needed to identify the optimal management of NAS infants.

NAS protocol standardization

- Grossman et al (2017) developed and evaluated methods to standardize nonpharmacologic care for NAS. Simplification of infant assessment was also implemented by discontinuing the use of Finnegan scoring and using three simple parameters: ability to eat, sleep and be consoled. Morphine was administered as needed if maximal nonpharmacologic interventions were unsuccessful. This methodology resulted in substantial and sustainable

	decreases in length of hospitalization and costs. • Bogen et al (2016) evaluated the protocols for the management of NAS in the Better Outcomes Through Research for Newborns (BORN) hospital network. Out of seventy-six hospitals located in 34 states, 80% had protocols for newborn drug exposure screening with 90% of these protocols risk-based approaches. Morphine was identified as the most common first-line pharmacotherapy followed by methadone. Infants requiring observation most often resided in level 1 nurseries with transfer to NICU when pharmacologic treatment was required. The observation periods ranged from two to ≥ five days for short-acting opioid exposure and from two to ≥ seven days for long-acting opioids. The data demonstrated wide variation in the NAS hospital policies and areas that require additional research in order to establish best practice standards. • A multicenter retrospective cohort study by Hall et al (2015) evaluated the effects of a standardized weaning protocol on the length of hospital stay and duration of opioid treatment in NAS treatment. Adoption of a protocol-driven weaning process for NAS was reported to significantly decrease the NAS treatment duration and amount of adjunctive treatment required. As a result, the infant's length of inpatient stay was also reduced. The authors noted that reduced LOS through home opioid weaning, however, may contribute to an overall longer duration of opioid treatment for the infant. • Kraft et al (2016) provided an overview of the current practices in the management of mother and neonate with prenatal opiate exposure. The authors indicate several treatment approaches are used in the management of NAS but no universal standard of care exists. The pharmacologic management of NAS varies with several different agents used. The use of opioids in pregnancy continued to increase and the optimal prenatal and postnatal care needs to be determined. • Dow et al (2012) crafted a clinical practice guideline on NAS in an effort to standardize the clinical management of the maternal dyad affected by substance abuse. The ultimate goal of the authors was to improve the outcomes of infants at risk for NAS. They felt that early identification of NAS with subsequent interventions could result in a shortened hospital stay. Recommendations for screening and scoring of NAS, pharmacological and non-pharmacological treatment, and discharge planning were included. • In 2014, Hall et al performed a retrospective cohort analysis of term and late preterm neonates who had received pharmacologic treatment for NAS in the hospital setting. This study analyzed the length of hospital stay and total duration of opioid treatment related to various pharmacologic treatment strategies. The included cohort of 547 infants contained 130 who were managed without an NAS weaning protocol and 417 who were managed with an established NAS weaning protocol. After accounting for hospital variation, the authors identified a significantly shorter duration of opioid treatment and hospital stay in the infants who received protocol-based weaning regardless of the treatment opioid utilized. • Bagley et al (2014) performed a systematic review on the assessment and management of NAS. The authors addressed studies related to NAS assessment tools, nonpharmacologic interventions and pharmacotherapy. The

need for standardized NAS scoring among healthcare providers was emphasized. The limited evidence related to nonpharmacologic treatment suggested these interventions may be effective in reducing clinical symptoms and subsequently the need for medication. Studies pertaining to NAS pharmacotherapy were noted as small and inconsistent in terms of assessment tools, weaning protocols and covariate adjustment. The authors indicated a need for additional high-quality randomized controlled trials to determine best practices in the pharmacologic management of NAS. Recommendations included the use of standard NAS protocols utilizing established assessment tools, accepted pharmacotherapy such as morphine and methadone and educational training for all staff involved in the care of NAS infants.

Outpatient/Home therapy

- A retrospective analysis by Lee et al (2015) noted that the number of NAS cases identified in this study increased steadily from 2007 to 2013. Infants who began methadone treatment inpatient and were discharged to complete treatment on an outpatient basis demonstrated a 55% reduction in LOS over infants who received their full methadone treatment as an inpatient. Out of 139 NAS cases included in this study, one infant was readmitted for NAS symptoms secondary to maternal inability to obtain the required methadone to complete outpatient therapy. The authors indicated a combined inpatient/outpatient methadone treatment protocol for NAS can reduce an infant's LOS and associated health care expenditures without increasing unfavorable events.
- A 2013 National Survey by Mehta et al outlined the variety of management strategies in NAS. The authors concluded that increased prenatal counseling and home treatment programs could improve the care of these infants.
- A retrospective cohort study by Kelly et al (2014) evaluated the safety and efficacy of at-home oral morphine weaning for NAS. Fifty-two out of 80 neonates treated for NAS completed their morphine weaning after they were discharged from the hospital. These infants received a longer duration of morphine therapy but demonstrated significantly less returns to the hospital for continued withdrawal treatment (1/52 home-based weaned infants versus 4/28 inpatient weaned infants). The authors concluded that in select cases, at-home morphine weaning may be considered a safe and cost-effective NAS management strategy.
- Smirk et al (2014) performed a retrospective review to evaluate and compare a home-based detoxification program for NAS with traditional inpatient management. Out of 118 infants treated for NAS, 38 were managed at home. The authors identified a shorter hospital stay, similar total NAS treatment duration and an increased rate of breastfeeding in the infants managed with home-based detoxification. The authors acknowledged the paucity of current literature on outpatient NAS therapy and emphasized the impact of patient selection on the safety of home-based detoxification.
- A retrospective review by Backes et al (2012) sought to compare the safety and efficacy of a combined inpatient/outpatient approach in opioid treatment weaning for NAS to the traditional inpatient weaning strategy. The treatment cohort included 121 infants, 75 of which completed methadone treatment in

	the inpatient setting and 46 infants who were initially treated with methadone inpatient but completed the weaning process in the outpatient setting. Phenobarbital was added as an adjunctive agent in infants with an inadequate response to methadone. Twenty-four percent of infants in the inpatient cohort and 28% in the combined inpatient/outpatient cohort required adjunctive inpatient phenobarbital to control withdrawal symptoms. No difference in the total duration of phenobarbital treatment was identified between the two groups. The duration of methadone weaning in the inpatient/outpatient cohort was found to be longer. However, the cumulative methadone dosage was similar between the two groups. The readmission rate and number of emergency room visits for NAS-related symptoms was similar in both cohorts. No difference in the proportion of infants requiring a restart of inpatient medication for NAS symptoms was identified. The authors concluded that a combined inpatient/outpatient NAS treatment program utilizing community based strategies would result in a shorter hospitalization with no increased risk of short-term adverse outcomes. It was noted that additional studies are warranted in order to evaluate the long-term benefits of combined inpatient and outpatient methadone treatment. **Maternal Maintenance** • Ordean et al (2015) reported on the results of multisite cohort study evaluating neonatal outcomes from a group of 94 methadone-maintained pregnancies from 1997 to 2009. The mean gestational age from this cohort was identified as 38 weeks and the mean birth weight was 2856 grams. Sixty-nine infants required NICU admission but only 27% of these infants required pharmacological therapy for NAS. Non-pharmacological interventions such as skin-to-skin contact and breastfeeding were identified as factors associated with a decreased severity of NAS and thus a reduced need for NAS medications. • A 2013 Cochrane review by Minozzi et al compared maternal maintenance treatment programs. Based on the authors' evaluations, maintenance treatment with buprenorphine appeared to result in less symptoms of substance withdrawal. • A prospective cohort study by Cleary et al (2012) reached conclusions that maternal opiate, benzodiazepine or cocaine use result in a longer neonatal hospitalization for NAS than maternal methadone-only maintenance. • A 2012 retrospective descriptive study by Pritham et al determined that infants born to mothers undergoing methadone maintenance therapy had longer inpatient stays for NAS than infants with mothers involved in buprenorphine maintenance therapy. They also determined that breastfed neonates had shorter hospitalizations than formula-fed infants. • A retrospective study by Wiegand et al (2015) compared the characteristics and prevalence of NAS between infants whose mothers were treated with methadone versus buprenorphine and naloxone in pregnancy. The number of infants diagnosed with NAS in the buprenorphine and naloxone cohort was approximately 50% less than those diagnosed with NAS in the methadone-exposed group. The infants exposed to buprenorphine and naloxone also demonstrated lower peak NAS scores with a shorter overall hospitalization.

- Patrick et al (2015) performed a retrospective cohort study with the goal to identify neonatal complications resulting from antenatal opioid pain reliever use. The study demonstrated NAS occurred more frequently in infants exposed to long-acting and maintenance opioids than in those exposed to short-acting opioids. Infants diagnosed with NAS were identified as more likely to be born preterm with a low birth weight, face feeding difficulties, have a respiratory diagnosis and experience seizures. The authors found wide variability in the risk for neonatal withdrawal symptoms based on opioid type and dose, SSRI utilization and amount of cigarette use by the mother.

- Review of data from a large multi-site randomized clinical trial was performed by Gaalema et al (2013). The authors compared the time to initiation of treatment for NAS between methadone- versus buprenorphine-exposed infants. The authors concluded that buprenorphine-exposed infants had less severe NAS than methadone-exposed neonates. However, the buprenorphine-exposed infants required treatment for NAS significantly later than the methadone-exposed neonates.

Drug Screening

- Montgomery et al (2006) evaluated the use of umbilical cord tissue in drug screening for fetal exposure to illicit drugs. Paired samples of both meconium and umbilical cord tissue were obtained from 118 patients who were suspected of using illicit drugs. Agreement between the two samples was found in 96.6% of the tests for amphetamines, 94.9% for opiates, 99.2% for cocaine and 90.7% for cannabinoids. The authors concluded that umbilical cord tissue could effectively be utilized in assessing fetal drug exposure with advantageous availability for immediate testing purposes.

- Patrick et al (2017) authors a policy statement from the AAP on opioid use in pregnancy. Punitive measures are noted as ineffective in improving the health of the mother or infant. Opioid agonist therapy with methadone or buprenorphine is now considered the standard for managing pregnancies associated with opioid use. Routine universal screening utilizing brief questionnaires is recommended by ACOG and AAFP and should be applied equally to all women regardless of socioeconomic status, age, ethnicity or race.

Breastfeeding/Rooming in

- A study by Rossen et al (2016) investigated how substance use, maternal-fetal bonding and mental health throughout pregnancy affected postnatal bonding at eight weeks. Data on the pregnancies of 372 women were reviewed in addition to eight week postnatal information. Women with higher antenatal bonding were identified as having increased postnatal bonding. Women with depressive symptoms in the second and third trimesters and also women with stress in the second trimester were identified as having worse eight week postnatal bonding. The authors stress the importance of maternal mental health assessment throughout pregnancy and indicate the need to promote maternal-infant bonding with intervention as necessary throughout pregnancy.

- A prospective cohort study by Patrick et al (2016) included development and implementation of a multicenter quality improvement collaborative to promote consistency in the care of infants with NAS. The 199 centers (n=3458 infants) participating in this effort reviewed their policies and infant data pertinent to

NAS with evaluations of patient outcomes over time. The Vermont Oxford Network (VON) toolkit was used as a model for the centers. A best practice curriculum included a comprehensive inpatient program which emphasized rooming-in and support in the care of substance-exposed infants.

- Saiki et al (2010) evaluated the care of infants with NAS who were left with their mothers on the postnatal floor versus those who were cared for in the neonatal unit. Their results indicated those neonates who stayed with their mothers on the postnatal floor required less treatment for NAS, a shorter duration of treatment for NAS, and a shorter hospital stay than the group of neonates who were cared for in the neonatal unit.

- The 2009 clinical protocol from the Academy of Breastfeeding Medicine makes recommendations for breastfeeding in drug-dependent women. These recommendations include the promotion of breastfeeding for select women who: are participating in substance abuse treatment, are stable methadone-maintained, have 90 day abstinence prior to delivery, received consistent prenatal care, are taking no psychiatric medication contraindicated in lactation, and have no medical contraindication to breastfeeding.

- Wong et al (2011) published a clinical practice guideline for managing substance abuse in pregnancy. Based on fair evidence, their recommendations encouraged facilities to develop a protocol for assessment and management of infants exposed to intra-uterine opiates and advised that the risks and benefits of breastfeeding should be evaluated on an individual basis.

Nicotine withdrawal

- A review by Garcia-Algar (2008) outlined the symptoms of nicotine withdrawal in newborn infants. Based on the published literature, the authors concluded that newborn infants exposed in utero to maternal tobacco use could exhibit early onset nicotine withdrawal symptoms (within 12-24 hours after birth) if labor and delivery had interrupted the continuous exposure to nicotine. These symptoms were typically mild with a short duration and generally did not require treatment.

Antidepressant Withdrawal

- A prospective controlled study by Laine et al (2003) examined the effect of selective serotonin reuptake inhibitors (SSRIs) on infant outcomes. Twenty pregnant women receiving citalopram or fluoxetine medication for depression (n=10) or panic disorder (n=10) were matched with 20 women who were not receiving this pharmacotherapy. Infants who were exposed in utero to SSRIs were found to have a 4-fold increase in serotonergic symptoms during the first four days of life and significantly lower cord blood 5-HIAA concentrations than their matched cohorts. The severity of their symptoms appeared to be related to their cord blood 5-HIAA levels.

- A cohort study by Levinson-Castiel (2006) examined the effects of SSRI exposure in utero. Out of the 120 infants included in this study, 60 of them had experienced prolonged in utero exposure to an SSRI agent. Finnegan scoring standard protocol was utilized including repetitive scores and cardiorespiratory monitoring until the score was normalized. All infants who had not experienced in utero SSRI exposure were found to have normal Finnegan scores after

	birth. Approximately 30% of the infants exposed in utero to SSRIs were found to experience symptoms with eight infants demonstrating severe symptoms and 10 infants displaying mild symptoms of NAS. **Costs** • Winkelman et al (2018) examined the cost trends of NAS in infants who were covered by Medicaid in comparison with other infants. Data was obtained from the National Inpatient Sample from 2004-2014. The authors noted that the total hospital NAS birth costs in this patient population increased from $65.4 million in 2004 to $462 million in 2014 (adjusted for inflation) with an increased proportion of hospital costs related to NAS from 1.6% in 2004 to 6.7% in 2014. Specialty Society Guidelines: • American Academy of Pediatrics. Committee on drugs, Committee on fetus and newborn- Neonatal drug withdrawal. (2012) • Academy of Breastfeeding Medicine Protocol Committee, clinical protocol #21: Guidelines for breastfeeding and the drug-dependent woman. (2009)

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Revision History

The following are approved changes incorporated into the revision numbers indicated below.

Revision	Date	Description of Change
V1.0	05/16/2013	New clinical guideline (MB)
V2.0	06/04/2014	Job aid revised into medical necessity clinical guideline. (CE)
V2.0	09/08/2014	Will replace JA2229742 on 01/01/2015. (CD)
V3.0	06/03/2015	Annual review with update by RS. (CD)
V4.0	05/05/2016	Annual review with revisions performed by RS. Information on NAS standardized protocols, buprenorphine, clonidine, and morphine weaning added. (CE)
V5.0	05/05/2017	Annual review by AJ. Information on lowest weaning dose, sum of three Finnegan scores and observation/supportive care added. (CE)
V6.0	05/04/2018	Annual review by AJ. Information on Finnegan scoring revised, dosing for buprenorphine and SSRI exposure/withdrawal added. Approved by MTAC 06/07/2018. (CE)