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Neonatal Abstinence Syndrome and the Relationship Between Respiration and Feeding

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Neonatal Abstinence Syndrome and the Relationship Between Respiration and Feeding

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by

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ABSTRACT

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Objective: The primary purpose of this study was to determine the relationship between respiratory status and feeding difficulties in infants with NAS in comparison to full-term infants with no exposure to opioids.

Methods: A group of infants with NAS (262) were compared to a group of full-term infants with no exposure to opioids (279). These groups were further divided into feeding and respiratory groups based on severity. These groups were analyzed for differences in behavior and outcomes.

Results: Infants with NAS are 34.23 times more likely to develop respiratory distress and 111.03 times more likely to develop severe feeding difficulty. For infants with NAS, respiratory and feeding impairment may occur in isolation, suggesting a different withdrawal-based etiology of impairment as compared to premature infants.

Conclusion: This study is unique in its size, scope, and attention to the respiratory factors involved in the feeding outcomes of infants with NAS.

DEDICATION

This study is dedicated to my wife, Mary Ellis, who has been an inestimable source of support in this project and whose "happy talent of composition and remarkable felicity of expression" are a constant inspiration.

To my parents, whose lifetime of support and wisdom have sustained and made possible my work in this study and the countless steps that have led toward it.

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LIST OF ABBREVIATIONS

NAS	Neonatal Abstinence Syndrome
FTNO	Full-Term No Opioid [Exposure]
SFD	Severe Feeding Difficulty
FC	Feeding Challenged
TF	Typical Feeding
RD	Respiratory Difficulty
TR	Typical Respiration

Chapter 1. Introduction

Nature and Purpose of the Study

Neonatal abstinence syndrome (NAS) is the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy (Kocherlakota, 2014). There were 769 cases of NAS in Tennessee in 2019 (Tennessee Department of Health, 2019). In more immediate terms, every 15 minutes an infant is born with opioid withdrawal in the United States, an increase from every 25 minutes in 2016 (National Institute on Drug Abuse, 2019). Thousands of infants are affected nationwide every year (Tolia et al., 2015) with significant consequences for family, health, and education systems.

Particular to the field of speech-language pathology, feeding and swallowing are impacted in some, but not all, cases of NAS (Kocherlakota, 2014). Studies report poor sucking performance in infants exposed to methadone. Specifically, infants spend less time sucking and further demonstrate decreased sucking pressure in comparison to control groups (Kron et al., 1975). Opiate-exposed infants have more feeding problems, specifically longer sucking bursts and fewer bursts per minute, than non-drug-exposed infants or even infants exposed to cocaine or other drugs (Legasse et al., 2003). These feeding problems have implications for an infant's health, such as poor weight gain and aspiration, and hospitalization in terms of longer lengths of stay and significantly higher costs (Patrick et al., 2015).

While there is research evidence that describes the symptoms of the feeding difficulties that infants with NAS experience (e.g., Gewolb, Fishman et al., 2004; Kocherlakota, 2014; Maguire et al., 2015), the underlying mechanism for their occurrence is not clear. Infant feeding difficulties generally appear in the premature infant population and clearly point to comorbidity of feeding problems and respiratory difficulties due to neurological immaturity (Gewolb & Vice, 2006; Goldfield et al., 1999; Hill & Rath, 2002). Yet the majority of infants with NAS are full-term (Kocherlakota, 2014). Comorbid respiratory and feeding difficulties are rare in infants born full-term who do not have other significant health problems, such as cerebral palsy, or syndromes (Gewolb & Vice, 2006; Goldfield et al., 1999).

The existing literature on feeding and swallowing for children with NAS, however, only hints at a potential relationship between respiration and swallowing during the feeding process. Research by Gewolb et al. (2004) point to abnormalities of interposition of respiration into rhythmic feeding and increased feeding-associated cessation of breathing for infants exposed to drugs, along with transient feeding inefficiency, especially in the first days of life. However, there are few studies on the interaction of feeding and respiration for full-term infants with NAS or infants who are opioid-exposed. To understand the underlying mechanism of the feeding difficulties in infants with NAS, it is important to determine if the well-documented comorbidity of feeding and respiration difficulties of infants born prematurely is applicable as a theoretical framework. Reynolds et al. (2017) provide some initial support for this model. They suggest that the swallowing mechanisms of infants with NAS do not constitute a new pathology but are highly similar and comparable to the swallowing mechanism of infants born prematurely.

With this theoretical model in mind, the current study seeks to explore the comorbidity of respiratory and feeding difficulties of infants with NAS as it compares to infants born typically at full-term, as well as infants without drug-exposure who are premature. If the relationship between feeding and respiratory difficulties is not like that of infants without drug-exposure who are premature, an alternate model would be indicated. It may be that the feeding problems of infants with NAS are the result of disturbances at the neurotransmitter level caused by withdrawal from opioids rather than the result of neurological immaturity (Reynolds et al., 2017;

Shaker, 2018). This study seeks to shed more light on the etiology of feeding difficulty in infants with NAS.

Need for the study. A deeper understanding of the relationship between feeding and respiration in infants with NAS may account for the etiology of the feeding disorder. Such knowledge would facilitate understanding of feeding and respiration impairments and the implications for selection of treatment approach, treatment and treatment outcomes in infants with NAS.

Understanding the relationship between feeding and respiration in infants with NAS or opioid exposure may have diagnostic and prognostic implications. For infants with comorbid disorders of respiration and feeding, such interactions may be an additional red flag among other risk factors and interactions for early initiation of assessment and treatment. Furthermore, an understanding of the outcomes associated with their clients' feeding and respiration may allow clinicians to meet needs specific to a diagnosis of NAS more effectively through their selection of intervention approaches and techniques.

Knowledge of the interaction between feeding and respiration in infants with NAS or opioid exposure could guide the clinician to provide the most efficacious treatment based on the child's needs. Taking etiology, symptomatology and mechanism interactions into account will allow healthcare providers to engage in informed care in assessing and treating infants with NAS.

Chapter 2. Review of the Literature

Neonatal Abstinence Syndrome

NAS occurs as the result of the maternal use of morphine, heroin, methadone, buprenorphine, prescription opioid analgesics, antidepressants, anxiolytics and/or other substances during pregnancy. NAS can occur either prenatally, wherein the mother stops drug use during the pregnancy, or postnatally when the infant discontinues receiving the drug after what is generally a full-term birth, respectively (Kocherlakota, 2014). Postnatal NAS is the subject of this study.

Although NAS is only rarely fatal, the withdrawal period from substance use can be severe and intense, with secondary and significant illness as well as prolonged hospital stays (Winkelman et al., 2018). Along with rising opioid distribution and addiction crisis in the United States, the number of infants with NAS has also increased (Patrick et al., 2015). The opioid crisis is the public health emergency of our time, and these infants are collateral damage. Due to the changing landscape of both prescribed and illicit drugs, NAS has become both more complex and more prevalent.

Prevalence. There were 769 cases of NAS in Tennessee in 2019 (Tennessee Department of Health, 2019), and the increase in NAS is tied to national increases in opioid use and prescription. Tennessee's rate of neonatal abstinence syndrome increased ten-fold from 2000 to 2010; at the same time, the national increase was only three-fold. Blue Cross Blue Shield of Tennessee and the Tennessee Department of Health reported 57 NAS cases in 2000; however, there were 525 cases in 2010 and 1,068 cases in 2016, the state's highest total to date as displayed in Figure 1 (Brantley, 2017; Tennessee Department of Health, 2019). In 73% of the cases, the drug associated with NAS was prescribed to the mother by a healthcare provider. The highest categories of exposure source were medication assisted treatment (67.7%), prescription opioid obtained without a prescription (30.4%), and other non-prescription substances (22.7%).

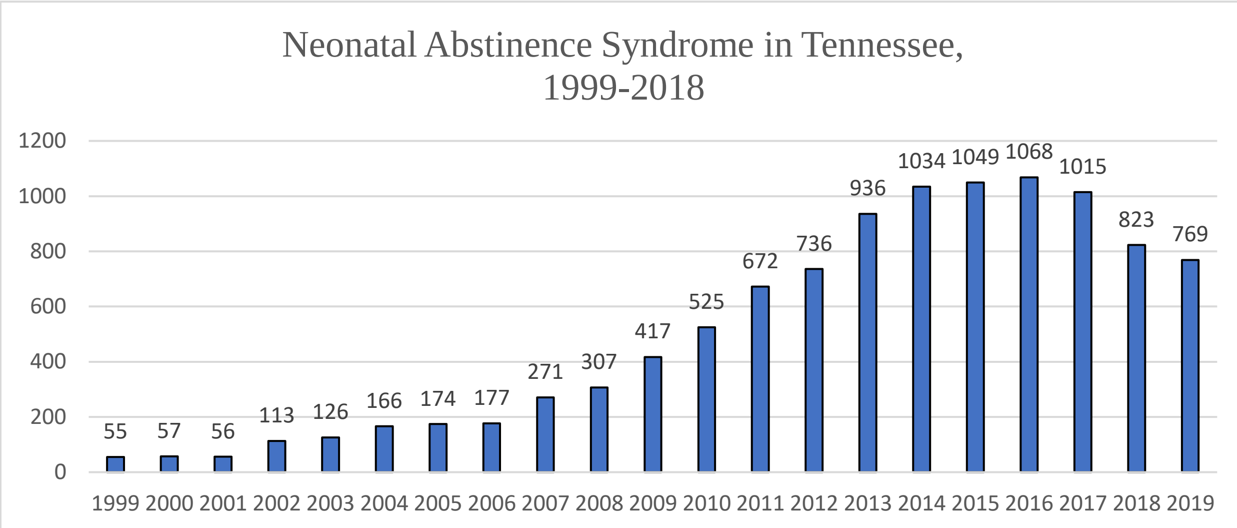

Figure 1: Number of inpatient hospitalizations with any diagnosis of NAS in Tennessee compiled from Tennessee hospitals (Brantley, 2017; Tennessee Department of Health, 2019)

The Centers for Disease Control and Prevention (CDC) reports that 2 million Americans are addicted to opioids, and that the increase in opioid use during pregnancy has mirrored that of the general population. In 2016, 6,000 pregnant women illicitly used heroin and opioid pain relievers, 1.9 million women had an opioid use disorder, and an unknown number of women legally used opioids such as methadone or buprenorphine in physician-assisted medication-assisted treatment (Critchfield & Hansen, 2018). Of those currently using heroin, 80% started their addiction by misusing prescription opioids.

Methadone and buprenorphine dosage amount do not have an effect on incidence of NAS in this population, but roughly 30-50% of infants experience postnatal withdrawal symptoms from methadone (Pizarro et al., 2011). According to McQueen & Murphy-Oikonen (2017), the number of infants experiencing NAS symptoms is actually closer to 54% than to 94%. In 2014, 8.0 infants with NAS were born per 1,000 births, and that rate consistently increased for 10 years prior. Over the past decade, there has been a 4.7-fold increase in maternal opioid use, and a subsequent 2.8-fold increase in incidence of NAS.

These increases include significantly higher costs for treatment and length of stay in hospitals. The cost for the infant who is typical and full-term is $4,237 with a 3.2-day length of stay. For an infant with NAS, the cost on average is $62,973 with a 32.5-day length of stay. In 2012, the Tennessee Medicaid program projected that infants with NAS accounted for 1.7% of live births, but 13.0% of expenditures on births (Patrick et al., 2015).

National increases in opioid use and NAS diagnoses disproportionately affect rural areas, particularly in Appalachia. For example, NAS cases tripled from 2008 to 2014 in Kentucky counties, with a 2013 NAS rate more than double the national NAS rate (Brown et al., 2018). Furthermore, rural and Appalachian counties saw an NAS increase per 1,000 births that was 2-2.5 times higher than urban or non-Appalachian counties, with a greater number of NAS births overall in Appalachian counties. Additionally, all opioid treatment facility types were further from rural patients than metropolitan patients, as well as further for Appalachian patients than non-Appalachian patients. A recent ethnography study by Kramlich et al. (2018) included interviews of rural Appalachian mothers and arrived at three subdomains of concern: challenges of getting treatment and care (service availability, distance/geographic location, transportation, provider collaboration/coordination, physical and emotional safety); opportunities to bond for mother infant (proximity, information); and the importance of relationships (respect, empathy, familiarity, inclusion, interactions with care providers). Gadomski et al. (2018) studied practices in rural hospitals and found that family-centered NAS treatment that employed a symptom-based oral morphine weaning protocol, lasted 2 to 3 days longer than in NICUs, largely as a result of social issues such as foster care arrangements and court appearances; however, hospital charges were lower largely because of shorter in-hospital treatment duration for weight loss and irritability. These are two of the most common symptoms of NAS.

Moreover, there is emerging evidence of long-term developmental and behavioral consequences for children born with NAS, such as ADHD, learning disorders, developmental delay and speech and language deficits (Fill et al., 2015; Galbally et al., 2017; Legasse et al., 2003).

Signs and symptoms. NAS includes a variety of signs and symptoms involving various bodily systems, most notably the central and autonomic nervous systems and the gastrointestinal tract. Recognized clinical signs of NAS include tremors, irritability, excessive crying, diarrhea, and possibly seizures. Central nervous system signs, such as irritability, jitteriness, tremors, and excessive crying, appear early, while symptoms of hyperirritability can lead to secondary agitation, difficulty sleeping, and inconsolable crying. Autonomic signs, often secondary to and associated with methadone withdrawal, include tremors, arrhythmic heart rate and respiratory rate, muscle tone, and other signs, such as temperature instability, sweating, sneezing, and mottling (Kocherlakota, 2014). Any of these disruptions may contribute to poor feeding, excessive motor activity, regurgitation, vomiting and diarrhea, with subsequently poor weight gain (Kocherlakota, 2014).

Other signs that are highly specific to NAS include: a distinctive, high-pitched cry and the presentation of a chemical odor depending upon the drugs in use (Kocherlakota, 2014). Some signs and symptoms of NAS require a differential diagnosis from other medical problems of infants with NAS. For example, hyperthermia is often confused with sepsis. Tachypnea, nasal flaring and nasal stuffiness are sometimes misinterpreted as respiratory distress in these infants. According to Patrick et al. (2015), consistent with the characteristics of the syndrome, when comparisons were made between non-opioid and opioid-exposed infants, those with NAS were more likely to have respiratory diagnoses (27.8% vs 10.1%), feeding difficulties (13.1% vs 2.6%) and seizures (3.7% vs 0.4%), which is particularly germane to the focus of the current study as infants with NAS may be predisposed to greater difficulties gaining weight due to the exacerbation of feeding and respiration.

Mechanisms of opioid withdrawal in infants. Although NAS can result from maternal use of a variety of drugs during pregnancy, the case of opioids is both highly frequent and illustrative of the mechanisms involved in NAS symptomatology. Opiates have low molecular weight, are water soluble and lipopholic, making opioid molecules easily transferable across the placenta. This transferability increases with the more highly synthesized nature of the opioid. In fact, the combination of cocaine or heroin with methadone leads to even greater permeability and a more rapid half-life in the fetus (Kocherlakota, 2014). With the caveat that an understanding of opioid withdrawal is complicated by immature neurologic development, immature neurological processing, and complex materno-feto-placental pharmacokinetics, opioids act mostly in the area of opioid receptors. These receptors are spread across the central and peripheral nervous systems, the gastrointestinal system and other systems, with indirect implications for other areas. For example, perturbations in the central and peripheral nervous system carry consequences for the rhythmic coordination of the respiratory system. According to Kocherlakota (2014), a lack of opioid in a chronically stimulated state increases activity in the opioid receptors, leading to boosted or depressed production of various neurotransmitters. See Figure 2 (Kocherlakota, 2014) for a more detailed illustration.

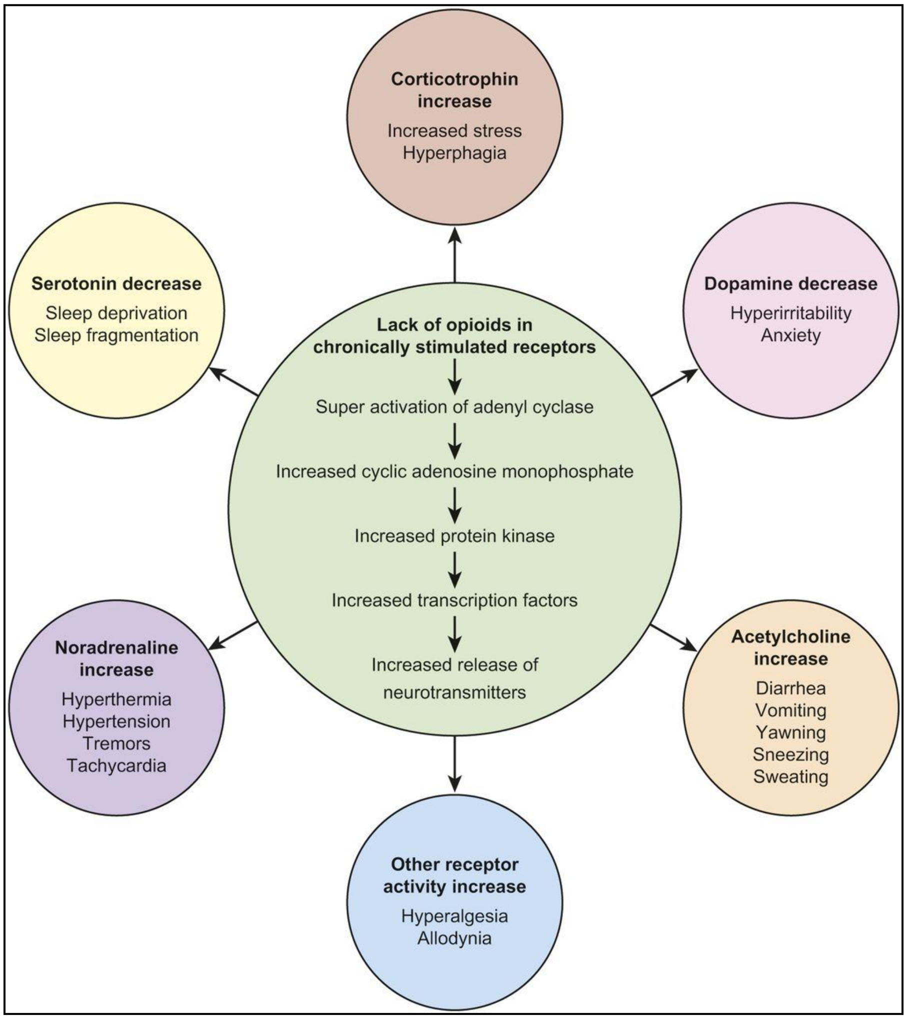

Figure 2: Mechanism of opioid withdrawal in neonates at the neurotransmitter level (Kocherlakota, 2014, p.551). Reproduced with permission from Journal Pediatrics, Vol. 134, Page(s) 551, Copyright 2014 by the AAP.

Specifically, a lack of opioids in receptors that were chronically stimulated throughout gestation leads to increased activation of the enzyme adenyl cyclase, which begins a pathway of opioid withdrawal on the neurotransmitter level. Typically, g receptors that are over stimulated throughout gestation also activate this system. Adenyl cyclase is an enzyme that catalyzes the cyclization of adenosine triphosphate (ATP), which provides energy for physiological processes such as muscle contraction, into an increased cyclic adenosine monophosphate, which affects signaling or coordination on the intracellular level. This in turn affects production of the protein kinase, which is an enzyme that modifies other molecules by adding phosphate groupings and therefore enhances and inhibits nervous system cell coordination on the molecular level.

Phosphate groupings impact the release of neurotransmitters through a process of phosphate transferal known as phosphorylation. In this process, kinase catalyzes the transfer of phosphates from ATP to specific substrates. Kinase can also catalyze the process of dephosphorylation, wherein a phosphorylated substrate transfers phosphate to adenosine diphosphate (ADP), thus completing the opposing cycle. The phosphorylation state of a molecule can heavily affect its activity, reactivity, and ability to bind with other molecules. As the balance of molecular influx and exodus along voltage-sensitive channels is directly related to the release of neurotransmitters, the interactions of these molecules by means of a chain of events begun by g receptors and specific enzymes can result in a distinct series of reactions in the brainstem and other nervous system areas (Kocherlakota, 2014).

The nervous system is essential to the function of the swallow because the mechanisms of swallowing are coordinated on a largely reflexive level at infancy by various levels of the nervous system (Groher & Crary, 2016). These include the cranial nerves, brainstem, cerebellum, and various cortices throughout the body (Groher & Crary, 2016), which are responsible not only for the sensory perception of the bolus, but also for the motoric impulses that drive the swallow through musculature and movement. A safe and efficient swallow is the result of a complicated series sensory and motoric interactions (Groher & Crary, 2016) that is made even more complex by the novelty of the action at infancy. When disruptions occur at the neurotransmitter level due to withdrawal, this disorganization can present in the functional presentation of the swallow as well as in the neural network.

The center of opioid withdrawal activity is the locus coeruleus of the pons, the principal noradrenergic nucleus of the brain; in other words, principally activated by the neurotransmitter norepinephrine, among others (Kocherlakota, 2014). The pons is implicated in many of the functions associated with NAS compared to non-exposed infants, including sleep, respiration, swallowing, chewing, hearing, equilibrium, taste, and motoric expression, particularly in the facial region. Typically, the pons region regulates these various functions on an automatic level, especially in infancy; the introduction of drug-related withdrawal disrupts these functions. Because of this region's sensitivity to neurotransmitter signaling along cranial nerve and other pathways from the thalamus to the cerebellum and medulla, a lack of opioids causes an increased production of norepinephrine (also called noradrenaline), decreased production of dopamine, and a decreased serotonin expression. The increase in norepinephrine is responsible for most of the general signs of NAS, while the lack of serotonin can lead to sleep disturbances. Opioid withdrawal may also lead to increased corticotrophin and acetylcholine release and decreased levels of dopamine (Critchfield & Hansen, 2018). It is these changes, especially in acetylcholine (Kocherlakota, 2014), that are implicated in the feeding difficulties associated with NAS and are tied to decreased arousal and vomiting.

Neurotransmitter mechanisms associated with feeding. It is essential to consider typical neurotransmitter function before describing mechanisms of withdrawal in infants with NAS. Importantly, not all neurotransmitters are affected on an equal basis. For unexposed infants, typical corticotrophin functions regulate stress and appetite for fairly consistent feeding and mood. Typical acetylcholine functions in the central and autonomic nervous systems to transmit and modulate information related to muscle movement and sleep cycles, keeping both of these areas regularized for effective movement and strength as well as needed rest, respectively.

Dopamine assists in keeping infants' mood and concentration at optimal functioning. Many neurotransmitters interact and work together to influence function in a single system.

For infants with NAS, increased corticotrophin release is generally associated with a suppressed appetite and decreased activation of the neuronal circuitry that drives appetite. This can result in diarrhea, vomiting, yawning, sneezing and sweating (Lawson et al., 2013). Corticotrophin increases may also lead to anxiety, depression, sleep disturbances and anorexia nervosa. Increased acetylcholine levels are linked with decreased arousal, while decreased levels of dopamine can affect mood, sleep, memory, concentration and motor control. As a result, infants with NAS commonly present with tremors, irritability, excessive crying, and diarrhea, with secondary poor weight gain and hyperphagia (Kocherlakota, 2014).

Neurotransmitter mechanisms associated with respiration. An understanding of typical function is also crucial in respiration. The central nervous system typically works to modulate crying and mood. The autonomic nervous system works to maintain consistent and regular heart rate, respiratory rate, and muscle tone (Kocherlakota, 2014) for unexposed infants, and these nervous system functions work together to ensure a stable internal status in instances of activity, such as feeding, and rest.

For infants with NAS, central nervous system instability is often the cause for the respiratory disruptions noted in infants with NAS, and this instability has consequences for feeding and weight gain outcomes, as well. Excessive and uncontrollable crying is one such symptom (Kocherlakota, 2014). The autonomic nervous system is also dysregulated in infants with NAS, and this can lead to impaired heart rate, respiratory rate, and muscle tone, as well as temperature instability, sweating, sneezing, and mottling due to an acetylcholine increase on a neurotransmitter level (Jansson et al., 2010; Kocherlakota, 2014). Tachypnea, nasal flaring, and nasal stuffiness, (Kocherlakota, 2014), still present obstacles to functional breathing and feeding for infants.

Normal infant feeding and swallowing. It is necessary to understand the normal feeding and swallowing process for infants who are full-term and typical before investigating atypical patterns that might be present in the population of infants diagnosed with NAS or with a history of prematurity. Knowledge of the typical swallow can shed light on deficiencies in the swallow of infants with feeding difficulty. Unlike the adult swallow, the typical infant swallow is under the influence of a series of ongoing bodily changes, including development of the head, neck, lungs, gut, and nervous system (Morris & Klein, 2000). The infant swallow is more reflexive (or involuntary) and dynamic, relying on patterns of developmental suckling and sucking. The anatomy of the infant swallow marks another difference, with a disproportionately large tongue, higher larynx, and buccal sucking pads (Delaney & Arvedson, 2008). All of these differences result in a series of protections against aspiration due to the fragility of the laryngeal and respiratory systems, even within the typical infant swallow.

The typical infant swallow is characterized by reflexes and movements required for the coordination of suck-swallow-breathe during feeding (Delaney & Arvedson, 2008). This process, familiar to the point of automatic motion for most adults, involves the synchronization of respiratory and swallowing needs in the pharyngeal space and develops early in the third trimester. In fact, the swallowing reflex is not completely functional until 34 weeks gestation. Normal swallowing can be demonstrated by infants at 26 weeks, but a rhythmic pattern does not emerge until 32-34 weeks (Shaker, 2018). Full coordination of sucking, swallowing, and breathing in a 1:1:1 ratio does not occur until 36-38 weeks. Breakdowns at any point of the suck-swallow-breathe process can have negative implications for the infant swallow, including choking, coughing, and aspiration, with the risk of further negative behavioral responses to feeding.

Suck-swallow-breathe typically occurs in response to stimulation at the level of the tongue or hard palate (Delaney & Arvedson, 2008). In response, the infant will exhale and seal his/her lips around the nipple and suck using a forward-backward motion of the tongue in the horizontal plane to express liquid through a series of pressure exchanges. Due to the relatively large size of the infant tongue, infants reflexively prefer nasal breathing during nipple feeding; alternating respiration between swallows is the last skill to develop in the suckling process (Shaker, 2018). Cessation of respiration should begin during deglutition and continue until the bolus passes into the esophageal phase of the swallow. The ideal pattern for the typical infant swallow is one of exhalation, lip seal, sucking, swallow, and inhalation. However, there are many differences in swallowing coordination even among typical infants; as such, there is no established ‘normal swallow’ even for typical infants.

Normal infant respiration. For the typical full-term infant, respiratory rate is 20-40 per minute; for the preterm infant, the rate rises to 40-60 per minute (Shaker, 2018). There is no typical respiratory rate published for infants with NAS. Simultaneous breathing and feeding requires sophisticated coordination of both systems involved in the maneuver, including muscles and neurological control. Coordinated development of buccopharyngeal functions typically occurs by 35 weeks post-conceptual age in infants but can be disrupted by respiratory disease or neuropathology (Miller & Kiatchoosakun, 2004). Infants with NAS perform feeding and breathing patterns in a manner significantly similar to preterm infants (Reynolds et al., 2017).

Diagnosis of NAS. The signs and symptoms associated with the mechanism of withdrawal are key to the diagnosis of NAS. Medical professionals most commonly use the Modified

Finnegan Scale (Jansson, Velez, et al., 2009) to assess the presence and severity of NAS as its items include the most common signs and symptoms Although the preferred and immediate treatment of NAS is through nonpharmacological measures, (McQueen et al., 2011) repeated assessment of symptomology and severity helps professionals to determine when pharmacological intervention may be necessary. Modified Finnegan Scale scoring includes an assessment of 20 signs of withdrawal: these include high-pitched cry, sleeping patterns, nasal stuffiness, tremors, poor feeding, fever, sneezing, and more. Modified Finnegan Scale assessment begins within 24 hours of birth and continues every 3-4 hours. Item scores between 1 and 3 are given for each area of assessment. For example, an infant presenting with less than one hour of sleep after feeding receives the most severe score in that category, while greater amounts of sleep after feeding result in milder scores (Finnegan, 2013; Kron et al., 1975). Scores greater than or equal to 12 lead to more pharmacological intervention, while scores less than or equal to 8 lead to non-pharmacological intervention and monitoring. There is no commonly accepted protocol or standard endorsed by the American Medical Association for non-pharmacological intervention and monitoring (Kocherlakota, 2014).

According to Kocherlakota (2014), non-pharmacological care can include gentle handling, swaddling, minimal stimulation with dim light and low noise, demand feeding or frequent feeds, high-calorie formula, thickened feeds, and maternal participation and/or rooming in of mother and infant. To date, no studies have compared the effectiveness of these measures in infants with NAS, although active maternal participation is considered best care (Kocherlakota, 2014).Current professionals describe such intervention as “the first line and the best treatment for these infants” (S.M. Hollinger, personal communication, September 7, 2019).

As an example of NICU criteria for intervention and monitoring from the Ballad Health System in Johnson City, Tennessee, doctors begin non-pharmacological intervention immediately if there is any evidence of exposure to opiates (S.M. Hollinger, personal communication, September 7, 2019). If, despite non-pharmacological intervention, infants still have significant symptoms and two consecutive Finnegan scores of 10 or higher, they are admitted to the NICU and pharmacological intervention (generally morphine) begins in addition to continuing non-pharmacological intervention (S.M. Hollinger, personal communication, September 7, 2019). Again, monitoring, intervention, and Modified Finnegan Scale procedures may vary by location.

Feeding and swallowing in premature infants. Infants born premature are often compared to infants with NAS in the existing literature as these infants also constitute a large portion of the NICU caseload. Babies born before 37 weeks of gestation are considered premature, and this population's swallow is affected by a range of developmental obstacles (Shaker, 2018). The full-term infant's swallow matures throughout infanthood and is still at a high risk for compromise; by comparison, the premature infant swallow is at even higher risk due to immaturity in respiration, physiological and reflexive development, and other challenges. Preterm infants display lower muscle tone, breathing difficulties due to differences in lung physiology and lack of surfactant, sensory aversions, and reflux. These factors can result in longer feeding times and higher risk of aspiration (DaCosta et al., 2008; Delaney & Arvedson, 2008). In simple terms, these infants are often unable to achieve effective coordination of sucking, swallowing, and breathing. During the esophageal phase of feeding, the bolus traverses the esophagus and lower esophageal sphincter, whose tone is also regulated by nuclei in the brainstem and modulated by respiratory drive. Although control gradually improves, there is a period of heightened difficulty for preterm infants and other infants with similar signs and symptoms.

Opioid-exposed infants present with a swallow that is similar in symptomatology to that of premature infants (Reynolds et al., 2017), but may have a different cause, such as neurological disruption rather than immaturity (Shaker, 2018). In such a neurological model of immaturity, feeding difficulty results from oral-motor patterns, muscle tone and coordination, state regulation and sensory processing. Reynolds et al. (2017) posit that the swallow of an infant with NAS does not represent a new pathology due to the functional similarity to the swallow of a premature infant. Because of these similarities, a lack of research on the swallow of the infant with NAS, and the practical familiarity that many speech-language pathologists have with the premature infant swallow, it is highly useful to consider the premature infant swallow as a theoretical model for comparison.

Wang et al. (2014) found that 27% of all late preterm infants had a clinical condition that necessitated the distribution of intravenous fluid, compared to only 5% of all full-term infants. The authors identified various clinical problems, including feeding problems as the dominant reason, which precipitated this treatment. Even late preterm infants had significantly more delayed discharges from hospital than full-term infants, which aligns with increased length of stay rates for infants with NAS or other opioid exposure (Wang et al., 2014). As comparisons between infants with prematurity and infants with NAS are rife, and infants with NAS are typically born later or at term, these comparisons may point to similar feeding-related difficulties for the NAS population.

Demauro et al. (2011) also compared early- and late-preterm infants to describe their feeding difficulty rather than report outcomes. Their study found that early preterm infants had more oromotor dysfunction and avoidant feeding behavior, although these improved over time. The most commonly reported form of oromotor dysfunction was choking and the most commonly reported form of avoidant behavior was spitting, indicating a degree of inefficiency in laryngeal closure and oral control for these early preterm infants. Both groups experienced poor appetite and subspeciality hospitalization at similar rates.

Medoff-Cooper et al. (2001) found that late preterm infants had more immature feeding behaviors at 35 to 36 weeks postmenstrual age than early preterm infants. The authors suggested that more experience with feeding for the early preterm group led to more advanced feeding skills. Goldfield et al. (1999) investigated the influence of respiration, also developmentally affected, in the preterm infant swallow. The authors compared the coordination of sucking and breathing in terms of pacifier behavior among three groups at 38-40 weeks post-conceptual age: healthy full-term infants, low-risk preterm infants, and high-risk preterm infants. Only infants in the high-risk group differed in the demonstration of breathing frequency and the coordination of breathing and sucking rhythms. For this group, breathing had less influence on respiratory frequency than sucking, and patterns of coordination were simpler.

Comparisons of early- and late-preterm infants in these studies point to greater difficulties for the earlier population linked to neurological and physiological immaturity. For all these groups, which are often compared to infants with NAS in a theoretical model, difficulty feeding is due to the coordination of breathing and sucking and decreased oral control. From the limited literature available on the feeding difficulties of infants with NAS, these observations support the current theoretical comparison between infants with prematurity and infants with NAS.

Feeding and swallowing in opioid-exposed infants. For opioid-exposed infants, feeding is characterized by irregularity, and the coordination of suck-swallow-breathe is complicated by disruptions in any of the three phases of the feeding process. Kocherlakota (2014) described a series of symptoms secondary to an affected autonomic nervous system that have implications for feeding and weight gain in the drug-exposed population, including tachypnea, nasal flaring, nasal stuffiness, excessive motor activity, regurgitation, vomiting and diarrhea, though diarrhea is more commonly associated with opiate withdrawal. Due to a widely recognized presentation of hyperphagia, infants with NAS may require intake of more than 150 calories per kilogram per day associated with increased appetite. Infants with NAS may also encounter a short but intense initial phase that includes heightened autonomic symptoms, with a corresponding spike in feeding difficulties. Health care professionals often utilize frequent feeds, high-calorie formula, and thickened feeds to meet the nutritional, metabolic and feeding needs of these infants (Gottesman et al., 2018).

Gewolb et al. (2004) found that in the first three days of life, infants prenatally exposed to drugs displayed a significantly higher percentage of apneic swallows (defined as runs of three or more swallows not associated with breathing movements) noted during feeding compared with a control group. This series of apneic swallows resulted in a disturbance of the typical feeding sequence, with arrhythmic swallows and negative feeding experiences for infant and caregiver.

According to Maguire et al., (2015), infant behaviors that disrupt feeding have not been well-studied in the population of infants exposed to drugs, especially since the Modified Finnegan Scale describes response to treatment in general, not feeding specifically. Using this tool, however, a study with 1,120 observations over 10 days indicated that the greatest or most frequent obstacles to treatment were increased tone, respiratory rate, and excessive sucking. (D'Apolito, & Hepworth, 2001).

In fact, the mechanics of swallowing are often impacted by drug withdrawal following birth, and the swallow of an infant exposed to drugs may appear radically different when compared to that of a typical full-term infant, although some of the obstacles are similar to those faced by the preterm population. Kron et al. (1975) reported poor sucking performance in 32 infants exposed to methadone, who also underperformed both another experimental group of 18 infants exposed to heroin and a control group of 20. Specifically, these infants spent less time sucking and further demonstrated decreased sucking pressure. In a large sample of 1,028 infants, Legasse et al. (2003) found that opiate-exposed infants had more feeding problems, specifically longer sucking bursts and fewer bursts per minute, than non-drug-exposed infants or even infants exposed to cocaine. The opiate-exposed infants demonstrated significant mechanical and behavioral differences, including dribbling milk, hiccoughing, spitting up, coughing, and rejection of the nipple. Opioid-exposed infants struggled to retain expressed liquid and to pharyngeally control liquid during the swallow.

In every study of this population, infants with a history of opioid exposure struggle to maintain consistent sucking pressure and coordinate inspiratory respiration and feeding.

Physiology of impaired respiration. Respiration is intertwined with the swallowing process and in weight gain outcomes for this population. Neonatal abstinence syndrome results in a constellation of signs and symptoms that affect the respiratory system. Excessive and uncontrollable crying is one such symptom (Kocherlakota, 2014) as a result of central nervous system instability. The autonomic nervous system is also dysregulated in infants with NAS, and this can lead to impaired heart rate, respiratory rate, and muscle tone, as well as temperature instability, sweating, sneezing, and mottling due to an acetylcholine increase on a neurotransmitter level (Kocherlakota, 2014; Jansson et al., 2010). Tachypnea, nasal flaring, and nasal stuffiness, which may be misinterpreted as respiratory distress in newborns (Kocherlakota, 2014), still present obstacles to functional breathing and feeding for infants.

Infants with NAS mainly exhibit abnormalities within the inspiration cycle of respiration, with profound effects for feeding and swallowing. Breathing rate is controlled by inspiratory and expiratory neurons in the pons and medulla oblongata. The respiratory cycle of inspiration and expiration is controlled by synaptic interactions of these neurons. Opioids exert neurological inhibitory effects mainly on the inspiratory neuron network in the medulla and only minor effects on the central respiratory rhythm by preinspiratory neurons.

Infants with NAS can be readily identified by their distinctive, high-pitched, and uncontrollable cry. As part of a longitudinal multisite study of the effects of prenatal opiate exposure on neurodevelopmental outcomes, Lester et al. (2002) performed an acoustic analysis on the cries of drug-exposed infants in order to more fully understand the relationship of this vocalization to infant respiration and weight gain, among other variables, including reactivity and neural control of the cry sound. Measures of cry acoustics reflect the mechanisms that mediate cry production, including central nervous system reactivity, respiratory control, and sound characteristics related to neural control of the vocal tract.

Lester et al. (2002) elicited cries by stimulation to the sole of the infant’s foot and analyzed infant crying using measures of threshold, latency, number of utterances (i.e., a cry during the expiratory phase of respiration lasting at least 0.5 seconds), number of short utterances, inspiratory period, fundamental frequency, and hyperphonation. Each 30-second cry signal was filtered above 5 kHz and digitized at 10 kHz by the cry computer, while a Fast

Fourier Transform computed the log magnitude spectrum for each 25-ms block of the cry utterance. Opiate effects on infant crying include shorter utterances and more hyperphonation, and general effects of prenatal drug exposure on the reactivity, respiratory and neural control components of the cry. Lester et al. (2002) also found effects between birth weight and the infant cry. Most of the observed birth weight effects were related to the respiratory control of cry production. Specifically, researchers observed that utterance measures and energy of the cry utterance were significantly correlated with weight gain. The researchers found independent effects of birth weight on cry analysis and describe birth weight as a moderator variable in the study. Lester et al. (2002) also tested the hypothesis that opiate effects could be masked by the inclusion of birth weight and the opiate by birth weight interaction. They found more evidence that the effects of opioids on cry are more visible when these variables were used as covariates than when they were not.

Animal studies of prenatal opioid exposure and respiration. Because of the limited nature of the research on respiration for the population of infants with NAS, several animal studies are included to more fully describe the effects of opioid exposure at the neurological and behavioral level. Respiratory depression occurs at the level of μ- and κ-opioid receptor agonists in the brainstem and spinal cord. This is caused by a combined and reversible presynaptic and postsynaptic inhibition of inspiratory neurons. Membrane properties of preinspiratory and most expiratory neurons are left unaffected, according to a study in which researchers investigated the effects of opioid exposure on the isolated respiratory network in neonate rats (Takeda et al., 2001). For example, resting membrane potential remained the same, but spontaneous release of neurotransmitters related to inspiratory respiration were heavily depressed. Gourevitch et al. (2017) investigated in utero methadone exposure of the ventral respiratory column in neonate rats to compare the development of medullary systems in response to opioid exposure. The changes they observed are congruent with the neuronal behavior observed by Takeda et al. (2001) and included higher neuronal firing rates and higher covariance between neuronal activity and motor output. These include disordered changes at the cellular, network and system level.

Wallisch et al. (2010) researched the effects of in vitro buprenorphine exposure on the respiratory systems of neonate guinea pigs in order to quantify this opiate's effect on both maternal and infant health. For the guinea pigs in the study, respiratory effects began on the third day and continued for two weeks. The youngest pups experienced significantly increased inspiratory effort, accompanied by extreme hyperventilation due to increased inspiratory minute ventilation. Expiratory time and the ratio of expiratory to inspiratory time was altered in the pups until the last study day, suggesting an abnormal neurological control of breathing during the acute withdrawal phase. Finally, Wallisch et al. found that the pups experienced a prolonged and exaggerated response to hypercapnia, or elevated carbon dioxide levels in the blood, outside of this typical withdrawal period, implying abnormal breathing control in the central nervous system, as well. These effects of opioid exposure are not only observable in inspiratory respiration, but also in expiration and crying.

Respiration and feeding for infants with NAS. Respiration is a vital part of the suck-swallow-breathe mechanism. However, there is relatively little literature on the respiratory status of infants with NAS, and still less on the interaction between respiration and feeding for this population. As with feeding difficulties, the more thoroughly researched population of premature infants offers a ready theoretical model for consideration of infants with NAS. This premature infant population also shows a distinct similarity to the respiratory and feeding function of infants with NAS (Reynolds et al., 2017). Furthermore, there is established evidence for the comorbidity of respiratory and feeding difficulties in the premature infant population (Demauro et al., 2011; Gewolb & Vice, 2006; Goldfield et al., 1999; Koenig et al., 1990; Thoyre & Carlson, 2003).

Respiratory, airway, and digestive co-morbidities significantly predict transition time and coordination (Gewolb & Vice, 2006; Jadcherla et al., 2010). Cardio-respiratory issues may result in problems maintaining adequate respiration with feeding, characterized by disorganized feeds, and may also result in pause periods due to a lack of reserves and the effect of continuous sucking (Craig et al., 1999). Impaired respiration and feeding together can result in respiratory fatigue and decreased endurance, increased effort to breathe, desaturation with feeding, unsafe swallowing, aversions, and delayed initiation of the swallow (Barlow et al., 2010).

When energy reserves are low, infants are forced to breathe faster; in turn, this increased respiratory drive can inhibit oral feeding (Timms et al., 1993). Decreases in oxygenation during feeding provide infant with negative feedback and result in loss of coordinated feeding behavior as the infant attempts to protect his/her airway (Medoff-Cooper & Ray, 1995). During the esophageal phase of feeding, the bolus traverses the esophagus and lower esophageal sphincter, whose tone is also regulated by nuclei in the brainstem and modulated by respiratory drive. Although control gradually improves, there is a period of heightened difficulty for preterm infants.

Many of the most acute feeding challenges for infants with NAS emerge in the first several days of life. Gewolb et al. (2004) and colleagues designed a study to investigate the differences in the rhythmicity of suck-swallow-respiration during feeding. They established that, during the first days of life, opioid-exposed infants are less efficient feeders and ingest less volume per run-swallow than infants in control groups. At the same time, these infants who were opioid-exposed appeared to compensate with a faster swallow rate. While there was no significant difference in suck rate, sucks per run, or in suck rhythm between the drug-exposed and control groups, the drug-exposed group had a significantly higher percentage of apneic swallows. These findings align with those of Legasse et al. (2003) in demonstrating longer sucking and swallowing bursts in drug-exposed infants; however, Gewolb et al. argue that subtle abnormalities in respiratory control and the related behavior of swallow rhythmicity are responsible for the impact on swallowing and feeding inefficiency overall. In general, "the newborn term infant maintains swallowing rhythm at the expense of normal breathing" (Gewolb et al., 2004, p. 700).

Several researchers describe abnormalities in the control of breathing during feeding for drug-exposed infants (Craig et al., 1999; Gewolb et al., 2004; Loughlin & Lefton-Grief; 1994), and these behaviors include decreased responsiveness to hypoxic and hypercarbic challenges, more frequent apneic episodes, longer duration of apnea, and less periodic breathing. These respiratory abnormalities can lead to disorganized feeding patterns and shorter feeding times due to arrhythmic feeding response (Gewolb et al., 2004). Infants with other disorders of respiration, such as bronchopulmonary dysplasia, experience the same patterns of discoordination (Gewolb & Vice, 2006; Craig et al., 1999). In both studies, the severity of BPD affected breathing rates by significantly reducing the duration and regularity of a breath while sucking during the intermittent phase of feeding.

Feeding drug-exposed infants also comes with behavioral challenges. Maguire et al. (2015) observed feeding interactions between drug-exposed infants and their mothers in an attempt to codify the interactions and any disruptive behaviors. They found that fussing behavior accounted for 40.2% of the feeding period, with fussing behavior including averting face, pulling or turning away or otherwise resisting, grimacing or frowning, hyperextended arms or legs, flailing arms, splaying fingers, pushing or spitting out the nipple, and vocal objections. Feeding accounted for only 24% of the feeding interactions observed, and including latching on the nipple, sucking and swallowing in a rhythmical pattern and only brief pauses.

Reynolds et al. (2017) propose that the development of suck-swallow-breathe rhythms during non-nutritive sucking may be an indicator of neurologic integrity. In their study, they compared a group of full-term infants with NAS, a group of low-risk preterm infants, and a control group in terms of swallow-breath interaction and phase of respiration. Measuring suckle, swallow, thoracic motion, and nasal airflow among a total of 22 infants, they found statistical differences among all groups. Specifically, the coordination of swallow-breathe in the NAS group was similar to that of the low-risk preterm infants, with fewer swallows with attenuated respiration and more with central apnea, supporting the findings of Gewolb et al. (2004). They conclude that this variability may represent neurologic dysfunction in the NAS group, and that the actual swallowing behavior makes this group very similar to the performance of preterm infants, rather than representing an entirely unique pathology.

Nevertheless, infants with NAS differ in key areas of swallowing and respiration from control groups of typical infants. Babies with NAS had significantly more swallows occurring with central apnea and fewer occurring with attenuated respiration than typical babies. There was a nonsignificant trend toward more swallows occurring with obstructive apnea in the NAS group, as well. When controlling for identified confounders with multivariate analysis, the researchers found that the differences in predicted distributions for central apnea and attenuated respiration were still present. Additionally, the difference in predicted percentage of swallows at obstructive apnea became statistically significant. Infants with NAS displayed an immature swallow pattern that improved over time (Reynolds et al., 2017). Many of these characteristics of infants with NAS can be directly compared to those of premature infants.

Interaction of feeding and respiration for premature infants. In a study of premature infants and the interaction of respiration and feeding, Lau et al. (2003) researched the coordination of suck-swallow swallow-breathe processes in preterm infants, a group that demonstrates swallow and respiration processes that are strikingly similar to those exhibited by infants with NAS (Reynolds et al., 2017). The researchers recruited 12 preterm and 8 full-term infants and recorded sucking, swallowing and respiration simultaneously when the preterm infants began oral feeding. Lau et al. used rate of milk transfer (ml/min) as an index of oral feeding performance, and they measured sucking and swallowing frequencies, average bolus size, and suction amplitude. Preterm infants swallowed preferentially at different phases of respiration than their full-term counterparts. As feeding performance improved, sucking and swallowing frequency, bolus size and suction amplitude increased. Lau et al. conclude that feeding difficulties in preterm infants are more likely to result from inappropriate swallow-respiration interaction than suck-swallow interaction, based on the measures of respiratory control observed within the cohort.

Hawdon et al. (2000) conducted a prospective study of 35 premature infants with an average age of 34 gestational weeks that support the findings of Gewolb et al. (2004). Hawdon et al. (2000) documented a high incidence (40%) of abnormal feeding patterns. The infants with prolonged respiratory support and delayed enteral and oral feeding were most affected. Infants with dysfunctional feeding were six times more likely to vomit and three times more likely to cough when offered solid food. At 12 months of age, they found significant differences between groups in the toleration of lumpy foods and mealtime enjoyment, with ongoing failure to thrive and psychosocial distress in this group of non-drug-exposed infants.

Modality of feeding. The feeding method utilized in the NICU can have a dramatic effect on outcomes for infants, including the opioid-exposed population. Recent advances in neonatal care have emphasized the use of cue-based feeding rather than the established volume-driven approach, which prioritizes intake as the most important measure of effectiveness during a feeding session. In cue-based feeding, a positive feeding experience is an interplay between the caregiver's understanding of the infant's needs and the infant's communication of those feeding needs by behavior and physiology (Thoyre et al., 2005). At its best, cue-based feeding represents the infant's ability to feed with support, rather than 'being fed.'

Researchers have investigated the efficacy of cue-based feeding with the preterm population. In one study with healthy preterm infants at 32-34 weeks PMA, McCain et al. (2001) offered bottle feedings to the experimental groups based on physiologic and behavioral responses. The experimental group gained more weight and achieved full bottle feeding sooner than the control group, which received standard volume-driven care. For infants with respiratory deficiencies, the results are similar. Infants with chronic lung disease (CLD) have altered suck-swallow-breathe patterns. In another study with preterm infants with CLD born at 24 weeks gestation, McCain, Moral, et al. (2012) offered bottle feedings based on cardiorespiratory and behavioral responses. These infants achieved full bottle feeding 5-6 days sooner than infants with CLD who were fed using the standard approach. Attention to signs of the infant's tolerance or intolerance also resulted in safer and less stressful feedings.

Breastfeeding. The modality of feeding can also often have an impact on weight gain and other related measures; in the case of NAS, modality may also affect the severity of onset. It is unclear why breastfeeding in particular appears to offer substantial benefits as residual and significant substance amounts do not travel via breast milk; however, several studies in recent years have attempted to determine the benefits of feeding method. In a retrospective chart review, McQueen and Murphy-Oikonen (2011) followed 28 term infants exposed to methadone and exhibiting signs of NAS. This group of infants was divided by feeding method, including predominantly breastfed (8), combination fed (11) or predominantly formula-fed (9). Researchers compared NAS scores and NAS treatment in the charts of these infants and found a statistically significant difference in the number of NAS scores recorded per group. Specifically, infants who predominantly breastfed had significantly fewer NAS scores and lower mean scores, suggesting decreased severity and duration of NAS symptoms when compared to infants who were either predominantly formula-fed or combination fed. As such, breastfeeding when possible may offer benefits for infants exposed to methadone.

A similar retrospective record review (Eliu et al., 2015) focused on the effects of infant feeding method on NAS onset and treatment level within the first two days of life for 194 mother-infant dyads exposed to methadone. Researchers categorized infants as predominantly breastfed, fed human breast milk, or formula fed. After using the onset of NAS as the outcome measure, Eliu et al. (2015) found no significant effect on the rates of NAS requiring treatment but discovered that breastfeeding significantly delayed the onset of NAS for this population.

If breastfeeding is not an option, however, infant formula is often recommended (Gottesman et al., 2018). The evidence is limited on the specific feeding protocols for this patient population, but recommendations have been made for providing higher calories (~150 to 250 kcal/kg/d). In their case study Gottesman et al. describe an infant born full-term and displaying symptoms of NAS, with three Finnegan scores of 8 or more. The baby was started on a transitional formula because his mother was not providing breast milk and the infant was less than 2500 g at birth. The physician's order included a formula at a minimum volume of 25 mL via oral intake every 3 hours. The feeding regimen provided approximately 64 kcalkg/d, 1.8-g protein/kg/d and 85-mL fluid/kg/d. A registered dietician nutritionist, nurses, physicians, and residents managed the case collaboratively. Staff monitored the infant for tolerance to feedings, daily weight gain, weekly head circumference and length measurements, monitoring changes in electrolytes and other biochemical values, and implementation of vitamins and minerals. Nutrition recommendations including oral feeding modifications, adjustment of formula goal rate, and evaluation of growth patterns. The infant's nutritional needs were estimated to be a minimum of 108 kcal/kg/d, 2.0- to 2.5-g. protein/kg/d, and 150- to 200-mL fluid/kg/d based on estimates of the Dietary Reference Intake. The weight gain goal established for the infant was approximately 33 g/d at 0 to 3 months and 17 g/d at 3 to 6 months. The nutritionist and other staff managed dietary presentation, titration of withdrawal medications, and other needs in response to infant behavior throughout length of stay.

The infant was discharged home to his parents on day of life 159. His recommended diet at discharge consisted of a 24-calorie per ounce term formula at a minimum volume of 130 mL via oral intake every 3 hours. While the infant's formula goals were continually adjusted to promote weight gain and growth and he experienced growth month after month, total gains in length, head circumference, and weight were less than desired. Management for weight gain and feeding behavior continued at a high-risk clinic for the following year (Gottesman et al., 2018).

Summary. Rates of NAS are on the rise, and this growing population is appearing on the caseloads of speech pathologists with increasing regularity (Patrick et al., 2015; Ratliff & Proctor-Williams, 2017). Feeding and swallowing interactions are essential to the integrity of swallowing in both exposed and unexposed infants, as the typical infant swallow is characterized by reflexes and movements required for the coordination of the suck-swallow-breathe reflex (Delaney & Arvedson, 2008). The ideal pattern for the typical infant swallow is one of exhalation, lip seal, sucking, swallow, and inhalation. However, there are many differences and no established norm. In full-term infants, feeding and/or breathing difficulties are rare in the absence of cleft lip and/or palate, laryngomalacia, and other comorbidities.

The relationship between respiratory and feeding difficulties in infants born prematurely is clear based on existing literature (Gewolb & Vice, 2006; Goldfield et al., 1999; Hill & Rath, 2002). Yet, for typical infants born at full-term, both respiratory and feeding difficulties are rare (Gewolb & Vice, 2006; Goldfield et al., 1999). Most infants diagnosed with NAS are born full-term (Kocherlakota, 2014); however, infants with NAS display a range of feeding difficulties (Gewolb et al., 2004; Kocherlakota, 2014; Maguire et al., 2015).

Feeding and swallowing are impacted in many, but not all, cases of NAS (Kocherlakota, 2014). Studies report poor sucking performance in infants exposed to methadone, with swallowing characterized by less time sucking and decreased sucking pressure (Kron et al., 1975). These feeding problems have implications for an infant’s health, such as poor weight gain and aspiration with resultant longer lengths of stay and increased cost (Patrick et al., 2015).

The existing literature on feeding and swallowing for children with NAS, however, only hints at a potential relationship between respiration and swallowing during the feeding process. Research by Gewolb et al. (2004) point to abnormalities of interposition of respiration into rhythmic feeding and increased feeding-associated cessation of breathing for infants exposed to drugs, along with transient feeding inefficiency, especially in the first days of life. However, there only a handful of studies on the interaction of feeding and respiration for the full-term NAS or opioid-exposed population, and the majority of these do not take the entire length of an infant's stay into consideration.

Purpose and questions. The primary purpose of this study was to determine the relationship between respiratory status and feeding difficulties in infants with NAS (NAS) in comparison to full-term infants with no exposure to opioids (FTNO). Because of ambiguity on the question of etiology of feeding difficulty in the population of infants with NAS, this study seeks to examine the relationship between feeding and respiration in light of the Developmental and the Withdrawal Disorganization models of NAS feeding difficulty. The models and their predictions are represented in Table 1.

Secondarily, this study investigates the impact of respiratory and feeding difficulties on length and cost of stay among subjects in these diagnostic groups.

The current study seeks answers to the following questions for full-term infants with a diagnosis of NAS (NAS) and those who are full-term non-opioid exposed (FTNO).

1. Are there differences in the likelihood of feeding and respiratory difficulties between infants with NAS and infants born FTNO?
2. Are there differences in the comorbidity of feeding and respiratory difficulties between infants with NAS and infants born FTNO?

It is predicted that there will be a difference in both likelihood and the comorbidity of feeding and respiratory difficulties for full-term infants with NAS and infants with FTNO. It is predicted that infants in FTNO group will present with neither feeding nor respiratory difficulties (Delaney & Arvedson, 2008). In contrast, literature suggests that infants with NAS have feeding difficulties (Jansson et al., 2010). There is literature suggesting they have respiratory difficulties (Kocherlakota, 2014) but this lacks specificity about severity. Because of a paucity of evidence regarding infants with NAS and/or a history of opioid exposure, there is no prediction about comorbidity of respiratory or feeding difficulties for these infants. Results of the study may provide clarity about the etiology of feeding difficulties for infants with NAS.

3. Is there a difference in outcomes for infants who have only feeding difficulties, only respiratory difficulties, comorbidity of respiratory and feeding difficulties, or no feeding nor respiratory difficulties as measured by length of stay and total cost?

It is predicted that there will be a difference in outcomes based on a history of only feeding difficulties, only respiratory difficulties, comorbidity of respiratory and feeding difficulties, and no feeding nor respiratory difficulties as measured by length and cost of stay. It is predicted that infants with only feeding difficulties will have extended length and cost of stay, although predictions for length of stay are unclear based on the limited available evidence. It is predicted that infants with a comorbidity of respiratory and feeding difficulty will have the longest length of stay (Gewolb & Vice, 2006; Jadcherla et al., 2010). It is predicted that infants with neither feeding nor respiratory difficulties will have the shortest length of stay and lowest cost of stay.

Table 1.

Etiological Models of Feeding and Respiration

Developmental Model			
	Diagnosis		
Area	**Premature**	**NAS**	**FTNO**
Feeding	Impairment	Impairment	No Impairment
Respiration	Impairment	Impairment	No Impairment
Comorbidity	Consistent	Consistent	NA

Withdrawal Disorganization Model			
	Diagnosis		
Area	**Premature**	**NAS**	**FTNO**
Feeding	Impairment	Impairment or Typical	No impairment
Respiration	Impairment	Impairment or Typical	No impairment
Comorbidity	Consistent	Inconsistent	NA

Chapter 3. Method

Research Design

To answer the questions described in the summary, the researcher utilized a descriptive cohort design method using a quantitative framework. The cohort research design is a type of observational study, in which participants are selected based on the exposure status of the individual; these individuals are then followed over time to evaluate for the occurrence and characteristics of the designated variable(s) (Barria, 2018). This type of study design was selected because of its strengths in identifying risk factors and prognostic indicators over time (Barria, 2018), as the questions of this study regarding etiology, symptomological interaction, and outcomes seek to do. While the study is descriptive in nature, the presence of a control group (FTNO) also characterizes the nature of this study as analytical (Barria, 2018). Only quantitative factors were utilized in this study.

Sample. The participants were drawn from an initial sample that included 770 infants who were patients in the Ballad Health hospital system in northeast Tennessee from January 1, 2011 to December 31, 2016. This hospital system and associated neonatal intensive care unit (NICU) serve a central Appalachian region consisting of northeast Tennessee, western North Carolina, southwestern Virginia, and southeastern Kentucky. The NICU is a level III facility in the Niswonger Children's Hospital, with 39 beds and a Special Care Unit for infants with special needs, such as NAS. Participants with NAS were an average age of 3.75 days old at the time they were admitted to the NICU and were an average of 15.18 days old (corrected for prematurity when applicable) at the time they were discharged from services.

Protection of participant privacy. Approval for a broader study of NAS, of which the current research is a component, was obtained from the ETSU Institutional Review Board (IRB). The thesis includes data from a deep retrospective chart review from the electronic medical record (EMR) of the participants. All participant data was deidentified following the IRB protection of privacy guidelines by parties not involved in this study. All participants were populated into a spreadsheet by a third party. Only the variables requested and reviewed as appropriate for the study were transmitted to the experimenter. The data used for group assignment, demographic information, and determination of feeding and respiratory status was extracted from this spreadsheet.

Participants. Purposive sampling was used in this retrospective cohort study by a third-party data collection and research group. They selected subjects that met diagnostic criteria for neonatal intensive care support within the Ballad Health system and matched them to infants FTNO based on delivery year (within one year); delivery hospital (exact match); maternal age at delivery (within 2 years); maternal marital status (exact match for status); maternal medical insurance (exact match for private or uninsured status); maternal smoking during pregnancy (exact match at time of delivery); maternal alcohol use during pregnancy (exact match); and infant gender (exact match).

Group assignment

Inclusion criteria. Group assignment was conducted on an *a priori* basis. To be included in the FTNO group, none of the following inclusion factors was present. In contrast, criteria for inclusion in the NAS group required Finnegan scores (Jansson et al., 2009) and/or recorded opioid exposure. Specifically, inclusion criteria for the NAS group included one or more of the following:

- NAS diagnosis;
- NAS diagnosis by ICD code
- NAS diagnosis per patient file

- Three Finnegan scores greater than 10
- Admission to the NICU for NAS
- Presence of a care plan for drug exposure
- Positive maternal prenatal UDS screen
- Any positive infant drug screen lab results
- Maternal report of opioid usage during pregnancy
- Maternal report of medication-assisted treatment.

Exclusion criteria. Criteria for exclusion from were based on existing literature and diagnostic or exposure factors. Specifically, exclusion criteria from the NAS group and the FTNO group included one or more of the following:

- Full-term infants exposed to opioids without formal NAS diagnosis
- Infants born before 37 weeks gestation, or preterm
- Infants born with cleft lip and/or palate

This study seeks to investigate the specific pathology and etiology of formally diagnosed NAS; opioid exposure alone represents a similar but separate set of signs and symptoms that is distinct from NAS. As a result, 133 full-term infants exposed to opioids without an NAS diagnosis were excluded from the initial sample of 770 infants (*n*=637).

Of this sample of 637, 67 infants with NAS who were born before 37 weeks of gestation were subsequently excluded, as these infants are considered premature (Shaker, 2018). This left a sample of 263 infants with NAS. As well, 26 infants with prematurity and no opioid exposure were also excluded leaving a sample of 281 in the FTNO group. Infants with a diagnosis of NAS and a history of prematurity experience two separate pathologies, both of which often result in feeding challenges (Reynolds et al., 2017). As it would be impossible to determine the effects of one pathology over another in a comorbid case, premature infants with a diagnosis of NAS were excluded. Infants with prematurity and no opioid exposure also were excluded to eliminate prematurity as a confounding factor in the FTNO control group.

Similarly, this sample does not include three infants, one with NAS and two FTNO born with cleft lip and/or palate, as these infants also experience pathologies that often result in feeding challenges (Mullens et al., 2019). Cleft lip and/or palate is more prevalent in infants with NAS (Mullens et al., 2019), and the current study would be unable to determine the effects of one pathology over another. The final NAS group included 262 participants. Following the exclusion of participants with cleft lip and/or palate, the final FTNO group included 279 participants (see Figure 3).

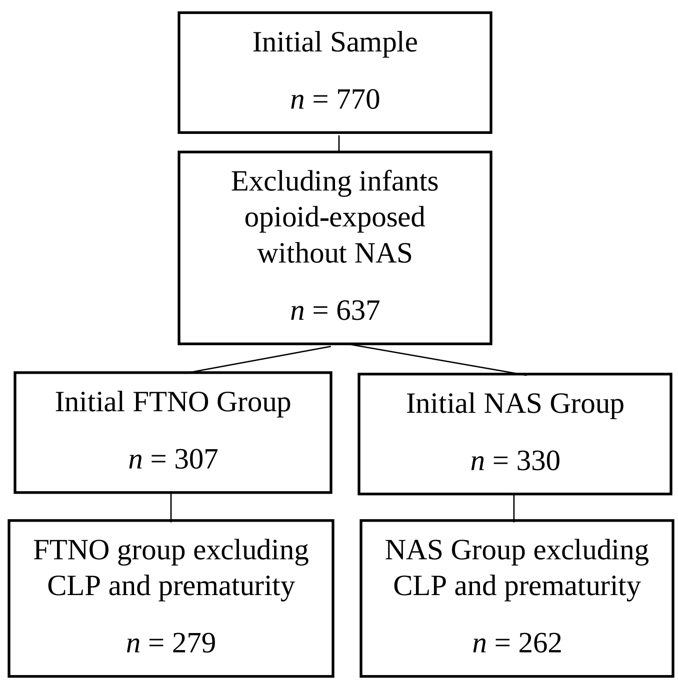

Figure 3: Flow chart of participant diagnostic inclusion

Demographics. This study gathered the following demographic variables for descriptive purposes only. These variables were not included as covariates in the statistical analysis pertaining to the questions. These variables include: (1) infant gender; (2) maternal race; (3)

maternal education level; (4) maternal access to the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) after delivery; (5) presence of prenatal care; and (6) number of visits and the week care began. Researchers confirmed maintenance of group matching (maternal age and access to insurance) after exclusions for opioid exposure without NAS, prematurity, and cleft lip and/or palate through means of t-tests and calculations of probability (all ps>0.35).

For infants with NAS, 114 infants were female, and 147 infants were male. For infants FTNO, 123 were female, and 157 were male. A two-tailed test of proportional differences indicated that there was no significant difference in infant gender between NAS and FTNO groups (p=0.95).

Maternal race by diagnosis is shown in Table 2.

Table 2.

Maternal Race by Diagnosis

Race	**NAS**	**FTNO**
White	251	265
Black	6	9
Hispanic	1	0
Other	2	4

In variables related to socioeconomic status (SES), the majority of mothers in both groups graduated high school (NAS=40.6%; FTNO=45.5%) and had access to WIC after delivery (NAS=78.4%; FTNO=74.5%). Maternal education level by diagnosis is displayed in Table 3.

Table 3.

Maternal Education by Diagnosis

Education	**NAS**	**FTNO**
Less than high school	10	7
Some high school	67	40
Graduated high school	106	127
GED	1	5
Some college	50	60
Associate degree	9	16
Bachelor's degree	5	11
Master's degree	0	1

For mothers of infants with NAS, 78.4% received WIC after delivery while 21.6% did not. For mothers of infants FTNO, 74.5% received WIC after delivery while 25.4% did not. A two-tailed test of proportional differences indicated that there was no significant difference between access to WIC after delivery between NAS and FTNO groups (p=0.3).

For mothers of infants with NAS, 97.2% received some level of prenatal care and 2.8% did not receive prenatal care. For mothers of infants FTNO, 87.8% received some level of prenatal care and 12.2% did not receive prenatal care. For mothers of infants with NAS, the mean number of prenatal visits was 8.44, while the mean number of prenatal visits was 10.69 for mothers of infants FTNO. Mothers of infants with NAS received a significantly fewer visits than mothers of infants FTNO, $t(310)=5.26$; $p<0.000001$. For mothers of infants with NAS, the mean week that prenatal visits began was 15.31 weeks, while the mean week that prenatal visits began was 11.99 for mothers of infants FTNO. Mothers of infants with NAS first began prenatal visits at a significantly later date than mothers of infants FTNO, $t(445)=4.88$; $p<0.00001$.

Procedures. Participants in the NAS and FTNO Diagnostic Groups were divided into subgroups based on respiratory and feeding status, as represented in the columns of Table 4 below.

Table 4.

Diagnostic, Feeding, and Respiratory Groups and Sample Sizes

Diagnostic	Feeding	Respiration
NAS (*n*=262)	Severe Feeding Difficulty (*n* =103)	Respiratory Difficulties (*n* =136)
FTNO (*n* =279)	Feeding Challenged (*n* =87)	Typical Respiration (*n* =434)
	Typical Feeding (*n* =380)	

Criteria for assignment of feeding status. Participants were categorized according to the level of their feeding difficulties. This study defined three feeding groups: (1) Severe Feeding Difficulties (SFD); (2) Feeding Challenged (FC); and (3) Typical Feeding (TF) based on severity to account for the range of data present in the medical chart and to more specifically address the study questions.

SFD group. This group included only those infants with at least one of the following non-Finnegan (Jansson et al., 2009) indications of significant feeding-related difficulty (see Table 5).

- Admission to NICU for poor feeding
- Speech consult
- Nutritional consult
- Feeding tube use

These indicators represent the most explicit and documented signs of feeding difficulty. These were exclusive to the SFD group.

*FC group***.** No infants in the FC group had any SFD indicators. Instead this group was defined using the Finnegan scoring system as described by Jansson et al. (2009). This group included only infants with feeding Finnegan ratio scores above the median of the NAS group to account for meaningful feeding difficulties over time (see Table 5). It represents a high number of feeding-related difficulties within the Finnegan scoring system, while controlling for the number of Finnegan scores recorded. Ratio scores were calculated by dividing the total number of feeding-associated Finnegan scores (i.e., scores of 1 for excessive sucking and 2 for poor feeding) as described by Jansson et al. (2009) by the score, of the remaining 19 possible Finnegan items, as described by Jansson et al. (2009) across all administered tests. The calculated median Finnegan ratio score was 0.51 for the NAS group. For example, consider a case in which an infant was administered 5 Finnegan tests as described by Jansson et al. (2009). The 5 feeding-related scores were 3, 2, 1, 2, and 3 (total of 11) and the 5 total scores of the remaining items were 3, 4, 5, 4, and 3, (total of 19). Thus, the feeding-specific total score (11) would be divided by the remaining Finnegan scores (19) for a ratio score (0.58). This infant would be included in the FC group as his or her ratio score of 0.58 is above the median of 0.51.

TF group. This group included infants with non-Finnegan indications of significant feeding-related difficulty or Finnegan indicators as described by Jansson et al. (2009) with ratios below 0.51 (see Table 5).

Variables for presence of ST Goals and Days on Feeding Tube were used to corroborate accuracy of variable entry and grouping.

Table 5.

Criteria for Assignment of Feeding Status

Variable	SFD	FC	TF
Admission to NICU for poor feeding	Positive	Negative	Negative
Speech Consult	Positive	Negative	Negative
Nutritional consult	Positive	Negative	Negative
Feeding Tube Use	Positive	Negative	Negative
Finnegan Feeding Marker Ratio	Not Applicable	Above Median	Negative/ Below Median

Criteria for assignment of respiratory status. As this study seeks to determine whether respiration interacts with feeding in this population or not, respiratory groups were dichotomized for the presence or absence of respiratory difficulties. Participants were automatically assigned to the Respiratory Difficulties (RD) group if they displayed at least one non-Finnegan respiratory indicator (see Table 6) as described by Jansson et al. (2009). These are the most explicit indicators of respiratory distress.

Participants also may have been assigned to the RD group after exceeding the upper quartile of Finnegan (Jansson et al., 2009) respiratory ratio markers; these upper quartile measures demonstrate meaningful respiratory difficulties over time. Ratio scores were calculated by dividing the total number of respiration-associated Finnegan scores (i.e., scores of 1 for frequent yawning, 1 for nasal stuffiness, 2 for nasal flaring and 1-2 for respiratory rate) by the score for the remaining 17 possible Finnegan items, across all administered tests. The calculated quartile Finnegan ratio score was 0.57 for the NAS group. Although median was calculated and used as a dividing measure for infants in the feeding groups, quartile divisions were used for respiratory status because of the greater number of identified variables used in this sampling and the binary nature of the respiratory grouping. Only infants with ratio scores in the upper quartile, indicating pronounced respiratory distress, were included in the RD group. For example, consider a case in which an infant was administered 5 Finnegan tests as described by Jansson et al. (2009). The 5 respiration related scores were 6, 6, 5, 4, and 6 (total of 27) and the 5 remaining scores of the tests were 7, 7, 8, 5, and 6, (total of 33). Thus, the respiration-specific score (27) would be divided by the total Finnegan scores (33) for a ratio score of 0.81. This infant would be included in the RD group as his or her ratio score is above the upper quartile of 0.57.

The variable of Days on O2 was used to corroborate accuracy of variable entry and grouping.

Table 6.

Criteria for Assignment of Respiratory Status

Variable	RD	TR
Admission to NICU for respiratory distress	Positive	Negative
O2 Assistance	Positive	Negative
Tachypnea	Positive	Negative
Care Plan for Respiratory Distress	Positive	Negative
Respiratory Consult	Positive	Negative
Finnegan Respiratory Marker Ratio	Upper Quartile	Negative/Below Upper Quartile

Impact on length and cost of stay. To address the secondary purpose of this research study, the impact of feeding and respiratory difficulty on cost and length of stay, outcome variables included:

1. Total cost in dollar amounts
2. Infant length of stay (LOS) in days. Length of stay is defined for the purposes of this study as the total length of time an infant spends in the hospital, not only the time the infant spends in the NICU.

Before analysis, valid *n* values were gathered for all relevant groups, including diagnostic, respiratory, feeding, and comorbid status.

Data analysis. Descriptive and inferential statistics were used to analyze the data to answer the study questions. Data was analyzed using the Statistica ® statistical software package, version 12.0 (Dell, 2013) and the MedCalc odds ratio calculator (MedCalc, 2019).

Demographic descriptions. Although demographics were only included in this study to describe groups, some statistical analysis was required in order to test differences between groups. For these purposes, researchers utilized a t-test and a two-tailed test of proportional differences in order to determine significant differences between groups.

Comorbidity of feeding and respiratory difficulties. The first question addressed potential differences in the comorbidity of feeding and respiratory difficulties between full-term infants with NAS and infants with a full-term history and no exposure. Inferential statistics for this question included a series of odds ratios and Chi-squared tests (χ^2).

The odds ratio (OR), its standard error and 95% confidence interval were calculated according to Altman (1991, as cited in MedCalc, 2019). The odds ratio equation is given by: OR = $\frac{a/c}{b/d}$ or $\frac{ad}{bc}$, where *a* is the given number in an exposed group with a positive (bad) outcome, *b* is the given number in an exposed group with a negative (good) outcome, *c* is the given number in a control group with a positive outcome, and *d* is a given number in a control group with a negative outcome.

The OR equation was selected for analysis of likelihood given diagnosis and each of the researched behaviors: respiration or feeding, independently. This statistical test was selected for its ability to detect the strength of association between two categorically determined variables; in this case, these variables include the presence of absence of NAS as compared to either the presence or absence of respiratory difficulty or feeding difficulty.

To analyze the comorbidity of respiratory and feeding difficulty, researchers applied the Chi-squared test analysis (χ^2). This test evaluates categorical data to determine how likely it is that any observed difference between the sets arose by chance. Researchers performed six Chi-square analyses to test the co-morbidity of NAS diagnosis, respiratory difficulty, and feeding difficulty. These analyses included two within-NAS group tests, two between-respiratory distress groups tests, and two between-typical respiration group tests.

Length of stay and total cost. The second question addressed whether there was a difference in outcomes for infants who have only feeding difficulties, only respiratory difficulties, comorbidity of respiratory and feeding difficulties, or no feeding nor respiratory difficulties as measured by birth weight, length of stay, and total cost. A one-way analysis of variance (ANOVA) test was used to analyze the interactions among diagnostic groups regarding length of stay, birth weight, and total cost in the second hypothesis. The one-way ANOVA was selected for its apt mixed analysis of in comparing the means of two or more categorical samples for significant differences. Six one-way ANOVA tests were conducted: two each, including either the categorical diagnostic (NAS and FTNO) with the comorbid combinations of feeding difficulty (SFD, FC, and TF) and respiratory status (RD and TR) and for each of the three continuous variables infant length of stay and total cost. As the groups included various numbers of participants the study used Unequal N HSD tests. This post hoc test can be used to determine the significant differences between group means in an analysis of variance setting (Dell, 2013).

Chapter 4. Results

Research Questions

The primary purpose of this study was to determine the relationship between respiratory status and feeding difficulties in infants with NAS in comparison to full-term infants non-opioid exposed (FTNO). Secondarily, this study investigated the impact of respiratory and feeding difficulties on length of stay and total cost among subjects in these diagnostic groups. The current study answers the following questions for children with a diagnosis of NAS or unexposed full-term birth:

1. Are there differences in the comorbidity of feeding and respiratory difficulties between full-term infants with NAS and infants with a full-term history and no exposure?
2. Is there a difference in outcomes for infants who have only feeding difficulties, only respiratory difficulties, comorbidity of respiratory and feeding difficulties, or no feeding nor respiratory difficulties as measured by length of stay and total cost?

Diagnostic group and likelihood of comorbidity. The first analysis examined the likelihood of infants with NAS having a respiratory or feeding difficulty compared to those in the FTNO group, independent of comorbidity. Table 7 shows the frequencies of occurrence of respiratory or feeding difficulty in each diagnostic group that was used in the odds ratio equations.

Infants in the NAS group were significantly more likely to have respiratory and feeding difficulties than those FTNO. Infants in the NAS group were 34.23 times more likely to develop RD than were the FTNO infants. (z=8.78; p<0.0001; 95% CI=15.55-75.32). Infants in the NAS group were 111.03 times more likely to develop SFD (z=7.84; p<0.0001; 95% CI=34.25-359.98) and 610.85 times more likely to develop FC (z=4.51; p<0.0001; 95% CI=37.48-9954.46) than FTNO infants

Table 7.

Frequency of Occurrence by Diagnostic, Respiratory, and Feeding Group

Group	**RD**	**TR**
NAS	122	139
FTNO	7	273

Group	**SFD**	**TF**
NAS	95	79
FTNO	3	277

Group	**FC**	**TF**
NAS	87	79
FTNO	0	277

Comorbidity of respiratory and feeding status. An essential question of this study is whether there are differences in the comorbidity of feeding and respiratory difficulties within and between the two diagnostic groups. A series of Chi-squared (χ^2) calculations were conducted to test differences in frequencies of comorbid presentations. First, these were conducted within the NAS group only, as the presentation of respiratory and feeding difficulties with the FTNO group was rare (3 cases out of 280). Next, between group (NAS vs FTNO) comparisons based on respiratory status were conducted.

Infants with NAS

Severe Feeding Difficulty and respiratory status. Within the NAS group, there was a statistically significant association between SFD and respiratory status (χ^2 (1, N=174)=19.94; p<0.0001). More infants with RD had SFD (38.51%) than those with TR had SFD (16.67%). More infants with TR had TF (28.74%) than those with RD had TF (16.09%), as shown in Table 8.

Table 8.

Differences in Comorbidity of SFD/TF by Respiratory Status for Infants with NAS

Groups	SFD	TF	Row Totals
RD	67 (38.51%)	29 (16.67%)	96 (55.17%)
TR	28 (16.09%)	50 (28.74%)	78 (44.83%)
Column Total	95 (54.60%)	79 (45.40%)	174

Feeding Challenged and respiratory status. In contrast, there was no statistically significant association between FC and respiratory status (χ^2 (1, N=166)=0.60; p<1.0) in the NAS group. The percentage of infants with RD who had FC (16.27%) was similar to those with TR who had FC (17.47%). As well, the percentage of infants RD who had TF (36.15%) was close to that of those with TR who had TF (30.12%), as shown in Table 9.

Table 9.

Differences in Comorbidity of FC/TF by Respiratory Status for Infants with NAS

Groups	FC	TF	Row Totals
RD	27 (16.27%)	29 (17.47%)	56 (33.74%)
TR	60 (36.15%)	50 (30.12%)	110 (66.27%)
Column Total	87 (52.41%)	79 (47.59%)	166

Calculation of the differences between the percentages of infants with NAS and RD with SFD (25.57%) or FC (10.31%) was significantly different (p<.0001).

Infants with RD

Severe Feeding Difficulty and diagnostic status. There was a statistically significant association between SFD and diagnostic status (χ^2 (1, N=105)=12.42; p<0.001). For infants with RD, more infants in the NAS group had SFD (63.81%) than infants in the FTNO group had SFD (0.95%), as shown in Table 10.

Table 10.

Differences in Comorbidity of SFD/TF by Diagnostic Status for Infants with RD

Groups	SFD	TF	Row Totals
NAS	67 (63.81%)	29 (27.62%)	96 (91.43%)
FTNO	1 (0.95%)	8 (7.62%)	9 (8.41%)
Column Total	68 (64.76%)	37 (35.24%)	105

Feeding Challenged and diagnostic status. There was a statistically significant association between FC and diagnostic status (χ^2 (1, N=64)=6.67; p<0.01). More children with RD and NAS had FC (42.19%) than children with RD and FTNO have FC (0.01%), as shown in Table 11.

Table 11.

Differences in Comorbidity of FC/TF by Diagnostic Status for Infants with RD

Groups	FC	TF	Row Totals
NAS	27 (42.19%)	29 (45.31%)	56 (87.50%)
FTNO	0 (0.00%)	8 (12.50%)	8 (12.50%)
Column Total	27 (42.19%)	37 (57.81%)	64

Infants with TR

Severe Feeding Difficulty and diagnostic status. There was a statistically significant association between TF and diagnostic status (χ^2 (1, N=349)=95.29; p<0.0001). More children with TR and NAS had SFD (8.02%) than children with TR and FTNO had SFD (0.57%). More children with TR and FTNO had TF (77.08%) than children with TR and NAS had TF (14.33%).

Table 12.

Differences in Comorbidity of SFD/TF by Diagnostic Status for Infants with TR

Groups	SFD	TF	Row Totals
NAS	28 (8.02%)	50 (14.33%)	78 (22.35%)
FTNO	2 (0.57%)	269 (77.08%)	271 (77.65%)
Column Total	30 (8.60%)	319 (91.40%)	349

Feeding challenged and diagnostic status. There was a statistically significant association between TF and diagnostic status (χ^2 (1, N=379)=174.32; p<0.0001). More children with TR and NAS had FC (15.83%) than children with TR and FTNO had FC (0.00%). More children with TR and FT had TF (70.98%) than children with TR and NAS had TF (13.19%).

Table 13.

Differences in Comorbidity of FC/TF by Diagnostic Status for Infants with TR

Groups	FC	TF	Row Totals
NAS	60 (15.83%)	50 (13.19%)	110 (29.02%)
FTNO	0 (0.00%)	269 (70.98%)	269 (70.98%)
Column Total	60 (15.83%)	319 (84.17%)	379

Comorbidity and outcomes. The second question of this study investigates differences in the outcome measures of length of stay and total cost based on diagnosis or respiratory and feeding comorbidity using ANOVA. When the ANOVA revealed a statistically significant outcome, it was followed by a planned Unequal N HSD analysis to more specifically test differences. Tables 14 and 15 show the relationship between these two outcome measures of the six comorbid groups.

Length of stay. The ANOVA comparing mean length of stay between NAS and FTNO groups as a whole revealed a statistically significant difference ($F(1, 539)=339.38$; $p<0.01$).

Because there was a significant difference between the main groups, the planned detailed analysis was justified. The ANOVA comparing mean length of stay measures between comorbid groups revealed a statistically significant main effect for the six comorbid groups ($F(1, 539) = 108.70$; $p<0.01$). Examination of differences between groups, using the HSD for unequal N, revealed that infants with RD and SFD had significantly longer LOS than all other groups (all *p*s $\leq .01$). Infants with TR and TF had significantly shorter LOS than all other groups (all *p*s $< .0003$). In addition, infants with RD and FC had significantly longer LOS than infants with RD and TF ($p = .036$). Finally, infants with RD and TF had significantly shorter LOS than infants with TR and SFD ($p = .032$).

Table 14.

Means and Standard Deviation of Length of Stay for Main and Comorbid Groups

Effect	N	LOS Mean	Std. Dev.
NAS	261	15.18	11.87
FTNO	279	2.05	1.09
RD/SFD	68	23.90	13.37
RD/FC	27	16.41	10.41
RD/TF	37	10.35	9.97
TR/SFD	30	16.17	10.25
TR/FC	60	11.17	9.73
TR/TF	319	2.91	3.16

Total cost. The ANOVA comparing mean total cost between NAS and FTNO groups revealed a statistically significant difference ($F(1, 539)=276.30$; $p<0.01$).

Because there was a significant difference between the main groups, the planned detailed analysis was justified. The ANOVA comparing mean total cost measures between comorbid group revealed a statistically significant main effect for the six comorbid groups ($F(1, 539) = 117.63$; $p<0.01$). Examination of differences between groups, using the HSD for unequal N, revealed that infants with RD and SFD had significantly higher cost than all other groups (all *p*s $\leq .0001$). Infants with TR and TF had significantly lower costs than all other groups (all *p*s < .001). In addition, infants with RD and FC had significantly higher costs than infants with TR and FC ($p = .01$). Finally, infants with TR and FC had significantly lower costs than infants with TR and SFD ($p = .007$).

Table 15.

Descriptive Statistics for Comorbid Groups and Cost

Effect	**N**	Mean Cost	Std. Dev.
NAS	261	$40,881.61	$37,412.32
FTNO	279	$3,627.76	$2,542.51
RD/SFD	68	$73,291.28	$40,799.84
RD/FC	27	$43,277.19	$29,905.28
RD/TF	37	$28,096.30	$31,704.72
TR/SFD	30	$42,786.70	$30,025.94
TR/FC	60	$22,951.18	$27,319.18
TR/TF	319	$5,747.15	$8,385.15

Chapter 5. Discussion

Diagnosis and Feeding-Respiration Interactions

The first question of this study posed in the summary section asks if there are differences in the comorbidity of feeding and respiratory difficulties between full-term infants with NAS and infants with a full-term history and no exposure. The differences are stark. Infants with NAS are 34.23 times more likely to develop RD, 111.03 times more likely to develop SFD, and 610.85 times more likely to develop FC than full-term typical infants born without opioid exposure. While the feeding difficulties of infants with NAS have received attention, there is no in-depth nor specific observation of the respiratory difficulties these infants experience in the known literature. This finding of respiratory difficulties in infants with NAS is not entirely unexpected, as Kocherlakota (2014) describes impairment of respiratory rate, heart rate, and muscle tone as a result of physiologic responses to withdrawal at the level of the autonomic nervous system (D'Apolito & Hepworth, 2001; Jansson et al., 2010); however, information on the degree of the relationship between a diagnosis of NAS and respiration is new.

Furthermore, there are significant associations between diagnostic, respiratory, and feeding status. For infants with NAS, comorbidity of SFD and RD was common (38.51%) as was FC and RD (16.27%) These findings are consistent with the research of Gewolb et al., (2004) and Loughlin & Lefton-Grief (1994), which found a relationship between diagnosis, feeding, and respiratory coordination resulting in decreased responsiveness to hypoxic and hypercarbic challenges, more frequent apneic episodes, longer duration of apnea, and less periodic breathing. However, Gewolb et al. (2004) did not comment on severity within the context of that study. In contrast, comorbidities in the FTNO group were rare. For infants FTNO with RD, only one had SFD and none had FC. These findings were as expected. Because of the rarity of these comorbidities for infants FTNO, this discussion now will focus primarily on infants with NAS, unless otherwise stated.

It is clear that respiration plays a large role in disrupting feeding patterns for infants with NAS, and this role is documented in the literature. Gewolb et al. (2004) designed a study to investigate the differences in the rhythmicity of suck-swallow-respiration during feeding. The researchers established that, during the first days of life, opioid-exposed infants are less efficient feeders and ingest less volume per run-swallow than infants in control groups. Gewolb et al. (2004) argued that subtle abnormalities in respiratory control and the related behavior of swallow rhythmicity are responsible for the impact on swallowing and feeding inefficiency overall. Reynolds et al. (2017) propose that the development of suck-swallow-breathe rhythms during non-nutritive sucking may be an indicator of neurologic integrity. In their study, they compared a group of full-term infants with NAS, a group of low-risk preterm infants, and a control group of unexposed full-term infants in terms of swallow-breath interaction and phase of respiration. The researchers found that the coordination of swallow-breathe in the NAS group showed fewer swallows with attenuated respiration and more central apnea, supporting the findings of Gewolb et al. (2004). This is consistent with the outcomes of the current study.

Infants with RD were significantly more likely to develop severe feeding difficulty (38.51%) than their counterparts with TR (16.09%). This suggests that a diagnosis of NAS may be an important predictor of feeding status, independent of respiration. These numbers stand in comparison to those of the FTNO group, where only 0.57% (2) infants with TR developed SFD and none developed FC.

Thus, diagnosis of NAS alone is a strong indicator that an infant will experience some level of feeding difficulties (70% of the NAS sample). The addition of respiratory challenges is likely to result in more severe feeding difficulties (36% of the NAS sample).

Etiological models. A primary purpose of this study was to determine how infants coordinate feeding and respiration in light of two possible models of pathological etiology. The Developmental Model posits a developmental cause for impairment, as in the case of premature infants, with simultaneously impaired feeding and respiration because of immaturity of the respiratory and neurological systems (Reynolds et al., 2017; Shaker, 2018). At the other end of the developmental continuum, with typical perinatal development of respiratory and neurological systems of healthy full-term newborns, neither system is impaired (Shaker, 2018). This model reflects the span of development of neurological substrates of respiration. Infants who are born prematurely have less-developed central and autonomic nervous systems, as well as less-developed lungs (Goldfield et al., 1999) than are necessary for breathing and feeding functions, while full-term infants' systems are sufficiently developed in the majority of cases.

The other model, the Withdrawal Disorganization Model, posits that withdrawal-related changes in neurotransmitters result in neurological disorganization (Kocherlakota, 2014) that affects coordination of suck-swallow-breathe during the infant's earliest experiences of feeding. Specifically, the withdrawal pathway involving abnormal increases and decreases in norepinephrine, acetylcholine, dopamine, and corticotrophin, among other neurotransmitters, results in the signs and symptomology associated with NAS. This model posits that such disorganization at the neurological and oro-respiratory level is a consequence of withdrawal, rather than delayed development as a result of exposure. In this model, feeding and respiratory difficulties can occur independently of one another as disorganization is the driving pathology, not generalized delay. However, because of the synergistic relationship of suck-swallow-breathe coordination, feeding problems (SFD and FC) are more likely when respiratory difficulties are present.

Developmental Model. In infants who are premature, the coordination of suck-swallow-breathe is compromised because of immature development of the lungs, the neurological system that governs oro-pharyngeal movement, coordination, and organization (DaCosta et al., 2008; Delaney & Arvedson, 2008; Shaker, 2018). According to Stumm et al. (2008), approximately 69% of preterm infants experience a comorbidity of feeding and respiratory difficulties, though this study included a relatively small sample size of 55 infants. If exposure to opioids prenatally slowed down development of these same systems, comparable comorbidity would be expected in infants with NAS. However, that was not the case; nor was it the case that these infants behaved like full-term typical infants. In general, infants with NAS showed a clear relationship between respiratory and feeding status, but with critical deviations from the developmental model of feeding and respiratory impairment.

Withdrawal Disorganization Model. The deviation from the feeding trends seen in premature and full-term healthy infants seems indicative of a model based on withdrawal disorganization (Kocherlakota, 2014), characterized by incongruities between feeding and respiratory status. A sizable segment of infants with NAS had feeding difficulties (33.59%) but did not have respiratory difficulties. Furthermore, 11.07% had respiratory difficulties but did not have feeding difficulties. This pattern suggests a clear deviation from the Developmental Model.

At the same time, the results do not suggest that respiratory and feeding difficulties are entirely unlinked in infants with NAS, nor is it reasonable to think that they would be given the synergistic relationship of suck-swallow-breath (Reynolds et al., 2017). Infants with NAS and

RD were significantly more likely to develop SFD (25.57.%) than FC (10.31%). This finding suggests that for infants with NAS, respiratory status may be predictive of the severity of feeding difficulty.

For infants with NAS, feeding and respiratory behaviors are not completely linked. However, comorbidity of NAS and respiratory impairment is more predictive of severe levels of feeding difficulty.

Clinical implications. The second question of this study examined the clinical consequences of respiratory and feeding difficulties as measured by length stay and cost. Regarding length of stay, there is a statistically significant difference between the NAS and FT groups. Infants with NAS stayed an average of 15.18 days, while infants FTNO stayed an average of 2.05 days. As expected, a comorbidity of RD and SFD yielded the highest average length of stay (23.90 days), while a combination of TR and TF yielded the lowest average length of stay (2.91 days). At the same time, a clear pattern emerged for comorbidities of RD, TR, FC, and SFD. When a typical status was present in a comorbid group, the more severe feeding status resulted in longer lengths of stay than respiratory factors. For example, the RD/FC (16.41 days) and TR/SFD (16.17 days) groups had longer lengths of stay than the RD/TF (10.35 days) and TF/FC (11.17 days) groups. Furthermore, there was a greater degree of variability as represented by the standard deviation for groups with a typical feeding or respiratory status.

Similarly, there is a statistically significant difference between NAS and FT groups for total cost. Infants with NAS presented with a total average cost of $40,881.61, while infants FTNO presented with an average total cost of $3,627.76. As expected, a comorbidity of RD and SFD yielded the highest average cost ($73,291.28), while a combination of TR and TF yielded the lowest average total cost ($5,747.15). At the same time, a clear pattern emerged for comorbidities of RD, TR, FC, and SFD that followed the trends described for length of stay.

When a typical status was present in a comorbid group, the more severe feeding status resulted in higher total cost than respiratory factors. For example, the RD/FC ($43,277.19) and TR/SFD ($42,786.70) groups had higher costs than the RD/TF ($28,096.30) and TF/FC ($22,951.18) groups. As with length of stay, there was a greater degree of variability in the standard deviation for groups with a typical feeding or respiratory status.

In considering further clinical implications, an essential point concerns when intervention should begin for infants at risk of longer lengths of stay and higher costs. Interprofessional protocols should be developed for feeding infants with NAS in general (Masten et al., 2019). For any infant with NAS, signs of respiratory distress should mark an automatic referral to the professionals in the NICU who have primary responsibility for feeding (e.g., speech-language pathologist, occupational therapist, lactation consultants) services. Such a referral policy would be a calculated and efficient use of resources, as the results of this study show.

As part of the speech-language pathologist's role in this interprofessional team of nurses, lactation consultants, dieticians, physical therapists, respiratory therapists and pediatricians (Masten et al., 2019), the SLP can contribute to the incorporation of these prognostic respiratory indicators into the care of infants with NAS in the NICU. Speech-language pathologists serve as the experts in the NICU regarding safe and efficient swallowing (Masten et al., 2019), and this role depends on cohesive team action for all the various respiratory, dietary, and feeding concerns managed by other professionals on the NICU team. In considering another respiratory deficit for infants in the NICU as an example, Casey et al. (2016) detail the progressive incorporation of bubble continuous positive airway pressure (CPaP) into care for premature infants (defined as <32 weeks gestation in study) as an evidence-based approach for interprofessional teams to treat Respiratory Distress Syndrome secondary to prematurity. The study recommends a program of regular and focused assessments of CPaP use, frequent sizing for proper fitting, and interprofessional training and practice for positioning of neonates. This program was managed by respiratory therapists and pediatricians, and it helped to promote the improved short- and long-term outcomes of these neonates (Casey et al., 2016). Although the respiratory concerns differ, the model of interprofessional practice and therapeutic management is relevant in consideration of the findings of this study. While this study shows that feeding impairment plays a greater role in long-term measures of health, such as length of stay and total cost, respiratory status is a red flag for more severe outcomes. SLPs can work within the interprofessional framework to improve outcomes for infants with NAS (Masten et al., 2019).

Respiratory indicators also offer information on directions for treatment. As respiration factors into feeding as a result of disorganization both of neurological messaging and interposition in the suck-swallow-breathe reflex (Gewolb et al., 2004), treatment should directly address this disorganization through responsive and protective measures. In addition, SLPs should work hand-in-hand with their partners in feeding and respiratory coordination (i.e., respiratory therapists, nurses, and lactation consultants) to introduce respiratory and behavioral supports for improved breathing and coordination.

It is clear from the literature with premature infants that feeding intervention is effective at ameliorating the difficulties that infants face in the first days of life (Howe et al., 2007; Shaker, 2018). Studies that discuss the benefits of the cue-based feeding approach, show a decreased length of stay and improvements in weight gain, without any negative outcomes (McCormick et al., 2010). For example, McCain et al. (2001) compared cue-based and volume-driven approaches for preterm infants and found that cue-based feeding shortened time to oral feeds by five days.

Furthermore, cue-based feeding places infants at a lower risk for reinforcement of inefficient habits and inhibition of feeding skill progression, along with long-term developmental difficulties, at least in comparison to volume-based approaches (Ross & Philibin, 2011). While cue-based feeding may not be the most appropriate intervention given this study's findings that infants with NAS do not demonstrate the same etiological pattern of immaturity, there is no evidence that a volume-based approach would be more effective. Cue-based feeding addresses the coordination of the suck-swallow-breathe reflex (Shaker, 2018), which is disorganized in the NAS population, and represents the best evidence-based approach available.

Constraints. This study is the first step in a needed research direction for this population; as such, the focus of this study on that population and relevant research questions was narrow by necessity. As such, this study only includes FTNO and NAS infants and does not include infants with a history of prematurity and no exposure. This limits the full examination of the Developmental Model of swallowing as preterm infants were considered on a theoretical basis only, albeit a well-established theoretical basis, for the purposes of this study.

Restrictions for this study also include: a lack of more comprehensive respiratory, feeding and nutrition measurements for infants with NAS, specifically in terms of reliable daily respiratory and weight measures as well as at birth and discharge. In the same way, this study lacks continuous data for respiration and feeding; as such, this study primarily uses descriptive and nonparametric analysis.

This study did not include information relating to maternal marital status or the involvement of the father, which can be helpful in more fully establishing SES for infants.

The infants included in this population were all born in central Appalachia, but NAS is prevalent across the United States. As such, this study is specific to its region of origin, and generalization should be qualified accordingly.

Finally, this study at times includes relatively small sample sizes for subgroups used in analysis, e.g., comorbid groups (RD/FC, RD/TF, and TR/SFD) with less than 50 infants, based on rates of prevalence in the collected sample. These subgroup sizes should factor into any consideration of this study.

Future directions. This study is a retrospective chart review; in the future, a prospective study may be an excellent way to further study this information and control for all relevant variables. A prospective study could expand on the current research, and it might include Finnegan and non-Finnegan indicators after diagnosis is made in order to track the feeding- and respiration-specific markers' progress over the length of stay. An interesting question concerns the differences in the presentation of disorder (swallowing and breathing in the presence of tachypnea) at resolution and just before discharge; such descriptive information would be invaluable to SLPs working in NICUs. In addition, a future study may compare the patterns of recovery for infants with RD and either FC or SFD.

Such a future study may also determine the relative benefits of feeding modality, either by bottle or breastfeeding, in outcomes, as well as the effects of other relevant factors on length of stay and cost. Also, the current study characterizes the Finnegan marker for nasal stuffiness as a respiratory prognosticator; however, it may also be reasonably characterized as an indicator of feeding, and future studies may investigate the relative differences in grouping and results.

Furthermore, this study investigates the effects of opioid-related NAS in the central Appalachian region. However, opioids do not represent the only drug associated with NAS, and rates of methamphetamine abuse are on the rise. As methamphetamine affects neurotransmitter interactions in a different manner than opioids, such an investigation would further study NAS behavior on a substance-based level. An examination of the differences, if any, between groups on the basis of drug exposure may yield information related to withdrawal-related symptoms (i.e., the effects of withdrawal on feeding and respiration) and drug type.

Pertaining to the Developmental model, more research is needed to establish the actual and relative maturity of the physiological subsystems related to feeding and respiration beyond their respective effects (i.e., effective breathing and nutrition) for infants with NAS.

Finally, it is clear from the research that the cue-based feeding model is effective for premature infants (Shaker, 2018). However, there are no randomized nor controlled trials of this feeding approach in comparison to a volume-based approach specifically for infants with NAS. As infants with NAS present with a distinct etiology, future research into the efficacy of this approach for the NAS population would not only be appropriate but also essential to actual practice in NICUs.

Conclusion. In this study, infants with NAS differed dramatically from infants FTNO in likelihood of feeding and respiratory impairment. In comparison to premature infants and the established Developmental Model of coordinated swallow function, respiratory and feeding difficulties can occur in isolation for infants with NAS. This is suggestive of a different etiological model: the Withdrawal Disorganization Model. Furthermore, respiratory difficulty generally leads to more severe feeding difficulty in this population, while feeding severity remains of vital importance as an indicator of hospital stay outcomes. As the professionals in the NICU responsible for safe and efficient feeding and swallowing, speech-language pathologists are positioned to use these prognostic respiratory indicators to improve outcomes for infants with NAS.

This study is unique in its size, scope, and focus on the interactions between respiratory and feeding for the NAS population over the course of NICU stay in hospitals across eastern Tennessee. There were 769 cases of NAS in Tennessee in 2019 (Tennessee Department of Health, 2019). In more immediate terms, every 15 minutes an infant with NAS is born in the USA, approximately the time it takes to read this discussion (National Institute on Drug Abuse, 2019). The incidence of NAS rose precipitously over the past decade in correspondence with the growing opioid crisis, and it is likely rates will only continue to grow. It is vital that research continue in order to better care for the thousands of infants born of the public health emergency of our time.

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