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Assessing Abstinence in Infants Greater Than 28 Days Old

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Assessing Abstinence in Infants Greater Than 28 Days Old

by

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DEDICATON

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LIST OF ABBREVIATIONS

Abbreviation:	Explanation:
AAP	American Academy of Pediatrics
AIC	Akaike Information Criterion
AR	Auto Regressive Model
ATVV	Auditory, Tactile, Visual, and Vestibular Rocking Stimulation
Bayley III	Bayley Scales of Infant and Toddler Development-Third Edition
BIC	Bayesian Information Criterion
BM	Bowel Movement
CINAHL Plus	Cumulative Index for Nursing and Allied Health Literature Plus
CNS	Central Nervous System
Df or DF	Degrees of Freedom
DOL	Day of Life
DV	Dependent Variable
EFA	Exploratory Factor Analysis
EMR	Electronic Medical Record
ESC	Eat, Sleep, Console
FDOH	Florida Department of Health
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus

IRB	Institutional Review Board
IT	Information Technology
IV	Independent Variable
JHACH	Johns Hopkins All Children's Hospital
KMO	Kaiser-Meyer-Olkin Measure of Sampling Adequacy
MAiN	Managing Abstinence in Newborns
MEDLINE	Medline Literature Analysis and Retrieval System Online
Modified-FNAST or M-FNAST	Modified-Finnegan Neonatal Abstinence Syndrome Scale Tool
MOTHER	Maternal Opioid Treatment: Human Experimental Research – (Study)
MOTHER NAS Scale	The Mother Opioid Treatment Experimental Research NAS Scale
MVA	Motor Vehicle Accident
NAS	Neonatal Abstinence Syndrome
NICU	Neonatal Intensive Care Unit
NIDA	National Institute on Drug Abuse
NNNS	NICU Network Neurobehavioral Scale
NWI	Neonatal Withdrawal Inventory
NWS	Neonatal Withdrawal Syndrome
PCA	Principal Components Analysis
PI	Principal Investigator
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SAMSHA	Substance Abuse and Mental Health Services Administration
SD	Standard Deviation
sFNAS	The Simplified Finnegan Neonatal Abstinence Scoring System

US	United States
USF	University of South Florida

ABSTRACT

There are currently no published scoring instruments with prior empirical evidence to support the validity and reliability of the accuracy of the drug withdrawal scores generated in infants greater than 28 days of life with a diagnosis of Neonatal Abstinence Syndrome (NAS). This study was done to identify the signs of withdrawal in infants greater than 28 days of life with NAS and determine if further adaptation of the modified-FNAST was necessary to accurately measure the severity of drug withdrawal in this sub population of infants. This aim could not analyzed due to limitations of the data.

The study was also done to describe the relationship between the medications used to treat the infant NAS and the longitudinal trajectory of the Finnegan scores. The results of the study revealed that the total modified-FNAST scores ranged from 0-21 on day 1 of life with a mean of 8.68 and a SD (4.127), and then gradually decreased with less variability over the length of the hospitalization until discharge. Four medications were used to treat the infants for NAS. The medications used to treat the infants for NAS included morphine (99%), phenobarbital (66.2%), clonidine (25.1%), and buprenorphine (1.9%). The minimum to maximum dosage and minimum to maximum duration of inpatient treatment days for each of the medications were explored and revealed, morphine (dosage range, 0.33-2.170 mg/kg/day and duration of 14-81 days), buprenorphine (dosage range 7.00-61.30 mcg/kg/day and duration of 4.00-30.00 days), clonidine (dosage range 3.97-28.93 mcg/kg/day and duration of 16.00-87.00 days), and phenobarbital (dosage range 3.00-16.00 mg/kg/day and duration of 2.00-84.00 days). Most of the infants received morphine alone or in combination with phenobarbital or clonidine consistent with the

established evidence-based NAS weaning protocol. The Mixed Effects Model Analysis revealed that there was an overall decrease in the total Finnegan scores over time ($p < 0.0001$). The mean total Finnegan scores showed a statistically significant difference in the groups treated with and without clonidine ($p = 0.0031$). The group treated with clonidine had higher mean total Finnegan scores. The infants treated with phenobarbital did not show a significant association with the total Finnegan scores ($p = 0.6852$). In addition, all other control variables failed to show significant associations with the repeated measures of total Finnegan scores including: gender ($p = 0.6257$), infant birth weight ($p = 0.9375$), gestational age ($p = 0.8444$) and the estimated number of cigarettes smoked by the mother during the pregnancy ($p = 0.7300$). The interaction between the infants treated with clonidine and phenobarbital were not statistical significant either. ($p = 0.6412$).

Key Words: Neonatal Abstinence Syndrome, opioid, modified-FNAST, reliable, valid, factor analysis

CHAPTER ONE:

BACKGROUND

Opioid Dependence during Pregnancy/Neonatal Abstinence Syndrome

Opioid dependence during pregnancy poses a serious health risk for the mother and her unborn child and places a significant social and economic burden on the United States. According to a recent national study, illicit drug use is estimated to be 14.6 % of teenage pregnant woman (15-17 years of age), 8.6% in pregnant women 18-25 years of age, and 3.2% among pregnant women 26-44 years of age (SAMHSA, 2014). These statistics cause more concern given that 55 to 94 % of infants born to drug dependent pregnant women will experience some form of withdrawal post-delivery following the abrupt cessation of the continuous supply of opioids that they have been exposed to over the duration of the pregnancy (Hudak & Tan, 2012). The increase in illicit drug use among pregnant women has led to a national epidemic of infants born with Neonatal Abstinence Syndrome (NAS). Neonatal abstinence syndrome (NAS) is the diagnosis used to describe the typical pattern of drug withdrawal seen in infants born to opioid-dependent mothers (Hudak & Tan, 2012; Kocherlakota, 2014). The incidence of NAS nationally has increased from 3.4 to 5.8 per 1000 infants born in the United States (Patrick, Davis, Lehman, & Cooper, 2015). This represents almost a five-fold increase from 2000 (Patrick et al., 2015). Recent local statistics released from the Florida Department of Health (FDOH) suggest an even more alarming 10-fold rate of rise in the number of infants discharged with the diagnosis of NAS between 1995 and 2014 (FDOH, 2014). Due to the risks associated with acute

drug withdrawal, which may include seizures, many infants with NAS require hospitalization within the Neonatal Intensive Care Unit (NICU) (Patrick et al., 2015). The average hospital length of stay for infants requiring treatment for NAS was estimated to be 25 days (Backes, et al., 2012) and more recently, 23 days (Patrick et al., 2015), but there is variability based on the pharmacological management and weaning practices of the institution (Zimmermann-Baer, Notzli, Rentsch, & Bucher, 2010). Medicaid was reported as the primary payer for the majority of costs associated with the care of this population of infants (estimated at approximately 82%) (Patrick et al., 2015; Winkelman, Villapiano, Kozhimannil, Davis, & Patrick, 2018). Total Medicaid covered costs increased from $65.4 million to $462 million in 2014 for NAS births, after adjusting for inflation (Winkelman, et al., 2018).

The Finnegan Abstinence Scale

The Finnegan scale was first developed over 40 years ago to quantify the severity of drug withdrawal in newborn infants with NAS (Finnegan, Connaughton, Kron, & Emich, 1975). Thirty-seven term and near term infants born to drug dependent mothers in Philadelphia were assessed using the Finnegan scale (Finnegan et al., 1975). The original Finnegan scale included 20 specific symptoms common to infants experiencing acute drug withdrawal (Finnegan et al., 1975). Evidence to support the face, content, and construct validity of the instrument was established based on the opinion of a panel of national experts. Psychometric testing (using test-retest) was also done to provide evidence to support the reliability of the instrument (Finnegan et al., 1975). Finnegan scores were obtained on all the infants every hour for the first 24 hours, then every 2 hours for the next 24 hours, and then every 4 hours until discharge. The nurses who participated in the study were trained to use the instrument and had achieved 90% reliability to assess affected infants using scoring instrument (Finnegan et al., 1975). Infants experiencing

drug withdrawal with score ranges up to 7 were provided with non-pharmacological measures and routine neonatal care (Finnegan et al., 1975). Infants with more severe drug withdrawal, with score values of 8 or greater were determined to be pathological, requiring treatment with phenobarbital or paregoric (Finnegan et al., 1975). Finnegan et al. (1975) suggested that the instrument was superior over subjective clinical assessment of withdrawal, which they described as the standard of care at that time. The investigators also reported that there was a reduction in the length of required treatment among the infants scored with the Finnegan scale (Finnegan et al., 1975). However, on balance, the instrument is lengthy and scoring is complicated by 7 items that list more than one value (including 4 that require discernment between excessive/continuous crying, hyperactive/markedly hyperactive Moro reflex, and mild/moderate to severe tremors) (Finnegan et al., 1975). The individual item scores range from 1 to 5, and total scores for the original version ranged from 0 to 46 (Finnegan et al., 1975).

The Modified Finnegan Abstinence Scoring System

The Finnegan scoring system was later modified to reduce and eliminate items that were found to be redundant or obsolete (Finnegan et al., 1975; Finnegan & Kaltenbach, 1992). Modification of the Finnegan Neonatal Abstinence Scoring Tool (FNAST) streamlined the clinical efficiency without compromising the validity of inferences about the higher order constructs in a population of infants experiencing acute drug withdrawal (Finnegan, 1990; Finnegan et al., 1975; Finnegan & Kaltenbach, 1992). Excoriation of the nose, knees, and toes (one point each) were reduced to “skin excoriation” (for one point only) after the “Back to Sleep” campaign reduced the incidence of infants presenting with the prior pattern of skin excoriation (Maguire, Cline, Parnell, & Tai, 2013; Finnegan, 1990; Finnegan & Kaltenbach, 1992). The modified-FNAST scoring system is considered the gold standard and continues to be

the most widely used measurement instrument to assess the severity of drug withdrawal in neonates born to drug dependent mothers in the United States (Hudak & Tan, 2012). The 21-item modified-FNAST assigns a numeric rating for observed infant withdrawal signs based on the level of severity in each of the four main physiologic categories (autonomic, gastro-intestinal, respiratory, and central nervous systems) (Finnegan, 1990; Finnegan & Kaltenbach, 1992). The range of possible scores that can be obtained using the modified-FNAST are a minimum 0, to a maximum of 37 (Finnegan, 1990; Finnegan & Kaltenbach, 1992). Additional psychometric testing of the modified-FNAST has been done since its original publication, which includes a factor analysis which was performed in infants with NAS who were less than or equal to 28 days of life (Maguire, Cline, Parnell, & Tai, 2013), and the instrument was tested in like (Finnegan et al., 1975) and divergent populations (Sarkar & Donn, 2006; Zimmermann-Baer, Notzli, Rentsch, & Bucher, 2010). This provides further evidence of the validity of inferences about the higher order constructs of the modified-FNAST in a population of infants less than or equal to 28 days of life with NAS (Shadish, Cook, & Campbell, 2002). Jones et al. (2016) demonstrated poor internal consistency of the instrument with Cronbach's alphas failing to exceed 0.62 at first administration, peak NAS score, and NAS treatment initiation. Finally, Gomez-Pomar et al. (2017) noted minimal influences of extraneous factors (daily census, time of day, day of the week) on observed scores further supporting the clinical utility of the instrument in the assessment and management of infants with NAS.

Other Published Neonatal Abstinence Scoring Instruments

In addition to the modified-FNAST, multiple other scoring instruments have been developed to measure the severity of drug withdrawal infants born to drug dependent mothers (Orlando, 2014). Six of the instruments provide a score level indicating when the infant has

reached a pathologic range requiring pharmacological management (Finnegan et al., 1975; Green, & Suffet, 1981; Lester, Tronick, & Brazelton, 2004; Lipitz, & Blatman, 1974; Jones, Kaltenbach, Hei, et al., 2010; Zahorodny, Rom, Whitney, et al., 1998). Four of the instruments were developed to rapidly assess drug withdrawal in infants (Chasnoff, & Burns, 1984; Jones, Harrow, O'Grady, Crocetti, Jansson, & Kaltenbach, 2010; Maguire, Cline, Parnell, & Tai, 2013; O'Brian, Hunt, & Jeffery, 2004). The advantages and disadvantages of the abstinence scoring instruments vary, and none of them have been tested in older age infants (greater than 28 days of life). According to Orlando (2014), existing instruments for assessment of drug withdrawal in infants (0-28 days of life) include the following:

(1) Neonatal Drug Withdrawal Scoring System (Lipitz, & Blatman, 1974; Lipsitz, 1975)

(2) Neonatal Narcotic Withdrawal Index (Green, & Suffet, 1981)

(3) The Moro Scale Score (Chasnoff, & Burns, 1984)

(4) Neonatal Withdrawal Inventory (Zahorodny, Rom, Whitney, et al., 1998).

(5) Measurement of Movement (O'Brian, Hunt, & Jeffery, 2004)

(6) Neonatal Network Neurobehavioral Scale Part II: Stress/Abstinence Scale (Lester, Tronick, & Brazelton, 2004)

(7) The Mother Opioid Treatment Experimental Research NAS Scale (MOTHER NAS Scale) (Jones, Kaltenbach, Hei, et al., 2010)

(8) Three-Sign Screening Index (Jones, Harrow, O'Grady, Crocetti, Jansson, & Kaltenbach, 2010)

(9) Finnegan Neonatal Abstinence Scale-Short Form (Maguire, Cline, Parnell, & Tai, 2013)

The Neonatal Drug Withdrawal Scoring System has a total of 11 items, 7 of the items (skin abrasions, respirations, tremors, irritability, reflexes, muscle tone, and stools,) are scored on

a scale of 0-3. The remaining 4 items (vomiting, sneezing, repetitive yawning, and fever) are assigned a score of 1 if present and 0 when absent. A score of 10 or greater, according to the authors, indicates the need for pharmacological treatment of the infant (Lipitz, & Blatman, 1974).

The Neonatal Narcotic Withdrawal Index was developed to simplify the assessment of narcotic withdrawal severity and was published complete with item definitions to promote interrater reliability (Green, & Suffet, 1981). The instrument includes 7 items: crying, tremors, muscle tone, respiratory rate, axillary temperature, vomiting, and other signs. Items are assigned a point value of 0-2, higher scores indicate greater severity of withdrawal symptoms (Green, & Suffet, 1981). The *other signs* category is scored for the presence of any of the following: sneezing, diarrhea, sweat, skin abrasions, generalized seizures, localized seizures, poor suck, salivation, yawning, stuffy nose, hiccoughs, and weight loss observed in the preceding 24 hours (Green, & Suffet, 1981). Infants are assigned a maximum item score of 2 in the *other signs* category when they are noted to have 5 or more of the operationally defined signs (Green, & Suffet, 1981). Pharmacological management is indicated by a cumulative score of 5 or greater on at least 2 evaluations within a 24-hour period (Green, & Suffet, 1981). According to the authors, a score of 3 or less by 24 to 36 hours suggests adequate treatment and weaning is recommended when scores drop to 3 or less for 48 to 72 hours (Green, & Suffet, 1981).

The Moro Scale Score was designed to provide a method of following the process of drug withdrawal in term infants over the first year of life, and to identify infants at risk for developmental delay (Chasnoff, & Burns, 1984). The instrument provides a means for assessing central nervous system (CNS) irritability over time, but is not recommended to be used as a basis to make pharmacological treatment decisions in the acute phase of drug withdrawal. The Moro

reflex which is present at birth is expected to gradually disappear by 3-4 months in healthy newborns. However, this reflex persists in opioid infants (Finnegan, et al., 1975). The intensity of all six movements that comprise the Moro response are examined using this instrument (Chasnoff, & Burns, 1984). The six movements evaluated include abduction at the shoulder, adduction at the shoulder, extension at the elbow, tremors, and the threshold that triggered a Moro response (Chasnoff, & Burns, 1984). Each of the items are scored 0-3, total scores range between 0-20 (Chasnoff, & Burns, 1984). The authors provide no definitions for the individual items, but the procedure for eliciting the Moro response is described (Chasnoff, & Burns, 1984).

Neonatal Withdrawal Inventory (NWI) is a 7 item rapid clinical assessment instrument designed to assess CNS, gastrointestinal, autonomic, and behavioral signs of withdrawal in drug exposed newborns (Zahorodny, et al., 1998). The signs include hyperactive Moro reflex, hypertonicity, tremor, sweating and mottling, recurrent yawning and sneezing, regurgitation and diarrhea, and behavioral distress (Zahorodny, et al., 1998). The NWI items are scored from 1 to 4 with higher values assigned to items with greater clinical importance (Zahorodny, et al., 1998). The possible score range for the NWI is from 0 to19, with a score of 8 or greater considered to be pathological requiring treatment (Zahorodny, et al., 1998). Interrater reliability for the NWI has been shown to be high mean reliability coefficient documented at 0.93 between 4 trained observes who completed 30 assessments (Zahorodny, et al., 1998).

Measurement of movement using an actigraph was studied by O'Brian, Hunt, and Jeffery (2004) to assess the degree of hyperactivity as a measure of severity of drug withdrawal in infants with NAS. The actigraph device was strapped to the infant's wrist or leg to detect and record movements (O'Brian, Hunt, & Jeffery, 2004). Measurements of hyperactivity obtained from the actigraph device are continuously compared with serial assessment performed by a

trained observer (O'Brian, Hunt, & Jeffery, 2004). Computer software developed for use with the device are required to analyze the activity log (O'Brian, Hunt, & Jeffery, 2004). The investigators compared the movement of NAS infants experiencing acute drug withdrawal to healthy term infants (O'Brian, Hunt, & Jeffery, 2004). The results of the actigraph recordings were compared with scores obtained from traditional scoring systems (O'Brian, Hunt, & Jeffery, 2004). The actigraph activity score calculated from analysis of motion identified those infants who required treatment on the basis of their traditional assessment score with high sensitivity and specificity (O'Brian, Hunt, & Jeffery, 2004). The costs associated with the purchase of an actigraph and required software for analysis were not reported. At this stage of testing, actigraph may have potential for screening infants for NAS however, further research is needed before the device can be used for clinical monitoring of infants with NAS (Orlando, 2014).

The NICU Network Neurobehavioral Scale (NNNS) is a comprehensive 115 item scale designed to examine maternal lifestyle and newborn outcomes following drug exposure prenatally (Lester, Tronick, & Brazelton, 2004). The stress/abstinence sub scale is a part of this comprehensive instrument which was developed for use in a multicenter research study (Lester, Tronick, & Brazelton, 2004). The stress/abstinence scale is divided into 7 sections including physiologic, autonomic, CNS, visual, skeletal, gastrointestinal, and state (Lester, Tronick, & Brazelton, 2004). There are no numeric scores assigned (Lester, Tronick, & Brazelton, 2004). Infants are given a yes if the item is present and no if it is absent (Lester, Tronick, & Brazelton, 2004). The authors suggest the instrument is appropriate for premature infants 30 weeks gestational age or greater and less than 48 weeks post corrected age (Lester, Tronick, & Brazelton, 2004). The NNNS Stress/Abstinence Scale is recommended to be used screen at risk infants for abnormal behaviors (Lester, Tronick, & Brazelton, 2004). Drug exposed infants who

screen positive may require additional evaluation with a comprehensive neonatal abstinence scoring system for the purpose of initiating pharmacological treatment and ongoing monitoring of the infant (Lester, Tronick, & Brazelton, 2004).

The Maternal Opioid Treatment: Human Experimental Research NAS Scale (MOTHER NAS Scale) was developed for use in a comprehensive treatment program for drug-dependent mothers and infants (Jansson, Valez, & Harrow, 2009). The instrument was first described as a modified version of the Finnegan Neonatal Abstinence Scoring System however, later publications referred to the instrument as the Maternal Opioid Treatment: Human Experimental Research NAS Scale (Jansson, Valez, & Harrow, 2009; Jones, Kaltenbach, Hei, et al., 2010). The instrument has 28 items, nineteen of the 28 items contribute to the total score and are used to determine when pharmacological treatment is indicated. The remaining 9 items are assessed as present or not but do not contribute to the total score (these items were assessed as part of the study protocol but were not used to determine the need for treatment) (Jones, Kaltenbach, Hei, et al., 2010). The scored items were given point values ranging from 1 to 3, except seizures which was given a point value of 8 (Jones, Kaltenbach, Hei, et al., 2010). The total score range is from 0 to 42 (Jones, Kaltenbach, Hei, et al., 2010).

Three-Sign Screening Index was developed as a rapid assessment screening instrument (Jones, et al., 2010). Three items from the modified Finnegan neonatal abstinence scoring instrument (the Maternal Opioid Treatment: Human Experimental Research NAS) were determined by the investigators to discriminate between opioid exposed and non-exposed infants (Jones et al., 2010). Hyperactive Moro reflex, mild tremors when undisturbed, and increased muscle tone were observed in the drug exposed group of infants and not in the non-exposed infants (Jones et al., 2010). The investigators proposed the 3-item index as a cost-effective

method of screening infants for opioid exposure when the infant has not been identified as high risk by maternal drug history (Jones et al., 2010). The instrument was not designed for use as assessment, monitoring, or weaning instrument. The Three-Sign Screening Index was meant to be used for screening potential at risk infants who need further evaluation using a more comprehensive assessment instrument (Jones et al., 2010).

The Finnegan Neonatal Abstinence Scale-Short Form was developed after factor analysis of more than 30,000 neonatal assessment scores to determine if the 21 item modified Finnegan scoring instrument could be reduced to the least number of items and still retain the reliability and validity of the instrument (Maguire, Cline, Parnell, & Tai, 2013). Factor analysis revealed a 2 factor solution which was labeled as early or mild signs, and moderate or progressing signs. The 7-item Finnegan Neonatal Abstinence Scale-Short Form included 3 mild signs (crying, sleep disturbances, and increased muscle tone), and 4 moderate or progressive signs (tremors, respiratory rate, sweating, and excessive sucking) (Maguire, et al., 2013). The instrument is scored using the same point values as the original instrument. Scores of 8 or greater are considered pathological and require treatment. The reduced number of items on the instrument may have significant advantages over existing instruments related to ease of use, and reduction in the necessary training time required to achieve inter-observer reliability (Maguire, et al., 2013). The short form may have utility for monitoring infants post discharge in the home or when followed up at the Pediatrician's office (Maguire, et al., 2013). The investigators caution that the short form may not be adequate to assess infants with rapidly escalating signs and symptoms of acute drug withdrawal, and therefore recommend that these infants be assessed with a more comprehensive instrument such as the 21-item modified-FNAST (Maguire, et al., 2013). The investigators also suggest that further testing is required before the Finnegan

Neonatal Abstinence Scale-Short Form can be recommended for widespread use (Maguire, et al., 2013).

More recently, two additional scoring instruments have emerged, the simplified Finnegan Neonatal Abstinence Scoring System (sFNAS) (Pomar, et al., 2017), and the Eat, Sleep, Console (ESC) (Grossman, Lipshaw, Osborn, & Berkwitt, 2018). Analysis of 40 294 observations using multiple statistical analyses (generalized estimating equations, linear regression, and correlation), and cross validation to simplify the Finnegan Neonatal Scoring System to 10 items. The sFNAS includes cry, tremors, increased muscle tone, sleep, nasal stuffiness, respiratory rate, excessive sucking, poor feeding, feeding intolerance, and stool assessments. Scores range from 0 - 23 with higher scores indicating more severe drug withdrawal. The authors recommend treating infants when scores are greater than 6 and 10 respectively (compared to two consecutive scores $\geq$8 or one score of 12, the cutoffs established for pharmacological management in the Finnegan Neonatal Scoring System). The scoring instrument demonstrated a high correlation (r = .914) with the Finnegan Neonatal Scoring System (Pomar, et al., 2017). Further empirical testing is needed to determine if the instrument has clinical utility, and establish the validity and reliability of the instrument (Pomar, et al., 2017).

The ESC is a neonatal drug abstinence scale developed to assess and treat only infants with NAS who are determined to be unable to perform essential functions characteristic of a healthy newborn (eat a minimum of at least 1 ounce per feeding or breastfeed, sleep $\geq$ to 1 hour, and be consoled within 10 minutes from a cry state) (Grossman, et al., 2018). The instrument was developed to assess the functional status of the infant and reduce the potential for over treatment of infant drug withdrawal based solely on the total infant withdrawal score. Infants with NAS who are eating, sleeping, and easily consoled are assessed to be stable. Infants with

NAS who are unable to maintain their functional status according to the established criteria are provided additional support with nonpharmacological treatment. If nonpharmacological treatment fail the infant was treated with an oral dose of morphine (0.05 mg/kg/dose) and then re-evaluated (Grossman, et al., 2018). A retrospective chart review was done to compare the treatment decisions of 50 infants with NAS who were clinically assessed using the ESC approach. The investigators reported that using the ESC criteria resulted in only 6 (12%) of the infants requiring treatment with morphine compared to 31 infants (62%) predicted to require treatment using the Finnegan Neonatal Abstinence Scoring System (which was statistically significant, $p < .001$). In addition, there were no adverse events or readmissions during the study period (Grossman, et al., 2018).

The modified F-NAST was developed to assess the severity of drug withdrawal in full term infants less than or equal to 28 days of life, however, the instrument is being used clinically on premature and infants greater than 28 days of life. The modified-FNAST has never been empirically tested for evidence of validity and reliability of the scores generated in NAS infants greater than 28 days or premature infants. Sleep wake cycles, one of the items assessed on the modified-FNAST, are known to change rapidly between the neonatal period and early infancy (Tarullo, Balsam, & Fifer, 2011). Newborn infants sleep at least 16-18 hours per day between feedings (Tarullo et al., 2011). As infants mature, the total sleeping time gradually decreases (Tarullo et al., 2011) and they begin to sleep longer at night (Hockenberry & Wilson, 2009), which has the potential to impact their modified-FNAST scores. Despite the lack of empirical evidence, the modified-FNAST is frequently used inappropriately in this sub-population of NAS infants because there are no instruments with empirical evidence to support the measurement of acute drug withdrawal for this group of infants. This poses a potential risk for these infants

because decisions regarding pharmacological management and discharge are frequently made based on the assessed modified-FNAST scores.

An exploratory factor analysis will be done to assess the degree to which the validity and reliability of the scores generated from the modified-FNAST can be extended to infants greater than 28 days of life. A series of factor analyses of the averaged modified-FNAST scores of NAS infants less than and greater than 28 days of life who are admitted to a 97 bed NICU between January 1, 2010-May 18, 2018 will be performed. The average modified-FNAST scores for the infants with NAS on day 1, 3, 7, and then weekly, and on the day of discharge from the NICU will be factor analyzed to determine the underlying dimensions to assess the similarities and differences over time. A factor analysis is a statistical approach used to establish empirical evidence of construct validity for a measurement instrument with sub scales. The approach is used to provide justification for the inclusion of the dimensions and their individual contribution to the accuracy of measuring the phenomena of interest in a specific population of patients (Waltz, Strictland, & Lenz, 2010). Given that the Finnegan includes all the common signs of drug withdrawal, the instrument should provide a good basis for performing a factor analysis. The factor analyses will be used to identify the signs that most accurately describe drug withdrawal in this population which may be different from infants less than 28 days of life. The identified signs of acute withdrawal can then be compared with what has been reported in the literature.

Statement of the Problem

There are currently no published scoring instruments with prior empirical evidence to support the validity and reliability of the accuracy of the drug withdrawal scores generated in infants greater than 28 days of life. This study was needed to identify the signs of withdrawal in

infants greater than 28 days of life with NAS, and determine if further adaptation of the modified-FNAST was needed to accurately measure the severity of drug withdrawal in this sub population of infants.

Statement of Significance and Innovation

The incidence of NAS has more than tripled over the past decade with approximately 3.4 out of every 1000 infants born in the United States diagnosed with this serious condition (Patrick et al., 2012). Most infants with NAS require hospitalization (NICU) for at least 5-7 days to monitor the infant for potential life threatening symptoms of acute drug withdrawal (Patrick et al., 2012). According to Patrick et al. (2012), Medicaid is the most frequent insurance provider for this population of infants, and the average cost for an infant diagnosed with NAS at discharge is $53 400 based on their 2009 data. The length of hospital stay for infants with NAS has been shown to be decreased as a result of the change in pharmacological management (treatment with buprenorphine as compared to methadone) (Noormohammadi et al., 2016), the implementation evidence-based practice weaning guidelines (Holmes et al., 2016; Murphy-Oikonen, Montlelpare, Bertoldo, Southon, & Persichino, 2012), rooming-in (Holmes et al., 2016), and the emergence of early discharge home weaning programs for eligible mother-infant dyads. Despite these advancements, there is still a sub population of NAS infants greater than 28 days of life who are potentially at greater risk because treatment decisions (weaning of opioid replacement and discharge) are based on modified-FNAST scores when there is no empirical evidence to support the scores in this group. The study is innovative because the design provides a cost effective and efficient method to discern the goodness of fit of the modified-FNAST in this previously unstudied population of high-risk NAS infants from an existing de-identified data source.

Purpose

The purpose of this study was to examine which items included in the modified-FNAST are observed in infants with NAS less than and greater than 28 days of life, explore how they are correlated with one another, and determine which items are most predictive of severity of drug withdrawal in infants greater than 28 days. The study explored the interrelationships among a set of variables in infants with NAS less than and greater than 28 days of age to determine the underlying structure in order to determine if there is a need for further customization of the modified-FNAST for use in infants greater than 28 days of life. In addition, the study described the relationship between the medications used to treat the infant NAS and the longitudinal trajectory of the Finnegan scores.

Hypothesis

The structure of the modified-FNAST (as determined by an exploratory factor analysis) in a sample of infants greater than 28 days of life diagnosed with NAS who are experiencing acute drug withdrawal will be different than prior research done in infants 0-28 days of life (see Figure 1. Logic Model, & Figure 2. Deconstruction of Logic Model below).

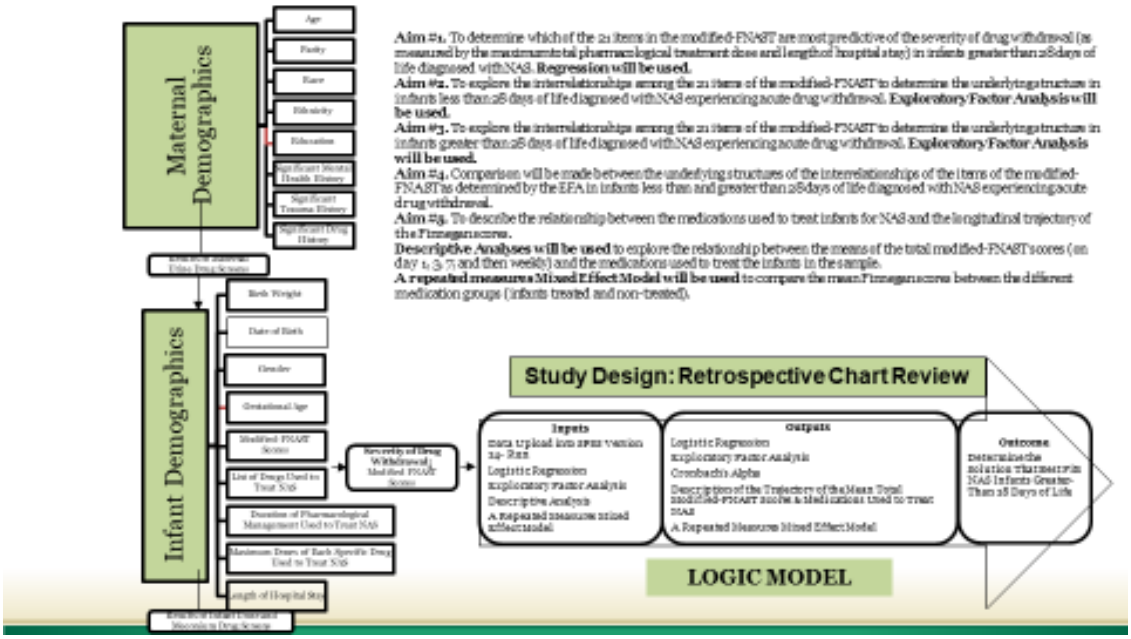

Figure 1. Logic Model

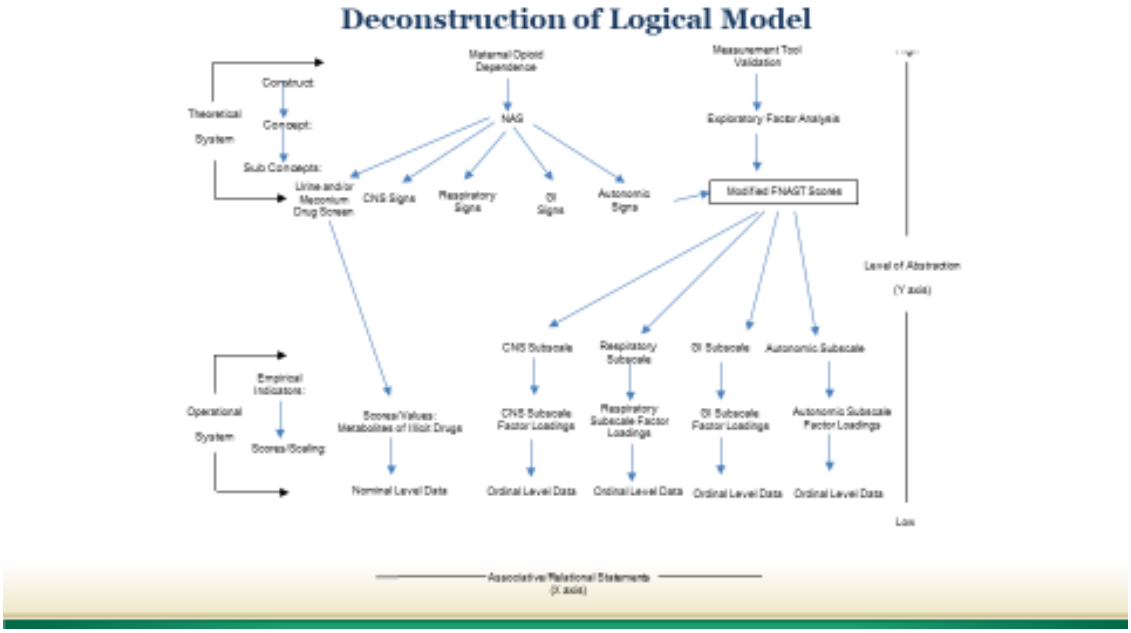

Figure 2. Deconstruction of the Logic Model

Study Aims

Aim #1. Determine which of the 21 items in the modified-FNAST are most predictive of the need for pharmacological treatment in infants greater than 28 days of life diagnosed with NAS.

Aim #2. Explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants less than 28 days of life diagnosed with NAS experiencing acute drug withdrawal.

Aim #3. Explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants greater than 28 days of life diagnosed with NAS experiencing acute drug withdrawal.

Aim #4. Compare the underlying structures of the interrelationships of the items of the modified-FNAST as determined by a series of exploratory factor analyses (EFA) in infants less than and greater than 28 days of life diagnosed with NAS experiencing acute drug withdrawal.

AIM #5. Describe the relationship between the medications used to treat the infants for NAS and the longitudinal trajectory of the Finnegan scores.

CHAPTER TWO:

LITERATURE REVIEW

The chapter includes an overview of the theoretical framework for this study, and a review of the literature relevant to the published screening and measurement instruments and the care and treatment of infants with NAS that informed the development of this study. The electronic databases of Cumulated Index of Nursing and Allied Health Literature Plus (CINAHL Plus) and Medical Literature Analysis and Retrieval System Online (MEDLINE) (via Pub Med) were searched to retrieve current relevant articles for inclusion in this review of the literature. The terms *neonatal abstinence syndrome, and care and treatment,* were used for the literature search. The search was limited to research articles published from 2010 to 2018, English language only, with a focus on the care and treatment of infants with NAS (nonpharmacological and pharmacological) and prior psychometric testing of the modified-FNAST. The article search retrieved a total of 124 potential abstracts from CINAHL Plus and a total of 274 from MEDLINE (via Pubmed). Twelve studies were added through other sources (n = 410). Duplicate abstracts (n = 80) were eliminated and 330 records were retained. Another 250 articles were removed after reviewing the abstracts (including non-research studies, or studies that were not relevant to the focus of this study). Eighty articles were then retained for eligibility. Each of the research articles were then read and those that provided relevant evidence related to the care and treatment of infants with NAS (nonpharmacological and pharmacological) and prior psychometric testing of the modified-FNAST were retained. A total of 34 research studies were included in the review of

the literature (see Figure 3. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram of Search Strategy (Care and Treatment of the Infant with NAS).

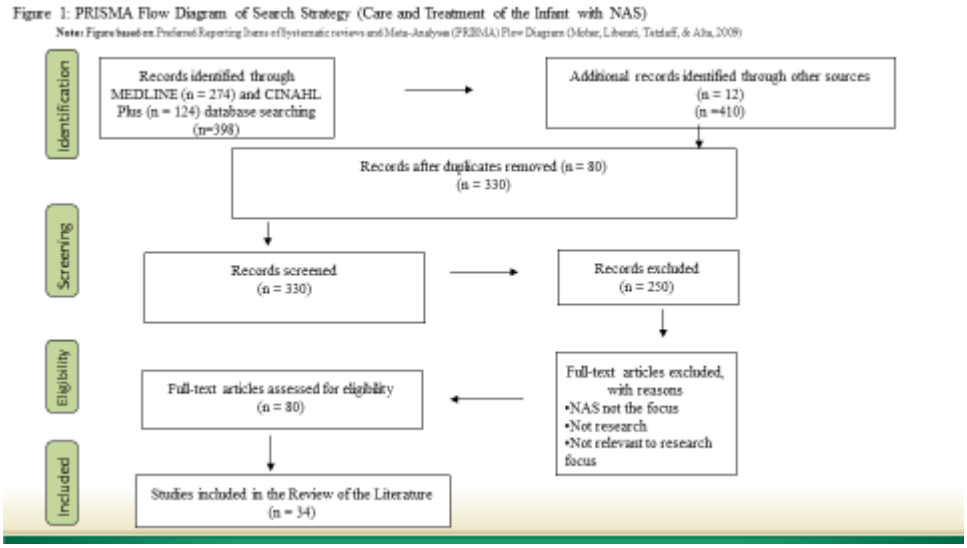

Figure 3. PRISMA Flow Diagram of the Search Strategy (Care and Treatment of the Infant with NAS)

The specific studies that provide empirical referents and related research on the care and treatment of NAS and prior psychometric testing of the modified-FNAST are detailed in Table 1. Synthesis Table (see Appendix A). The table provides an overview of rigor and quality of the evidence related to this concept. The supplemental table provides the author(s), year, title, purpose, target population, inclusion and exclusion criteria, sample size, response rate, design, statistical method, variables, instruments, interventions, selected findings, clinical significance, and limitations of the study.

The review of the literature related to the care and treatment of infants with NAS identified several important substanitive themes that provide further clarification of the term

NAS. The themes include definitions of NAS, screening and measurement instruments for infants at risk, pharmacological, and non-pharmacological interventions for infants with NAS.

Theoretical Framework: The Biological (Disease) Model of Addiction

According to the National Institute on Drug Abuse (NIDA) (2016), addiction is defined as, "a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences. It is considered a brain disease because drugs change the brain; they change its structure and how it works. These brain changes can be long lasting and can lead to many harmful, often self-destructive, behaviors" (NIDA, 2016, p, 1). The biological (disease) model of addiction will be used for the purpose of this proposed research study as the theoretical framework. The biological (disease) model Leshner (1997) is the most widely accepted theory on addiction and provides a basis to understand the complexity of addiction and recovery in the context of the opioid dependent mother and her infant with NAS (Leshner, 1997; NIDA, 2016).

According to this model opioid addiction begins with the initial experimentation with the drug. It is thought that the most susceptible females may experience the greatest pleasurable effects from the drug (Leshner, 1997). With continued use of the drug the girl or woman becomes physically dependent to the drug (NIDA, 2016). Physical dependence is defined as the need to consume the drug in order to avoid experiencing withdrawal symptoms (Leshner, 1997; NIDA, 2016). Addiction is considered a brain disease because with continued use there is down regulation of the dopaminergic receptors in the brain such that the women requires higher amounts of the drug to experience the same euphoric effects from the drug that she once experienced when she first began experimenting with the drug (Leshner, 1997; NIDA, 2016). In addition, the effects of the drug do not last as long. As a result, drug dependent women frequently keep increasing the amount of the drug chasing a high they may never achieve again

(Leshner, 1997; NIDA, 2016). The phenomena of dose escalation that is seen in addicts often leads to overdose and death especially for addicts who do not enter drug treatment (NIDA, 2016).

As the drug levels fall, the drug-dependent women experiences intense drug craving and increasing signs of acute drug withdrawal which leads to drug seeking behaviors despite increasing negative consequences (loss of job, family, home) (NIDA, 2016). Over time the drug dependent women without treatment becomes completely consumed with securing drugs to reduce drug craving and signs of acute drug withdrawal (NIDA, 2016). Consumed by the power of drug addiction, the drug dependent woman who is not in treatment may place herself in high risk environments, commit crimes in order to secure funding to purchase drugs (prostitution, shop lifting), neglect her own physical, mental, and dental health, and neglect or abuse their own children (NIDA, 2016).

Addiction is a chronic disease that is best treated using an evidence-based comprehensive treatment program (NIDA, 2016). NIDA (2012) outlines 13 principles to guide effective treatment programs. It is recommended that pregnant opioid dependent women receive treatment for at least 90 days to 1 year for it to be most effective (Casey, Makin, & Finigan, 2012). The women do not need to enter treatment voluntarily to benefit from treatment, therefore, opioid dependent women are frequently mandated into drug treatment by the drug courts (Casey, Makin, & Finigan, 2012). As part of a comprehensive drug treatment program, pregnant opioid dependent women are started on methadone or buprenorphine to prevent drug craving and acute drug withdrawal which can be life threating to the fetus (Hudak, & Tan, 2012). Pregnant women in drug treatment on opioid replacement therapy have been shown to have improved prenatal care, better weight gain, and perinatal outcomes that were superior compared to pregnant women

who continue to use illicit drugs (Hudak, & Tan, 2012). Infants who are born to pregnant women on opioid replacement therapy are at risk for developing NAS (Hudak, & Tan, 2012). Infants with NAS are not psychologically addicted, but they are physically dependent on the drug and will experience signs of drug withdrawal. Therefore, they need to be monitored and if they reach a pathological state of withdrawal they will be treated with pharmacological management and gradually weaned off the drug (Hudak, & Tan, 2012).

Definitions of NAS

NAS is not defined in the Merriam-Webster's Collegiate Dictionary (2014), however, the individual terms are defined. The adjective *neonatal* is defined as, "of, relating to, or affecting the newborn and especially the human infant during the first month after birth" (Merriam-Webster's Collegiate Dictonary, 2014, p. 831). The noun *abstinence* is defined as, "voluntary forbearance especially from indulgence of an appetite or craving or from eating some foods" (Merriam-Webster's Collegiate Dictionary, 2014, p. 5). Syndrome is defined as, "a group of signs and symptoms that occur together and characterize a particular abnormality or condition" (Merriam-Webster's Collegiate Dictionary, 2014, p. 1268). The Taber's Cyclopedic Medical Dictionary (2009) defines NAS as, "any of the adverse consequences in the newborn from exposure to addictive or dangerous intoxicants during fetal development" (Taber's Cyclopedic Medical Dictionary, 2009, p. 1588).

Congenital morphinism/congenital neonatal addiction. The first documented case of neonatal drug withdrawal in Western culture was reported in 1875 in Germany (Menninger-Lerchenthal, 1934), followed by reported cases in the United States in 1892 (Happel, 1892). The emerging understanding of the clinical presentation of the newborns with drug withdrawal termed *congenital morphinism* (Goodfriend, Shey, & Klein, 1956; Perlstein, 1947; Pettey, 1912).

Congenital Neonatal Addiction. Rosenthal, Patrick, and Krug (1964) later termed the condition *infant addiction* or *congenital neonatal addiction*. Finnegan et al. (1975) described NAS as a medical condition observed in infants experiencing opiate withdrawal and developed a scoring instrument to measure the severity of withdrawal. The Finnegan scale was originally developed to measure the severity of drug withdrawal in infants with NAS born to heroin dependent mothers (Finnegan et al., 1975). The Finnegan scoring system was later modified to remove items that were later noted to be repetitive or outdated without compromising the validity of inferences about the higher order constructs in a population of NAS infants (Finnegan, 1990; Finnegan et al., 1975; Finnegan & Kaltenbach, 1992). NAS was later defined as a constellation of drug withdrawal symptoms observed in infants born to opioid-dependent mothers following the abrupt termination of intrauterine exposure to opiates (Hudak & Tan, 2012).

The pattern of NAS may include central nervous system, respiratory system, gastrointestinal system, and autonomic system related signs (see Table 1) (Finnegan, et al., 1975; Hudak, & Tan, 2012).

Table 1. *Signs of Withdrawal Characteristic of NAS*

Central Nervous System	Respiratory System	Gastrointestinal System	Autonomic System
Increased muscle tone	Tachypnea	Excessive, uncoordinated sucking	Mottling
Tremors	Retractions	Poor feeding	Sweating
High-pitched cry		Vomiting	Sneezing
Apnea		Diarrhea	Yawning
Seizures			Nasal congestion

Neonatal Withdrawal Syndrome (NWS). NWS is a term that was first introduced in the healthcare literature to describe the range of neurological and behavioral symptoms observed in neonates born to mothers with a history of illicit drug use (Levy & Spino, 1993). Some authors suggest the terms NAS and NWS can be used interchangeblely to describe the physical

dependence of infants born to drug dependent mothers (Hekman, Grigorescu, Cameron, Miller, & Smith, 2013; Kocherlakota, 2014). Although opioids are the most common intrauterine drug exposure known to cause NAS, some definitions include multiple illicit drugs as possible causes of NAS (Roussos-Ross, Reisfield, Elliot, Dalton, & Gold, 2015). This broader view of the term is relevant given the fact that many drug dependent women are poly-drug users. The use or abuse of prescription and non-prescription drugs, opioids, and other psychoactive substances such as alcohol, benzodiazepines, cocaine, nicotine and selective serotonin reuptake inhibitors (SSRI) by pregnant women are therefore included in some broad definitions of NAS (McLemore, Lewis, Jones, & Gauda, 2013; Patrick et al., 2012; Roussos-Ross et al., 2015).

Neonatal Abstinence Syndrome. NAS is a consequence of in utero exposure to drugs from their drug-dependent mother. NAS is characterized by a constellation of withdrawal behaviors involving central nervous system (CNS) related signs (tremors, increased muscle tone, seizures and high-pitched cry), respiratory system related signs (tachypnea, and retractions), gastrointestinal system related signs (poor feeding, vomiting, diarrhea, and uncoordinated and excessive sucking), and autonomic system related signs (mottling, nasal stuffiness, excessive yawning, sneezing, and temperature) (Finnegan et al., 1975; Hudak & Tan, 2012).

Neonatal Opioid Withdrawal Syndrome (NOWS) is now being used more commonly to describe the specific clinical presentation and treatment of acute infant drug withdrawal from in utero exposure to opioids (Marcellus, 2018; Sutter, Leeman, & His, 2016). These infants are seen as a subpopulation of infants with NAS. Factors that may impact the severity of NOWS include the specific opioid of exposure, gestational age of the infant, maternal history of polydrug use, tobacco, the infant's own genetic predisposition for state regulation, rooming-in, and breastfeeding (Sutter, et al., 2016).

Expectant management for the opioid dependent pregnant women includes opioid maintenance therapy with methadone or buprenorphine (Noormohammadi et al., 2016; Women & American Society of Addiction, 2012). NAS associated with in utero buprenorphine exposure is less severe than exposure to methadone, suggesting that buprenorphine may be a more effective treatment option for the newborn provided the mother's addiction can be safely controlled (Hudak & Tan, 2012). Gaalema et al. (2012) described different clinical profiles between infants with NAS born to mothers dependent on methadone (undisturbed tremors and hyperactive Moro reflex) versus infants exposed to buprenorphine (nasal stuffiness, frequent sneezing, and loose stools) based on secondary analysis of data collected from the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study. The onset and severity of NAS is dependent on the primary substance the infant is withdrawing from, the combination of substances the infant was exposed to, and the gestational age of the infant.

A recent study revealed that premature infants were just as likely to be monitored for NAS but had lower modified-FNAST scores and were less likely to receive treatment than full term infants (Ruwanpathirana et al., 2015). The investigators questioned whether this was due to physiologic immaturity for less severe withdrawal. Cramton and Gruchala (2013) suggest premature infants have been shown to experience a milder form of NAS which is thought to be related to immaturity of the CNS, lower fat deposits of the drug, and lower amounts of total drug exposure. Maguire et al. (2016) caution that the premature infants may have a less robust response to drug withdrawal given their level of immaturity, and the current instruments may not be sensitive enough to accurately assess the severity of drug withdrawal in this population.

The short half-life of opiates is responsible for the rapid onset of the symptoms characteristic of NAS, which usually are noted within 72 hours after birth in infants born to

mothers who are opioid-dependent (Cramton & Gruchala, 2013). Methadone exposed newborns present with symptoms 2-6 days after birth, and sedative-hypnotics (benzodiazepines and barbiturates) exposed newborns in comparison may not manifest symptoms of NAS until a week or more after birth (Cramton & Gruchala, 2013). Gaalema et al. (2012) reported a significant difference between infants with NAS exposed to methadone who required treatment at 36 hours compared to infants with NAS exposed to buprenorphine who required treatment at 59 hours of age.

Polysubstance abuse (opioids and benzodiazepines in particular) have been shown to produce more severe symptoms of NAS when compared to exposure to a single substance (Cramton & Gruchala, 2013). The dose of opiate the infant was exposed to in utero does not seem to correlate with the severity of NAS (Thajam, Atkinson, Sibley, & Lavender, 2010). Wachman et al. (2014) reported that opioid exposed infants with a more severe phenotype of NAS (who had an increase in DNA methylation of 3 CpG sites in the OPRM1 promoter region) experienced more severe signs of NAS, consistent with gene silencing.

Screening & Measurement Instruments for Infants at Risk for NAS

Maternal and Infant Screening for NAS. AAP guidelines (2012) recommend a maternal screening instrument be used along with infant urine and meconium testing to identify infants with NAS and the specific drug(s) of fetal exposure (Hudak & Tan, 2012). Universal maternal screening utilizing interview and drug testing is recommended given that the self-reported rates of illicit drug use during pregnancy is often under reported when drug history is obtained by interview alone (Hudak & Tan, 2012). Murphy-Oikonen, Montelpare, Southon, Bertoldo, and Persichino (2010) completed a one year retrospective chart review to analyze whether the consistent use of a standardized screening protocol would accurately detect infants at

risk for developing NAS. The standardized screening protocol combined the sensitivity of the maternal self-report, urine drug screen, and meconium testing in an attempt to better identify infants with NAS and ascertain the most accurate method of detecting substance exposure. The investigators reported that there were discrepancies between the mother's self-report and the urine and meconium drug screen results (Murphy-Oikonen et al., 2010). The urine drug screen provided a faster screen and the results were available to the practitioners within 24 to 72 hours, however, the meconium drug screen provided a more accurate reflection of the maternal drug use over the pregnancy (Murphy-Oikonen et al., 2010). To achieve the most accurate reflection of the maternal drug use over the duration of the pregnancy and identify which infants are at greatest risk for NAS, the authors recommended using a combination of all three screening approaches due to the specific limitations of each approach when implemented alone (Murphy-Oikonen et al., 2010).

Modified-Finnegan Neonatal Abstinence Scoring Tool (Modified-FNAST). The Finnegan scale was developed to measure the severity of drug withdrawal in infants with NAS (Finnegan et al., 1975). The Finnegan scoring system was later modified to reduce and eliminate items that were found to be redundant or obsolete. The instrument was later modified to eliminate redundant items without compromising the validity of inferences about the higher order constructs in a population of NAS infants (Finnegan, 1990; Finnegan et al., 1975; Finnegan & Kaltenbach, 1992). The modified-FNAST scoring system is the most widely used measurement instrument to assess the severity of drug withdrawal in neonates born to drug dependent mothers in the United States (Hudak & Tan, 2012).

Inter-rater reliability using the Modified-FNAST. In order to promote consistency and accuracy of withdrawal scores among nurses, D'Apolito (2014) suggested that NICU nurses

receive additional knowledge and training to become reliable in scoring the modified-FNAST. D'Apolito and Finnegan (2010) developed an educational program to establish interrater reliability among staff when scoring the modified-FNAST. The program includes the standard definitions for each item on the modified-FNAST, a demonstration of each, and the nurses are required to achieve at least 90% agreement scoring an infant using the modified-FNAST (D'Apolito, & Finnegan, 2010). Accuracy of the withdrawal score is essential because pharmacological treatment and discharge decisions are made based on the infant's assessed score (D'Apolito, 2014). Infants are recommended to be assessed using the instrument every 3-4 hours according to their feeding schedules (Finnegan, 1990; Finnegan & Kaltenbach, 1992).

Pharmacological Treatment of NAS

There is still considerable variability regarding the pharmacological management of infants with NAS. Despite continuing research, there is currently no standardized national pharmacological treatment guidelines established for this high-risk population. Drugs used to treat this population have included methadone, morphine, buprenorphine, tincture of opium, alone or in combination with adjunctive therapies such as phenobarbital and clonidine (Hudak & Tan, 2012). The 2012 AAP guidelines recommend that pharmacological management of infants with NAS due to prenatal exposure to an opioid include treatment with an opiate derivative (Hudak & Tan, 2012). According to the 2012 AAP recommendations, morphine and methadone are considered first line therapy, while phenobarbital and clonidine are considered adjunctive therapies for NAS infants with persisting CNS signs despite treatment with an opiate derivative (Hudak & Tan, 2012). The pharmacological management of infants with NAS is indicated when the non-pharmacological interventions alone have not been able to relieve moderate to severe signs of acute drug withdrawal (Hudak & Tan, 2012). The 2012 AAP guidelines also caution

against the unnecessary pharmacological treatment of infants with NAS which can prolong drug exposure and increase the length of hospitalization, posing significant risk to maternal-infant bonding (Hudak & Tan, 2012).

Opioids. Osborn, Jeffery, and Cole (2010a) conducted a meta-analysis of all randomized and quasi-randomized studies on opioids in the treatment of NAS. Nine studies were critiqued and appraised by the authors to assess the effectiveness and safety of using an opioid compared to a sedative or non-pharmacological intervention for the treatment of NAS due to withdrawal from opiates as part of this meta-analysis (Osborn et al., 2010a). The authors concluded that due to the methodological limitations of the studies reviewed, there was not enough evidence to determine if one opioid is better than another (Osborn et al., 2010a). They also could not recommend a specific algorithm for treating infants with NAS (Osborn et al., 2010a). Finally, Osborn et al. (2010a) suggest that opioid treatment should be limited to NAS infants exposed to opioids in utero.

More recently, the safety and efficacy of methadone compared to morphine has been studied in several randomized clinical trials (Brown, Hayes, & Thornton, 2015; Davis, et al., 2018). Brown, et al. (2015) reported that of the 198 opioid exposed infants (methadone and buprenorphine) who were admitted to the NICU during the study period, 94 patients met the treatment requirements, and 16 were excluded because of identified life threatening clinical conditions, congenital anomalies, or were unavailable for consent. Seventy eight were determined to be eligible however, 47 mothers declined consent because they wanted to know what medication would be used to treat the infant (Brown et al., 2015). Thirty one were randomized, resulting in 15 in the methadone group and 16 in the morphine group. The results revealed that length of opioid treatment was shorter for the methadone group (median = 14 days)

as compared to the morphine group (median = 21days) which was statistically significant (p = 0.008) (Brown et al., 2015). The small sample size from one NICU pose limitations to the generalizability of the study findings. Similarly, Davis et al. (2018) conducted a randomized, double-blind, intention to treat trial to compare the safety and efficacy of methadone and morphine for the treatment of infants with NAS. The investigators consented 183 opioid dependent mothers and identified 117 infants who required treatment for NAS. Fifty nine infants were randomized to the methadone group and 58 were randomized to the morphine group (Davis et al., 2018). The methadone group was reported to have a 14% decreased length of stay (relative number of days attributable to NAS decreased by 2.7 days). In addition, the length of treatment was decreased by 16% (2.3 days) in the methadone group when compared to the morphine treated group (Davis et al., 2018). There were 13 adverse events which were similar between groups which included oxygen desaturation, shallow respirations, vomiting, lethargy, and low temperature. The protocol was amended to allow for faster weaning based on the observed adverse events. The study was limited by an inability to meet targeted recruitment goals (Davis et al., 2018).

Although the emerging evidence suggests that methadone compared to morphine may result in reduced in length of stay and length of treatment, Burke and Beckwith (2017) completed a small retrospective study and reported lower Bayley Scales of Infant and Toddler Development-Third Edition (Bayley III) mean composite cognitive and motor scores in methadone-treated infants compared to those treated with morphine. Developmental outcomes were assessed in 36 infants treated for NAS (17 treated with methadone and 19 treated with morphine). The infants were assessed using the Bayley III. The infant scores in the cognitive, language, and motor domains were examined for comparison. The infants in the morphine group

were noted to have statically higher scores in both the cognitive (91.3 vs. 83, $p = 0.3410$) and total motor composite scores (96.3 vs. 89.6, $p = 0.0149$) (Burke, & Beckwith; 2018).

Buprenorphine. Buprenorphine is a long acting synthetic opiate which has been shown to be safe in the treatment of opioid addicted pregnant women (Gaalema et al., 2012; Shainker, Saia, & Lee-Parritz, 2012). The use of buprenorphine to treat withdrawal in infants with NAS is the focus of current neonatal studies because the drug is known to have less respiratory depression when compared to other opioid agonists (Kraft & van den Anker, 2012). Kraft et al. (2008) conducted a randomized, open-label, active-control study of sublingual buprenorphine for the treatment of opiate withdrawal to determine the safety and efficacy of buprenorphine. The sample consisted of 26 infants who were randomized to treatment or control groups. Thirteen infants were randomized to receive oral buprenorphine and 13 infants were randomized to receive neonatal opium. The modified Finnegan scores of the infants in both groups were followed to measure the ability of the drugs to control withdrawal symptoms. The authors reported that sublingual buprenorphine at a dose of 13.2 to 39.0 mcg/kg/per day, administered in 3 divided doses which represented a higher maximum starting, higher maximum daily dose, and higher titrating dose, was safe. Kraft et al. (2011) completed a similar study to determine the safety and effectiveness of buprenorphine compared to oral morphine in the treatment of infants with NAS born to mothers with opioid dependence. Term infants ($n = 24$) requiring pharmacological treatment for NAS were randomized ($n = 12$) to receive buprenorphine and ($n = 12$) to receive neonatal opium. They reported that sublingual buprenorphine at a dose of 15.2 to 60 mcg/kg/per day, administered in 3 divided doses which represented a higher maximum starting, higher maximum daily dose, and higher titrating dose, was safe. After completing a second study, Kraft and van den Anker (2012) combined the results of the first study with the

results of the second (n = 50) and again reported that buprenorphine can be safely administered to full term infants who have been exposed to opioids (Kraft et al., 2008; Kraft & van den Anker, 2012).

More recently a prospective, double blind, RCT was conducted to compare the outcomes of 78 eligible infants treated for NAS with methadone compared to morphine (Brown, Hayes, & Thornton, 2015). The investigators reported that 47 of the mothers declined consent because they wanted to know what medication was going to be used to treat their infant. Thirty one infants were randomized, 15 in the methadone group, and 16 in the morphine group. The length of opioid treatment was noted to be significantly shorter (p = 0.008) in the methadone group (a median of 14 days) when compared to the morphine group (who were treated a median of 21 days) (Brown, et al., 2015). The efficacy of methadone vs. morphine was also compared in a more recent RCT with a larger sample size of 116 analyzed infants treated for NAS (Davis, et al., 2018). The infants were randomized (n = 59) to the methadone group and n = 58 to the morphine group. The length of stay was decreased in the methadone group (decreased by a mean of 2.9 days) which was statistically significant (p = 0.046) and length of treatment (decreased by a mean of 2.3days) (Davis, et al., 2018). Despite these encouraging findings, Burke and Beckwith (2017), after completing a retrospective chart review to compare the neurodevelopmental outcomes using the Bayley Scales of Infant and Toddler Development- Third Edition (Bayley III) of 36 infants treated for NAS with methadone (n = 17) vs. morphine (n = 19) cautioned that the infants in the methadone group had lower mean cognitive composite (91.3 vs. 83; p = 0.03410) and lower mean total motor composite scores (96.3 vs. 89.6; p = 0.0149) when compared to the morphine group.

Additional large scaled randomized controlled trials are necessary to determine which opioid derivatives are the most efficacious and pose the least possible risk to the infant. The most commonly used opioids (methadone, morphine, buprenorphine, alone and in combination with phenobarbital and clonidine) need to be tested side by side in multiple arms of methodologically sound randomized controlled trials to provide replicable empirical evidence, possibly leading to the development of standardized medication treatment protocols for this high-risk population of NAS infants. Infants with NAS who have been exposed prenatally to opioids and benzodiazepines must be included in these studies as this sub-population of high-risk infants has historically been excluded from previous drug studies and represents an increasing number of infants.

Second-line drugs (phenobarbital and clonidine). According to the 2012 AAP guidelines, second-line drugs are indicated when the NAS infant has persisting signs of withdrawal despite adequate treatment with an opioid derivative such as the presentation often seen with NAS infants with prenatal opioid and benzodiazepine exposure (Hudak & Tan, 2012). Phenobarbital is preferred over diazepam to reduce persisting CNS related symptoms in infants being treated with an opioid for NAS (Osborn, Jeffery, & Cole, 2010b). There is no evidence to support the use of chlorpromazine in the treatment of infants with NAS (Osborn et al., 2010b). Clonidine is being used more commonly in NICUs as an adjunct medication to treat infants with NAS displaying persisting CNS signs. Agthe et al. (2009) conducted a randomized controlled trial to test the effectiveness of clonidine and tincture of opium, compared to a placebo and tincture of opium, in reducing the total number of days of required treatment on tincture of opium for infants with NAS exposed to prenatal heroin and methadone. Forty infants were randomized to the treatment group and 40 infants were randomized to the control group. The

investigators reported that the median length of opioid treatment was 27% shorter in the clonidine plus opioid group (Agthe et al., 2009). Surran et al. (2013) conducted a prospective randomized controlled trial to compare the length of treatment of NAS infants treated with morphine plus clonidine vs. those treated with morphine plus phenobarbital. The study found that infants in the clonidine plus morphine treated group (n = 34) required less total treatment days without requiring an increase in their morphine dose (Surran et al., 2013). Infants in the phenobarbital plus morphine group (n = 34) required treatment longer, an average of 3.8 months, with a range of 1-8 months, but were discharged home from the hospital sooner (Surran et al., 2013). The cost savings associated with discharging infants with NAS sooner on phenobarbital need to be carefully weighed against the potential risk of poor neurodevelopmental outcome related to prolonged exposure to the medication. More recently, Gullickson, Kuhle, & Campbell-Yeo (2018) conducted a retrospective study to compare the length of treatment in infants treated for NAS with (n = 22) morphine monotherapy vs. (n = 100) treated with morphine and clonidine. The infants in the morphine combined with clonidine group were noted to have a longer length of treatment (p = 0.004) and higher peak morphine doses were also observed (p = 0.045). Future studies need to focus on testing standardized treatment and weaning protocols for both phenobarbital and clonidine to reduce unnecessary variation in the lengths of treatment and risks associated with prolonged exposure. Studies are also needed to determine the long term risks associated with clonidine in this high-risk population.

Non-pharmacological Treatment of NAS

Infants with NAS are known to have difficulty with sensory integration, as even small amounts of stimulation may be overwhelming for these infants to manage. State regulation and sleep and wake cycles are frequently disorganized in this high-risk population of infants (Sublett,

2013; Velez & Jansson, 2008). Non-pharmacological interventions are therefore frequently used prior to pharmacological treatment to help the infant with NAS cope with all the sources of environmental stress they may experience (Sublett, 2013; Velez & Jansson, 2008).

Reduction of environmental stimuli. Two descriptive case series studies suggest that interventions designed to reduce environmental stimuli such as providing a dark quiet environment, private patient rooms, and clustered care are all therapeutic interventions that can provide support for infants with NAS (Green & Goodman, 2003; Marcellus, 2007). Additional interventions such as gentle handling, swaddling the infant, positioning the infant on their back or side in a fetal position, or providing containment are also frequently used clinical interventions employed to decrease hyper-arousal and tremors in this population (Green & Goodman, 2003; Marcellus, 2007).

Holding, Rocking, & Massage. Holding and gentle slow vertical rocking has been suggested to provide soothing effects in promoting maternal-infant bonding and foster calm interactions between infants experiencing acute drug withdrawal and their opioid-dependent mothers (Marcellus, 2007; Velez & Jansson, 2008). White-Traut et al. (2002) conducted a randomized controlled trial to compare the responses of non-exposed and drug exposed infants to an intervention which included auditory, tactile (massage), eye-to-eye contact and vertical rocking. The treatment group in this study received an integrated intervention that included twice-daily 15-minute stimulation using the ATVV (auditory, tactile, visual, and vestibular-rocking stimulation) (White-Traut et al., 2002). Infant behavioral state and pulse rate were measured in the two groups. The study found that the ATVV intervention promoted normal physiologic and behavioral function in the drug-exposed infants (White-Traut et al., 2002).

Non-nutritive sucking, & laser acupuncture. Providing pacifiers for non-nutritive sucking to promote infant self-soothing behavior and decrease skin excoriation from frantic, erratic infant movements was shown to be a therapeutic intervention to support infants experiencing acute drug withdrawal in two case series studies (Green & Goodman, 2003; Velez & Jansson, 2008). Wolfgang, et al. (2015) conducted a prospective, randomized controlled, blinded, single-center trial to determine if infants randomly allocated to laser acupuncture (combined with pharmacological therapy of morphine and phenobarbital) or control group (pharmacological therapy alone) would reduce the duration of treatment required in NAS infants. The sample consisted of 28 infants with NAS, 14 were randomized to the treatment group (laser acupuncture combined the pharmacological therapy), and 14 were randomized to the control group (pharmacological therapy alone). Infants born to mothers who self-reported poly drug use were excluded from participation in the study. The investigators reported that the infants in the treatment group (who received a combination of laser acupuncture and pharmacological management) had shorter duration of oral morphine treatment when compared to infants in the control group (pharmacological management only). The acupuncture group was noted to require oral morphine for 28 days vs. 39 days in the control group. The small sample size posed a limitation to the study findings (Wolfgang, et al., 2015).

Water bed, rocking bed, vs. standard crib. Infants with NAS positioned on non-oscillating water beds were shown to require less medication to control their withdrawal symptoms and demonstrated a better pattern of weight gain when compared to the control group (Oro & Dixon, 1988). D'Apolito (1999) conducted a repeated measure experimental study of 14 infants with NAS, who were randomized to treatment or control groups, to determine the effect of a rocking bed vs. a standard bed on reducing withdrawal symptoms. The 14 infants in the

study were prenatally exposed to methadone and other illicit drugs (D'Apolito, 1999). The study results suggested that the infants in the intervention group who were placed in the rocking beds became hyper-stimulated and were not able to sleep, had higher withdrawal scores, and sub-optimal neurodevelopmental behavior at 7-days compared to infants in the control group (D'Apolito, 1999). The author concluded that the rocking bed was over stimulating to NAS infants during the acute withdrawal period and did not recommend the use of this intervention in this population without further study (D'Apolito, 1999). The type of bed and positioning of infants with NAS needs further empirical testing, especially in light of the campaign to reduce sudden infant death which recommends infants be placed on their backs, on firm bedding, offered a pacifier, avoid overheating the infant, and not have any soft toys or bedding in their crib.

Breastfeeding. Exclusive breastfeeding is recommended for infants for the first 6-months of life by the AAP, unless there are known contraindications, because of the overwhelming evidence of the benefits it provides which include reduced health related costs, protection from infectious diseases, asthma, reduced risk of SIDS, reduction in the incidence of type 1 and type 2 diabetes, and higher performance on tests of cognitive development (Gartner et al., 2005). Breastfeeding also provides benefits for the mother including reduced incidence of postpartum bleeding, earlier return to pre-pregnancy weight, decreased risk of breast cancer and ovarian cancer and possibly decreased risk of hip fractures and osteoporosis (Gartner et al., 2005). Breastfeeding also promotes mother infant bonding and reduces maternal depression (Pritham, 2013). The 2012 AAP guidelines no longer restrict breastfeeding in mothers of infants experiencing acute drug withdrawal provided they are negative for human immunodeficiency

virus (HIV), illicit drugs, follow the established guidelines for minimal alcohol consumption, and are enrolled in a supervised drug maintenance program (Hudak & Tan, 2012).

Methadone and buprenorphine levels in breastmilk are low regardless of maternal dose, and are determined to be safe to be fed to infants with NAS (Jansson et al., 2008; Jansson, Velez, & Harrow, 2004). McQueen, Murphy-Oikonen, Gerlach, and Montelpare (2011) completed a retrospective chart review and found that in a sample of 28 predominantly breastfed infants being treated with methadone for NAS required less withdrawal scores to be taken, and had lower mean scores when compared to infants who received partial breastmilk feedings and formula. Suggesting that breastfeeding compared to formula feeding may lower the severity and duration of NAS (McQueen et al., 2011). Pritham, Paul, and Hayes (2012) conducted a similar retrospective descriptive study and found an association between infants experiencing acute drug withdrawal who were breastfed only, compared to formula-fed and neonates who received partial breastmilk and formula feedings, and a decrease in the rate of treatment for withdrawal in both methadone and buprenorphine prenatally exposed neonates. The study provides some evidence that breastfeeding should be encouraged in this high-risk population to shorten the length of stay (Pritham et al., 2012).

The literature suggests that there are many potential barriers to opioid dependent mothers initiating and continuing breastfeeding, especially in the NICU environment. Proposed strategies to promote breastfeeding include providing current, and accurate information on breastfeeding, ensuring knowledgeable lactation consultants are readily available, providing kangaroo (skin-to-skin) care, and providing rooming-in options to keep the mother and infant together (Pritham, 2013). O'Connor, Collett, Alto, and O'Brien (2013) completed a retrospective chart review for all infants born to opioid dependent mothers treated in an integrative buprenorphine maintenance

program between 2007 and 2012. Sixty five mothers who enrolled in the program decided to breastfeed. The comprehensive program included obstetrical and addiction medicine specialist care and a 1-hour per week counseling session (O'Connor et al., 2013). The group was facilitated by a psychologist with advanced training in addiction. Physicians, practitioners, social workers, obstetric nurses, and lactation specialists frequently attended the group. The program did not have a specific curriculum, the topics of discussion were frequently determined by the questions raised by the mothers, however, the clinicians facilitating the groups ensured that breastfeeding education and treatment options for infants with NAS were frequently discussed (O'Connor et al., 2013). Of the 65 mothers enrolled in the sample, 66% were still reported to continue breastfeeding at 6-8 weeks postpartum (O'Connor et al., 2013). In contrast, Wachman, Byun, and Philipp (2010) conducted a retrospective chart review of opioid dependent mothers who delivered at a designated Baby-Friendly-Hospital in Boston Medical Center July 2003-January 2009 and identified 276 dyads. Sixty-eight percent of the mothers identified were determined to be eligible to breastfeed, and of those mothers, only 24% actually breastfeed to some extent during their NAS infant's hospitalization (Wachman et al., 2010). Sixty percent of the mothers who initiated breastfeeding discontinued breastfeeding after an average of 5.88 days (Wachman et al., 2010). The differences in breastfeeding initiation and duration between these two studies suggests that an integrated comprehensive program targeting the common barriers to breastfeeding in this population may be more successful. Future studies need to focus on how best to educate narcotic addicted mothers on the benefits of breastfeeding their infants and test strategies to determine which strategies or combination of strategies are most successful in promoting and sustaining breastfeeding in this high-risk population.

Rooming-in. Newman et al. (2015) conducted a retrospective chart review to explore the effect of a rooming-in program designed to provide opioid-dependent mother-infant dyads with uninterrupted contact with their infants. The study suggested that there was a reduction in the proportion of infants requiring pharmacotherapy and their average length of hospital stay was reduced (Newman et al., 2015). Rooming-in programs have been shown to mitigate the relationship between maternal methadone dosage and the need to treat the infant for NAS (Hodgson & Abrahams, 2012). Rooming-in programs have also been suggested to be a safe alternative to the current standard of care that separates the dyad and promotes maternal infant attachment and breastfeeding in this high-risk population (Hodgson & Abrahams, 2012; Newman et al., 2015).

Home-based weaning. Home-based weaning strategies have been proposed as a cost effective alternative to traditional NICU hospitalization for the treatment of infants with NAS and as approach to promote parent infant bonding. However, the potential benefits of home-based weaning must be balanced against the potential safety risks for the infant (need for protective services and foster care placement related to neglect or abuse). Careful selection of mother infant dyads using strict criteria is critical to the success of home based weaning programs, along with ongoing outpatient monitoring of the safety of the infant. Multiple retrospective chart reviews have been conducted to evaluate the safety and efficacy of the traditional NICU inpatient only weaning approach compared to a combined inpatient and outpatient weaning strategy (Brackets et al, 2012; Smirk, Bowman, Doyle, & Kamlin, 2014). Brackets et al. (2012) reported that in carefully selected infants, combined inpatient/outpatient weaning compared to traditional NICU inpatient only weaning was associated with reduced hospital length of stay, total methadone treatment duration, and increased rates of breastfeeding.

The investigators reported that breast feeding rates were improved, 24% combined group vs. 8% in the traditional group, ($p < .05$). In addition, the length of hospital stay decreased ranging from 25 $\pm$ 15 days for the traditional group, compared to 13 $\pm$ 5 days for the combined group. The total duration of methadone treatment was longer 37 $\pm$ 20 days in the traditional group vs. 21 $\pm$ 14 day, ($p = < 0.001$) in the combined group. The average cost for an infant in the combined group was $13 729, compared to $27 546 for an infant in the NICU hospitalized traditional group. The investigators reported an estimated cost reduction of $635 000 in a 2 year period. In addition, patient safety data revealed that there were no infant deaths. However, two infants in the combined group required a referral to child protective services for alleged neglect or abuse. The readmission rates were reported to be comparable between the two groups (5% in the traditional group, vs. 7% in the combined group) (Brackets, et al., 2012)

Smirk et al. (2014) reported similar findings based on data from a retrospective chart review of 118 infants with NAS treated for in utero exposure to opioids (methadone or buprenorphine). Of the 118 infants, 38 were carefully selected for home based weaning and 80 were weaned as traditional NICU inpatients. The investigators reported that the infants in the home based weaning group had decreased length of hospital stay (mean 19 days vs. 41 days in the traditional combined group). The mothers in the home based weaning group had reportedly higher rates of breastfeeding at the time of discharge (45% vs. 22% in the traditional inpatient group). In addition, there were no increased incidence of patient safety issues (need for child protective services and foster care placement) or serious adverse events noted between the two groups (Smirk, et al., 2014).

Summary. In summary, the empirical evidence related to the care and treatment of infants with NAS and their mothers was reviewed. The review of the literature revealed four

relevant substantive themes related to this proposed research study including: definitions of NAS, screening and measurement instruments for NAS, pharmacological management of infants with NAS, and non-pharmacological management of infants with NAS. Critique and appraisal of the existing evidence was provided and revealed critical gaps in the existing literature including a lack of national standards and guidelines for pharmacological management of the infant with NAS, limited empirical evidence to support the non-pharmacological interventions commonly used in this high-risk population, and lack of abstinence scoring instruments with prior evidence for the validity and reliability of scores generated in infants greater than 28 days of age.

CHAPTER THREE:

METHODS

This chapter presents the study methods. It is organized by institutional approvals, funding, design, setting, sample, sampling plan, population, theoretical and operational definition of terms, measures, and study procedures. The chapter concludes with a detailed description of the data analysis plan according to the specific study aims.

Institutional Approvals

Approval for the study was obtained from the Johns Hopkins All Children's Hospital (JHACH) and the University of South Florida (USF) Social and Behavioral Institutional Review Boards (see Appendix B).

Funding

The study was supported by a monetary award from the JHACH Novice Nurse Researcher: Nursing Excellence Guild Fund.

Design

The proposed study was a retrospective chart review of infants less than and greater than 28 days of life with a primary diagnosis of NAS (hospitalized in the NICU between January 1, 2010-May 18, 2018).

Setting

The study was conducted at JHACH, a 97 bed level IV NICU, located in St. Petersburg, Florida.

Sample/Sampling Plan

The partial medical records of an estimated 300 infants diagnosed with NAS who had documented modified-FNAST scores and were hospitalized in the NICU at JHACH between January 1, 2010 and May 18, 2018 and meet the inclusion criteria (and did not have any exclusionary criteria) comprised the convenience sample.

Population (Inclusion/Exclusion Criteria)

To meet the eligibility criteria the infants must have been born to an opiate-dependent mother, admitted to the NICU with a primary diagnosis of NAS (within day of life 3) and required pharmacological management. NAS infants who had life threatening conditions in which NAS was only a secondary diagnosis, were discharged from other in patient units, or were premature (less than 37 weeks), were excluded from participating in the study.

The standard of care for infants with NAS was to assess the severity of drug withdrawal using the modified-FNAST every 3-4 hours post feeding. Infants diagnosed with NAS at JHACH had an average length of stay of 30.2 days (based on JHACH internal data from January 2013-Janary 2015). Thus, the number of assessments for each infant was expected to yield 181-242 assessments. There were 122 infants in 2014 identified as having NAS. Assuming there were at least that many in 2015, the estimated number of infants with NAS would be about 610 infants. This would yield an approximate total of 110,532-147,376 assessments. Given that 261 of the 309 (84%) total infants hospitalized with the diagnosis of NAS (based on JHACH internal data from January 2013-Janary 2015) were greater than 28 days of life, it was anticipated that we would be able to obtain an adequate number of modified-FNAST scores to perform a meaningful factor analysis. The modified-FNAST assessments for each NAS infant who met the established inclusion criteria was evaluated independently, as was the process of Factor Analysis.

Theoretical and Operational Definition of Terms

Theoretical Definition of Maternal Opioid Dependence. NAS is a consequence of in utero exposure to drugs from their opioid-dependent mother (Hudak & Tan, 2012; Kocherlakota, 2014). Expectant management for the opioid dependent pregnant women includes opioid maintenance therapy with methadone or buprenorphine (Hudak & Tan, 2012). The onset and severity of NAS is dependent on the main substance the infant is withdrawing from, the unique combination of substances the infant was exposed to, and the gestational age of the infant. The short half-life of opiates is thought to be responsible for the rapid onset of the symptoms characteristic of NAS, which usually are noted within 72 hours after birth in infants born to mothers who are opioid-dependent (Cramton & Gruchala, 2013). In contrast, methadone exposed newborns present with symptoms 2-6 days after birth, and sedative-hypnotics (benzodiazepines and barbiturates) exposed newborns which may not manifest symptoms of NAS until a week or more after birth (Cramton & Gruchala, 2013). Polysubstance abuse (opioids and benzodiazepines in particular) during the pregnancy has been shown to produce more severe symptoms of withdrawal when compared to exposure to a single substance (Cramton & Gruchala, 2013). The dose of opiate the infant was exposed to in utero does not seem to correlate with the severity of NAS (Thajam et al., 2010).

Operational Definition of Maternal Opioid Dependent Mother. For the purposes of this study, opioid-dependent mothers were operationally defined as a mother who has a documented history of opioid dependency. The history of maternal opioid dependency was confirmed by documentation in the admission history of the EMR of the newborn and urine drug screen.

Theoretical Definition of NAS. NAS is the term used to describe the specific acute drug withdrawal pattern observed in infants born to opioid-dependent mothers. NAS is characterized by a typical pattern of withdrawal behaviors involving central nervous system (CNS) related signs (tremors, increased muscle tone, seizures and high-pitched cry), respiratory system related signs (tachypnea, and retractions), gastrointestinal system related signs (poor feeding, vomiting, diarrhea, and uncoordinated and excessive sucking), and autonomic system related signs (mottling, nasal stuffiness, excessive yawning, sneezing, and temperature) (Finnegan et al., 1975; Hudak & Tan, 2012; Kocherlakota, 2014). The American Academy of Pediatrics (AAP) recommends that the infants at risk for NAS be monitored and the severity of drug withdrawal be measured using an instrument with empirical evidence to support the validity and reliability of the scores obtained in this population (Hudak & Tan, 2012).

Operational Definition of NAS. For the purposes of this study, an infant with NAS was operationally defined as a term infant who was exposed to opiates prenatally, presented with signs of acute drug withdrawal and was diagnosed as having abstinence syndrome requiring pharmacological treatment and hospitalization in the NICU at JHACH. The diagnosis of NAS was confirmed by documentation in the admission or discharge notes of the electronic medical record (EMR) of the newborn and confirmed by urine and/or meconium drug screen when available.

Measures

Modified-FNAST Scores. The severity of drug withdrawal was quantified as the modified-FNAST scores of the infant. The assessments were documented in the EMR every 3-4 hours by the bedside nurse. Each of the 21 items in the modified-FNAST were scored, as well as the total score.

Demographic Instrument. A demographic instrument was created specifically for this study to collect the maternal and infant data required for analysis of the specific study aims.

Study Procedures

Data Collection. After obtaining IRB and the necessary administrative approvals, the data was extracted from the electronic medical record (EMR) of the eligible infants in order to measure the achievement of the specific study aims. Based on the evaluation from the JHACH DataLine Senior IT representative it was only possible to extract a portion of the infant's demographic data de-identified from the data warehouse. Therefore, the remaining demographic data on the infant including, all drugs used to treat NAS, max total dose of each drug prescribed, and the duration of pharmacological management for each drug used to treat the infant was manually extracted by the study team. Demographic data on the mother including age, race, ethnicity, education, significant mental health and trauma history, significant drug history, and urine drug screen result were manually extracted using the patient medical record number. The maternal demographic data was manually extracted from the infant's medical record (provider admitting note and/or social services note) and entered de-identified directly into REDCap (coded using the unique participant ID number) by the PI and co-investigators who had completed the necessary protection of human subjects training.

The complete list of demographic data collected on the infant included the medical record number, birth weight, day of life, gender, gestational age, verification of admitting diagnosis of NAS, all modified-FNAST total scores, individual 21-item modified-FNAST scores and total scores for each assessment, list of drugs used to treat NAS, duration of pharmacological management for drug used to treat NAS, maximum doses of each specific drug used to treat NAS, date of discharge, urine and meconium drug screen results. These data were collected on

all infants admitted to the NICU with a diagnosis of NAS as part of the standard of care. The portion of the data extracted from the infant's medical record by the DataLine (from the data warehouse) was combined with the data manually extracted. The combined data was exported as an excel spread sheet file that was uploaded directly into SPSS coded only with the participant unique study ID number for analysis. The de-identified SPSS file was stored in a secure password protected Johns Hopkins (JH) and USF boxes accessible only by the study team members.

Protection of Human Subjects

Potential Risk to the Participants. This was a minimal risk study (retrospective chart review) involving data extraction, however, there was a risk for breach of confidentiality if the temporary key code that linked the patient identification number to the unique identifier of the patient was compromised. There were no experimental procedures or interventions implemented as part of this study.

Potential Benefit to the Participants. There were no direct benefits to participants and society however, this retrospective study may provide empirical evidence to promote the development of a reliable and valid instrument for assessing abstinence in infants greater than 28 days old in the future. The potential future benefit outweighed the risk for this minimal risk study.

Alternatives to Participation. The alternative to participation was no participant involvement in the study (no extraction of partial medical records).

Measures to Protect Human Subjects. To protect the confidentiality of the human subjects in this research study, all patients were assigned a unique patient identifier number. In order to extract the retrospective data from the EMR, a waiver of consent and HIPAA was

requested from the IRB. A waiver of consent and HIPAA was necessary because the study team did not have the necessary contact information to obtain consent from the eligible participants. The demographic data on the mother was manually collected by the PI and study team members who had all completed the required protection of human subjects training. The maternal demographic data and infant data fields unavailable from the data warehouse were then entered into a secure REDCap data base, coded using only the unique patient identifier number, and later downloaded into the SPSS file for analysis. A portion of data on the infant was extracted from the infant's medical record by the DataLine (from the data warehouse) as an excel spread sheet file which was uploaded directly into SPSS coded only with the participant unique study ID number. The SPSS file was stored in secure password protected JH and USF boxes accessible only by the study team members.

In order to accurately identify the eligible NAS infants and manually extract the maternal demographic data, a temporary key code was maintained to link the medical identification numbers of the infant to the unique identifier code. This temporary key code was stored in a separate password protected computer file from the SPSS data file in the JH and USF boxes that was only accessible by the PI and the study team members. The key code was destroyed once all the data had been collected and analysis was completed. Only de-identified data was retained for five years as required by the IRB. In addition, only the de-identified, aggregate data will be disseminated in any future posters, podium presentations, and manuscripts, which may result following the completion of this study.

Data Analysis Plan

Data analysis was performed using the statistical package for the social sciences (SPSS) version 24.0 (IBM, Armonk, NY).

Aim #1. To determine which of the 21 items in the modified-FNAST are most predictive of the need for pharmacological treatment in infants greater than 28 days of life diagnosed with NAS, Logistic Regression was used (Tabachnick, & Fidell, 2013).

Aim #2. To explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants less than 28 days of life diagnosed with NAS experiencing acute drug withdrawal. Exploratory Factor Analysis was used (Tabachnick, & Fidell, 2013).

Aim #3. To explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants greater than 28 days of life diagnosed with NAS experiencing acute drug withdrawal. Exploratory Factor Analysis was used (Tabachnick, & Fidell, 2013).

Aim #4. Comparison was made between the underlying structures of the interrelationships of the items of the modified-FNAST as determined by the EFA in infants less than and greater than 28 days of life diagnosed with NAS experiencing acute drug withdrawal.

AIM #5. The relationship between the medications used to treat infants for NAS and the longitudinal trajectory of the Finnegan scores was described. Descriptive Analyses were used to explore the relationship between the means of the total Finnegan scores (on day 1, 3, 7, and then weekly) and the medications used to treat the infants in the sample. A repeated measures Mixed Effect Model was used to compare the mean Finnegan scores between the different medication groups (Tabachnick, & Fidell, 2013). The trajectory of the mean Finnegan scores and the relationship between the medication groups was reported in run charts using excel.

Exploratory factor analysis was used in the analysis of aims 2-4. Exploratory factor analysis of the average individualized and total modified-FNAST scores of infants less than and

greater than 28 days of life were performed on day 1, 3, 7, then weekly, and on the day of discharge to determine the underlying dimensions and explore the similarities and differences between the groups (see Table 2).

Exploratory Factor analysis is a statistical method used to assess construct validity (Polit, 2010; Tabachnick, & Fidell, 2013). Factor analysis is a measure to assess various dimensions or subcomponents of a phenomena of interest to empirically justify these dimensions or factors (Polit, 2010; Tabachnick, & Fidell, 2013). This process helps to understand the most important patterns of a phenomena (Polit, 2010).

Table 2. Factor Analysis Plan (Pallat, 2013; Polit, 2010; Tabachnick, & Fidell, 2013)

Exploratory factor analysis of the average individualized and total modified-FNAST scores of infants less than and greater than 28 days of life will be performed on day 1, 3, 7, then weekly, and on the day of discharge to determine the underlying dimensions and explore the similarities and differences between the groups. The factor analyses will include the following steps each time the analyses is performed.		
Step 1. Assessment of the Suitability of the Data for factor analysis	**Step 2. Factor Extraction (Principal Components Analysis & Principal Axis Factoring)**	**Step 3. Factor Rotation and Interpretation**
Sample size- >150 **Strength of the Relationship of the Items of the modified-FNAST** **If there are few correlations > .3** a factor analysis may not be appropriate. **Bartlett's chi-square test** **Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy**	**Goal:** obtain a solution with the smallest number of factors that can be used to represent the interrelationships among a set of variables, and explain as much of the variance as possible. *The Components Matrix, Pattern, & Structure Matrixes from SPSS will be reviewed and the following analyses will be performed: **Kaisers Criteria-** only factors with an eigenvalue above 1 will be retained. **Catell's (1966) Scree Test-** plot each of the eigenvalues of the factors by inspecting the plot produced by SPSS and identify the area above the elbow, and retain only factors above the elbow. **Horn's (1965) Parallel Analysis-** involves comparing the size of the eigenvalues with those obtained from a randomly generated data set of the same size. Using this approach, only eigenvalues that exceed the corresponding values from the random data set are retained for the final solution. This test has been shown to be the most accurate of the three.	**Goal:** Rotation does not alter the underlying solution. It presents the patterns of loadings in a manner that is easier to interpret by depicting which variables cluster together. The goal according to Thurstone (1947) is to obtain a simple solution (is when you have high factor loading on only one factor). Ideally, the factor loadings are as close to 1.00 as possible for the variables aligned with a factor, and the loadings are as close to 0.00 as possible for variables not aligned with the factor. **Orthogonal Rotation-** assumes that the factors are not correlated. Generates a factor solution that is at a 90 degree angle. The most widely used orthogonal rotation is Varimax rotation. Since the factors are known to be correlated this approach would not be appropriate.

Table 2. Factor Analysis Plan Continued

		Oblique Rotation- assumes that the factors are correlated. The most widely used oblique rotation is Direct Oblimin rotation, which allows the axis to deviate from a 90 degree angle. **Label the factors** Items with high loadings on one and only one factor (**marker variable**) will be used to assist with labeling. The original items will be reviewed to determine what the cluster items have in common with each other to further refine the label for the factor. **Internal Consistency Reliability Analysis-** Cronbach's Alpha.

Three main steps were planned to be performed to complete the Factor Analysis (see Table 2). Step one includes the assessment of the suitability of the data for factor analysis (Pallat, 2013). Two main issues were evaluated to determine if the data were suitable for factor analysis (sample size and the strength of the relationship of the items of the modified-FNAST) (Pallat, 2013). Tabachnick and Fidell (2013) suggest that a sample size greater than 300 is most ideal, however, they do acknowledge that a smaller sample size (approximately greater than or equal to 150) may be sufficient if solutions are noted to have several high loading marker variables above .8. Nunnally (1978) suggests that 10 cases for each item to be factored should be adequate. Given the M-FNAST is a 21 item instrument a sample size of 210 should be sufficient based on this criterion. The Senior IT Analyst from DataLine estimated that there are approximately 209 infants who met the inclusion criteria without any exclusionary criteria, therefore, we anticipated having an adequate sample size to meet the assumptions to accurately perform a factor analysis.

To assess the strength of the inter-correlations among the items, the correlation matrix was inspected for evidence of coefficients greater than .3 (Pallat, 2013). If the inspection

revealed that there are few correlations greater than .3, factor analysis may not be appropriate (Pallat, 2013). Two statistical tests were also planned to be performed, Bartlett's chi-square test (Bartlett, 1954), and Kaiser-Meyer-Olkin Measure of Sampling Adequacy (Kaiser, 1970, 1974). The Bartlett's test of sphericity should be significant with a p value < .05 (Pallat, 2013; Polit, 2010). The Bartlett's test of sphericity tests the null hypothesis that the correlations in the matrix are zero (that the correlation matrix is an identity matrix) (Polit, 2010). If the null hypothesis cannot be rejected than factor analysis is not appropriate (Pallat, 2013; Polit, 2010). The KMO index is the ratio of sum of squared correlations to the sum of squared correlations plus the sum of squared partial correlations (Polit, 2010). The KMO test is a measure of sampling adequacy that compares the magnitude of correlation coefficients to the sizes of partial coefficients. In this context, the partial correlation coefficient between two variables is the correlation after controlling for the effects of all other variables (Polit, 2010). Values range between 0-1, values approaches 1 if the partial correlations are small. Values of .8 or greater are considered good, .7 fair, and values below .5 are considered unacceptable for factor analysis (Polit, 2010).

Factor extraction is the second step in the process of factor analysis (Pallat, 2013; Polit, 2010). Factor extraction involves determining the smallest number of factors that can be used to best represent the interrelationships among a set of variables (Pallat, 2013; Polit, 2010). There are multiple approaches that can be used to extract the underlying factors or dimensions (principal components analysis, and principal axis factoring with or without orthogonal or oblique rotation are the most common) (Pallat, 2013; Polit, 2010). The factor solution that best addresses two conflicting goals would then be selected. The goal was to obtain the solution with as few factors as possible, and which explained as much of the variance in the original data as possible (Pallat, 2013; Polit, 2010). Multiple statistical techniques were planned to be used to

assist in the decision making process on the final number of factors to retain including: Kaiser's criterion, scree test, and parallel analysis (Pallat, 2013; Polit, 2010). The Kaiser's criteria or eigenvalue rule is the most commonly used technique. According to this rule, only factors with an eigenvalue of 1.0 or greater would be retained (Pallat, 2013; Polit, 2010). The eigenvalue of a factor represents the amount of the total variance explained by the factor (Pallat, 2013; Polit, 2010). The Kaiser criteria has been criticized because it may result in the retention of too many factors in some situations, therefore, it should not be used as the only criteria (Pallat, 2013). Catell's (1966) scree test involves plotting each of the eigenvalues of the factors and inspecting the plot to identify the area at which the shape of the curve abruptly changes direction and becomes horizontal (the elbow). Catell (1966) recommends only retaining all the factors above the elbow. Parallel analysis as described by Horn (1965) involves comparing the size of the eigenvalues with those obtained from a randomly generated data set of the same size. Using this approach, only eigenvalues that exceed the corresponding values from the random data set would retained in the final solution (Pallat, 2013). This test has been shown to be the most accurate of the three (Pallat, 2013).

Factor rotation and interpretation are the last step in the process of factor analysis (Pallat, 2013; Polit, 2010). Once the number of factors has been decided, it is necessary to interpret the meaning of the factors (Pallat, 2013; Polit, 2010). Rotation (orthogonal and oblique) can be used to assist in the interpretation of the factors (Pallat, 2013; Polit, 2010). The process of rotation does not alter the underlying solution (Pallat, 2013; Polit, 2010). Rotation presents the patterns of loadings in a manner that is easier to interpret by depicting which variables cluster together (Pallat, 2013; Polit, 2010). The final interpretation should be based on current theory and past research (Pallat, 2013; Polit, 2010).

There are two main approaches to rotation: orthogonal which assumes that the factors are not correlated, and oblique which assumes the factors are correlated (Pallat, 2013; Polit, 2010). Tabachnick and Fidell (2013) suggest, orthogonal rotation generates factor solutions that are positioned at a 90 degree angle, easier to interpret, and the researcher must assume that the underlying constructs are not correlated (which is usually an incorrect assumption). The most widely used orthogonal rotation is Varimax rotation and this can be performed in SPSS (Pallat, 2013; Polit, 2010). In contrast, oblique rotation allows the axis to deviate from a 90 degree angle, and allows for factors to be correlated, however, they are more difficult to interpret (Pallat, 2013; Polit, 2010; Tabachnick, & Fidell, 2013). The most commonly used oblique rotation is direct oblimin rotation and this is available in SPSS (Pallat, 2013; Polit, 2010). In reality, the two approaches often produce similar results especially when the correlations between the items are more obvious (Tabachnick, & Fidell, 2013). Because of this phenomena, many researchers conduct both orthogonal and oblique rotations and then report the one that is the most clear and interpretable (Pallat, 2013; Polit, 2010). According to Thurstone (1947), the goal of rotation is to obtain a simple structure. A simple structure is a rotation solution where the variables have a high loading on only one factor. Preferably, the factor loadings are as close to 1.00 or -1.00 as possible for the variables aligned with a factor, and the loadings are as close to 0.00 as possible for variables not aligned with the factor. The factors are then labeled by identifying the marker variables and reviewing the original items to determine what the cluster of loadings on a factor have in common (Pallat, 2013; Polit, 2010). A Cronbach's alpha was also to be analyzed to determine the internal consistency reliability (Pallat, 2013; Polit, 2010).

A series of Exploratory Factor Analyses (EFA) were to be performed on the modified-FNAST scores of infants less than and greater-than 28 days of life admitted to the JHACH 97

bed NICU (between January 1, 2010-May 18, 2018). Exploratory factor analysis was planned to be used in the analysis of aims 2-4. Exploratory factor analysis of the average modified-FNAST scores of infants less than and greater than 28 days of life were to be performed on day 1, 3, 7, then weekly, and on the day of discharge to determine the underlying dimensions and explore the similarities and differences between the groups. Principle Component Analysis was to be conducted to extract variables that accounted for the greatest amount of variance. The serial EFA were to be conducted on the two groups of infants (less than and greater than 28 days old) and compared in order to determine if the validity and reliability of the inferences of the abstinence scores could be extended to infants greater than 28 days of life. In order to fully describe the sample population the demographics of the mother and infant dyads were described. The infant's medical record were also reviewed to verify the results of any maternal and infant urine and/or meconium drug screen results. The demographic data were analyzed using descriptive statistics (frequency and percent) and the results were presented in a table.

The relationship between the medications used to treat infants for NAS and the longitudinal trajectory of the Finnegan scores were described using frequency and percent. Descriptive Analyses were used to explore the relationship between the means of the total Finnegan scores (on day 1, 3, 7, and then weekly) and the medications used to treat the infants in the sample. A repeated measures Mixed Effect Model was used to compare the mean Finnegan total scores between the different medication groups after controlling for multiple extraneous variables (Tabachnick, & Fidell, 2013). The trajectory of the mean total Finnegan scores and the relationship between the medication groups were reported in run charts using excel.

Summary. In summary, this chapter reviewed the specific study methods. It was organized by institutional approvals, funding, design, setting, sample and sampling plan,

population, theoretical and operational definition of terms, measures, and study procedures. The chapter ended with a detailed description of the data analysis plan according to the specific study aims.

CHAPTER FOUR:

RESULTS

The chapter provides a detailed review of the study results. The chapter begins with a description of the demographics of the study sample including critical characteristics on both the infants with NAS and their mothers. In addition, the chapter provides a presentation of the study results with respect to each the five study aims according to the a priori data analyses plan.

Aim #1

To determine which of the 21 items in the modified-FNAST are most predictive of the need for pharmacological treatment in infants greater than 28 days of life diagnosed with NAS, Logistic Regression was used (Tabachnick, & Fidell, 2013).

Aim #2

To explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants less than 28 days of life diagnosed with NAS experiencing acute drug withdrawal. Exploratory Factor Analysis was used (Tabachnick, & Fidell, 2013).

Aim #3

To explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants greater than 28 days of life diagnosed with NAS experiencing acute drug withdrawal. Exploratory Factor Analysis was used (Tabachnick, & Fidell, 2013).

Aim #4

Comparison was made between the underlying structures of the interrelationships of the items of the modified-FNAST as determined by the EFA in infants less than and greater than 28 days of life diagnosed with NAS experiencing acute drug withdrawal.

AIM #5

The relationship between the medications used to treat infants for NAS and the longitudinal trajectory of the total Finnegan scores was described. Descriptive Analyses was used to explore the relationship between the means of the total Finnegan scores (on day 1, 3, 7, and then weekly) and two of the medications (clonidine and phenobarbital) used to treat the infants in the sample. A repeated measures Mixed Effect Model was used to compare the mean total Finnegan scores between the different medication groups (infants treated and non-treated with clonidine and phenobarbital) (Tabachnick, & Fidell, 2013). The infants treated with clonidine and phenobarbital were selected because there were ample infants in both the treated and non-treated groups for comparison. The trajectory of the mean total Finnegan scores and the relationship between the medication groups (infants treated and non-treated with clonidine and phenobarbital) were reported in run charts using excel.

Demographics of the Sample

The partial medical records of 208 infants diagnosed with NAS who had documented modified-FNAST scores, hospitalized in the NICU at JHACH between January 1, 2010 and May 18, 2018, and met the inclusion criteria without any evidence of exclusionary criteria comprised the convenience sample. To meet the inclusion criteria, the infants must have been born to an opiate-dependent mother, admitted to the NICU with a primary diagnosis of NAS (between the date of birth and day 3 of life), and required pharmacological treatment. Infants diagnosed with

NAS who had life threatening conditions in which NAS was a secondary diagnosis, or were discharged from other inpatient units, or premature (less than 37 weeks) were excluded from the study.

Infant Demographics. The de-identified demographic data on the infants in the study sample extracted from the electronic medical record (EMR) are described below in Table 3 (including birth weight, gestational age, gender, day of life admitted to the NICU, summary of the drugs used to treat the infants drug withdrawal, and the results of the urine and meconium drug screen results when performed). The infants in the sample were all born at outlying hospitals and transported to the study site hospital (a 97 bed level 4 NICU located within a free standing children's hospital in south west, Florida). The infants were admitted to the NICU between days 1-3, with a median admission date of 1.12 days. The gestational ages of the infants ranged from 37 to 42 weeks with a mean gestational age of 38.91 weeks and a standard deviation (SD) of 1.133 weeks. The infants birth weights ranged from 1.99 – 5.09 kg, SD = 0.479 kg. Methadone (*n* = 138, 66.7%) was the most common drug reported positive on the infant urine drug screen followed by morphine (*n* = 59, 28.5%) (likely due to the timing of the drug screen after the infant was already started on treatment for NAS), benzodiazepines (*n* = 23, 11.1%), oxycodone (*n* = 12, 5.8%), and other drugs (*n* = 97, 46.9%) (including opiates, THC, amphetamine, temazepam, oxazepam, and alprazolam). Only 9 (4.3%) infants did not have a urine drug screen result documented in the EMR. In contrast, only two (1%) of the infants in the sample had a meconium drug screen result documented and both were positive for methadone. The four most common drugs used to treat the infants for NAS were consistent with the JHACH weaning protocol and included, morphine (*n* = 205, 99.0%), phenobarbital (*n* =137, 66.2%),

clonidine (*n* = 52, 25.1%), and buprenorphine (*n* = 4, 1.9%). No infants were treated with methadone.

Table 3. Demographics: Infants

Characteristic	(*n*=207)
Birth weight; range, mean, (SD)	1.99-5.09 kg, 3.067 kg (0.479)
Gestational age; range, mean (SD)	37-42 weeks, 38.91 weeks (1.133)
Gender *n* (%):	
Male	100 (48.3%)
Female	107 (51.7%)
Day of life admitted to the NICU range in days, mean in days	1-3 (1.12)
Drugs used to treat NAS *n* (%)	
Morphine	205 (99.0%)
Buprenorphine	4 (1.9%)
Clonidine	52 (25.1%)
Phenobarbital	137 (66.2%)
Methadone	0 (0%)
Urine drug screen result	
None	19 (9.2%)
Methadone	138 (66.7%)
Morphine	59 (28.5%)
Marijuana	3 (1.4%)
Cocaine	11(5.3%)
Oxycodone	12 (5.8%)
Hydromorphone	5 (2.4%)
Methamphetamine	7 (3.4%)
Benzodiazepine	23 (11.1%)
Barbiturates	2 (1.0%)
Other (opiates, thc, amphetamine, temazepam, oxazepam, and alprazolam)	97 (46.9%)
Unknown/Not Reported	9 (4.3%)
Meconium drug screen	
Methadone	2 (1%)
Unknown/Not Reported	204 (98.6%)

Note: Exclude listwise was executed in SPSS to run the analyses.

Maternal Demographics. The mothers were inpatients of the referral hospital, and consequently were not hospitalized at the same institution as the infant. The de-identified demographic data on the mothers were obtained from the documentation in the medical NICU admission, discharge, or social work notes, sections of infant's EMR are described in Table 4 (including age, race, ethnicity, highest education level achieved, significant mental health and

trauma history, significant drug history, and urine drug screen results when performed). Most of the mothers (*n* = 182) self-reported that they were in a drug treatment program and were treated with opioid replacement therapy over the course of the pregnancy including, 174 (84.1%) treated with methadone, and 8 (3.9%) treated with buprenorphine respectively. The maternal urine drug screen results revealed 92 (44.4%) of the mothers were positive for methadone. Other drugs reported as positive on the urine drug screens of the mothers in the sample included, 13 (6.3%) marijuana, 19 (9.2%) oxycodone, 35 (16.9 %) benzodiazepines, and 35 positive for other illicit drugs including (opioids, amphetamines, clonazepam, dilaudid, and THC), No urine drug screen results were reported for 37.2% of the mothers (*n* =77). Smoking was self-reported by (*n* = 157, 75.8%) of the mothers. Of the mothers who reported smoking, 17 (8.2%) reported smoking 1-5 cigarettes per day, 64 (30.9%) reported smoking 6-10 cigarettes per day, 8 (3.9%) reported smoking 11-15 cigarettes per day, 30 (14.5%) reported smoking 16-20 cigarettes per day, and 3 (1.4%) reported smoking greater than 2 packs per day.

The ages of the mothers ranged from 18-47 years. Several maternal characteristics were not documented in the EMR for most of women including maternal race (unknown *n* = 202, 97.6%), ethnicity (unknown *n* = 202, 97.6%), and highest education level (unknown *n* = 206, 100%) respectively. The mothers self-reported multiple common mental health conditions including anxiety (*n* = 58, 28%), and depression (*n* = 65, 31.4%). The mental health history for 83 (40.1%) of the mothers was unknown. Other mental health or trauma related histories were reported in the mothers (*n* = 89, 43%) including, post-traumatic stress syndrome, rape, domestic violence, motor vehicle accidents (MVA), death of a child, incarceration, HIV, suicide attempt, panic disorder, baker acted, and bi polar disorder.

Table 4. Demographics: Mothers

Characteristic	
Age in years, range, mean)	18-47, 28.45
Race *n* (%):	
American Indian or Alaska Native	
Asian	1 (0.5%)
Black or African American	
Native Hawaiian or Other Pacific Islander	
White	3 (1.4%)
Other	
Unknown/Not Reported	202 (97.6%)
Ethnicity *n* (%):	
Hispanic or Latino	
Not Hispanic or Latino	4 (1.9%)
Unknown/Not Reported	202 (97.6%)
Highest level of education achieved, mean (SD)	
Unknown/Not Reported	206 (100%)
Mental health, trauma history, mean (SD)	
None	1(0.5%)
Anxiety	58 (28%)
Depression	65 (31.4%)
Post-Traumatic Stress Syndrome	5 (2.4%)
History of Physical Abuse	1 (0.5)
Other	89 (43%), (Included Reports of: MVA, Domestic Violence, Incarceration, Rape, HIV, Suicide Attempt, Panic Disorder, Baker Acted, and Bipolar Disorder)
Unknown/Not Reported	83 (40.1%)
Maternal self-reported drug history	
None	3 (1.4%
Methadone	174 (84.1%)
Morphine	5 (2.4 %)
Buprenorphine	8 (3.9%)
Heroin	4 (1.9%)
Xanax	22 (10.6%)
Marijuana	24 (11.6%)
Cocaine	18 (8.7%)
Roxycodone	13 (6.3%)
Oxycodone	37 (17.9%)
Hydrocodone	4 (1.9%)
Tylenol #3	1 (0.5%)
Valium	7 (3.4%)
Hydromorphone	11 (5.3%)
Zoloft	4 (1.9%)
Tramadol	2 (1.1%)
Demerol	2 (1%)
Alcohol	20 (9.7%)
Benzodiazepine	7 (3.4%)

Table 4. Demographics: Mothers Continued

Other	63 (30.4%) (Included Reports of: illicit opioids, recreational drug use, Abilify, Seroquel, Flexeril, Lamictal, Tegretal, Chewing Tobacco, Citalopram, Amitriptyline, Clonazepam, Crack, Dilaudid, Cymbalta, Floracet, Lexapro, THC, Lortab, Nicoderm Patch, Percocet, Prozac, Soma, Temazepam, Tylenol, Vicoden, Wellbutrin, Zofran, Phenergan, and Zolpidem)
Unknown/Not Reported	2 (1%)
Maternal urine drug screen result	
None	9 (4.3%)
Methadone	92 (44.4%)
Xanax	3 (1.4%)
Marijuana	13 (6.3%)
Cocaine	17 (8.2%)
Roxycodone	1 (0.5%)
Oxycodone	19 (9.2%)
Valium	2 (1.0%)
Hydromorphone	1 (0.5%)
MDMA (ecstasy)	2 (1.0%)
Benzodiazepine	35 (16.9%)
Barbiturates	3 (1.4%)
Other	35 (16.9%) (Included Reports of: Opioids, Amphetamine, Clonazepam, Dilaudid, and THC)
Unknown/Not Reported	77 (37.2%)
Smoking History	
Smoker	157 (75.8%)
Non Smoker	35 (16.9%)
1-5 Cigarettes per day	17 (8.2%)
6-10 Cigarettes per day	64 (30.9%)
11-15 Cigarettes per day	8 (3.9%)
16-20 Cigarettes per day	30 (14.5%)
21-30 Cigarettes per day	0 (0%)
31-40 Cigarettes per day	2 (1.0%)
Greater than 40 Cigarettes per day	3 (1.4%)
Unknown/Not Reported	46 (22.2%)

Note: Exclude listwise was executed in SPSS to run the analyses.

Results of Aim 1

To determine which of the 21 items on the modified-FNAST were most predictive of the need for pharmacological treatment in infants less than and greater than 28 days of life diagnosed with NAS, regression analysis was planned using SPSS version 24. Logistic regression

procedure was attempted with all 21 predictors or independent variables (IV) (which included all *21 item scores on the modified-FNAST* entered at the same time) regressed on the dichotomized dependent variable (DV), *need for pharmacological treatment* (morphine yes/no, buprenorphine yes/no, clonidine yes/no, phenobarbital yes/no).

Preliminary analyses were performed on the 21-items of the modified-FNAST specific variables necessary to perform the exploratory factor analyses (including graphing the variables using histograms and scatterplots) and it was determined there were significant violations to the assumptions of normality, and linearity. Statistical tests to determine normality (including Kolmogorov-Smirnov and Shapiro-Wilk) were performed on each of the 21-item modified-FNAST variables and both tests were noted to be statistically significant ($p < 0.0001$) for each of the variables on day of life (dol) one suggesting that the variables were not normally distributed (see Table 5).

Table 5. *Tests of Normality for Each of the 21-Item Modified-FNAST Variables (DOL 1)*

DOL 1	Kolmogorov-Smirnov			Shapiro-Wilk		
Modified-FNAST Item	Statistic	*df*	Sig.	Statistic	*df*	Sig.
Bowel Movement	.519	207	.000	.214	207	.000
Convulsion	.523	207	.000	.043	207	.000
Crying	.432	207	.000	.547	207	.000
Excoriation	.532	207	.000	.111	207	.000
Feeding	.435	207	.000	.565	207	.000
Moro	.450	207	.000	.474	207	.000
Mottling	.482	207	.000	.435	207	.000
Muscle Tone	.412	207	.000	.625	207	.000
Nasal Flaring	.535	207	.000	.136	207	.000
Nasal Stuffiness	.510	207	.000	.269	207	.000

Table 5. *Tests of Normality for Each of the 21-Item Modified-FNAST Variables (DOL 1)Continued*

Respirations	.486	207	.000	.355	207	.000
Sleep	.398	207	.000	.580	207	.000
Sneeze	.485	207	.000	.384	207	.000
Suck	.468	207	.000	.450	207	.000
Sweat	.515	207	.000	.234	207	.000
Temperature	.481	207	.000	.398	207	.000
Tremors Disturbed	.390	207	.000	.682	207	.000
Tremors Undisturbed	.451	207	.000	.480	207	.000
Vomiting	.535	207	.000	.168	207	.000
Yawning	.523	207	.000	.043	207	.000

Note: DOL= day of life; Sig = .000 = $p < .0001$; and *df* = degrees of freedom.

This same pattern of non-normality was also observed on dol 3, 7, and then weekly until discharge. In addition, the correlation matrix generated from the data was examined and it revealed violations to the assumption of multicollinearity, and singularity. The correlation matrix revealed many correlations between the different variables below 0.3, and multiple correlations greater than 0.7, with some as high as 0.995 (with exclude listwise executed) and as high as 1 (pairwise executed). As a result, the relationships between the 21 items of the modified-FNAST, and the need for pharmacological treatment could not be further analyzed.

Results of Aims 2 and 3

To explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants less than and greater than 28 days of life, diagnosed with NAS and experiencing acute drug withdrawal, multiple exploratory factor analyses (EFA) were attempted using SPSS version 24. Multiple EFAs were attempted to examine the data sets

(on day of life 1, 3, 7, and weekly) from a sample of infants who were admitted to the JHACH NICU between January 1, 2010 to May 18, 2018 with a diagnosis of NAS requiring pharmacological treatment, and were scored on the 21 items from the modified- FNAST to assess the severity of their drug withdrawal. The 21 items included the following signs of acute drug withdrawal (Finnegan & Kaltenbach, 1992).

1. Cry: Excessive high pitched cry, Continuous high pitched cry
2. Sleep: Sleeps < 1 hour after feeding, Sleeps < 2 hours after feeding, Sleeps < 3 hours after feeding
3. Moro reflex: Hyperactive Moro reflex, Markedly hyperactive Moro reflex
4. Tremors: Mild tremors when disturbed, Moderate-severe tremors when disturbed, Mild tremors when undisturbed. Moderate-severe tremors when undisturbed
5. Increased muscle tone
6. Excoriation (chin, knees, elbow, toes, nose)
7. Myoclonic jerks (twitching/jerking of limbs)
8. Generalized convulsions
9. Sweating
10. Hyperthermia: Hyperthermia (37.2-38.3 C), Hyperthermia (>38.4C)
11. Frequent yawning (>3-4 times per scoring interval)
12. Mottling
13. Nasal stuffiness
14. Sneezing (>3-4 times per scoring interval)
15. Nasal flaring
16. Respiratory: Respiratory rate ((>60/min), Respiratory rate (>60/min with retractions)
17. Excessive sucking
18. Poor feeding (infrequent/uncoordinated suck)
19. Regurgitation: Regurgitation ($\geq$2 times during /post feeding); Projectile vomiting
20. Loose stools (curds/seedy appearance)
21. Watery stools (water ring on diaper around stool)

The analysis plan was to include a comparison of the Factor Solutions at multiple critical intervals according to the study aims. To determine how many components (factors) to extract the SPSS output from the 207 infants was to be examined on day 1, 3, 7, and weekly until discharge, Principal Component Analysis (PCA) with and without Oblimin rotation analyses was to be performed. Factor Solutions were then to be evaluated for eigenvalues greater than 1, the largest total variance explained by the solution, and the change in the shape (or elbow) of the

Screeplot. In addition, Parallel Analysis was to be performed as the third method to determine the number of factors to retain. Monte Carlo PCA for Parallel Analysis is performed (by entering the number of variables (21), number of participants in the sample (207), and the number of replications performed (100 specified). The eigenvalues obtained from SPSS analysis were then to be compared to the randomly generated samples from the Monte Carlo PCA Parallel Analysis. Only eigenvalues greater than the criterion values generated from the Parallel Analysis were to be retained as factors. The factor solution which explained the greatest amount of the variance with the least number of factors were to be retained. The decisions regarding how many factors to extract and the most appropriate factor extraction and rotation method to use to generate the final solution was to be determined by running multiple approaches separately and then comparing them. The goal was to obtain a simple solution to provide clear results by maximizing the separation between factors with high loadings and factors with low loadings. The factor loading would be inspected to determine the marker variables indicated by variables with high factor loadings (.8 or greater) on ideally only one factor and close to zero on the rest would be used to label the factor. The factors would be labeled by comparing the item stems of the marker variables to determine what the factor loadings with similar high loadings have in common. The factor solution which is noted to explain the greatest amount of the variance with the least number of factors, and the purest interpretation would be retained.

Determination of Suitability of the Data Sets for Factor Analysis. The specific variables related to the 21 items of modified-FNAST from the data set extracted from the DataLine warehouse were examined and found to have several limitations. Two of the modified-FNAST score items (myoclonic jerks and convulsions) were coded as dichotomized variables (with values of 0 or 1) indicating the absence or presence of the symptom respectively. In order

for SPSS to accurately execute the analyses these items needed to be entered as averaged score values and coded as scale variables which was not done. All other modified-FNAST score items were coded as scale variables, and reflected the mean score for that item over the 24 period. Infants are assessed and scored for severity of drug withdrawal using the 21 item modified-FNAST every 3-4 hours after feeding. Further inspection of the data also revealed that the last 2 items on the modified-FNAST (loose and watery stools) were coded as one variable bowel movement (BM) according to how the instrument appeared on the drop down screen in the EMR when the nurses chart. The specific variables of the modified-FNAST data sets on day of life 1, 3, 7, and weekly were determined to be unsuitable for factor analyses due violations to the assumptions of normality and linearity as described above. Further inspection of the Correlation Matrices produced from the specific data sets revealed most correlation coefficients below 0.3, and multiple correlation coefficients greater than 0.7 and as high as 0.995 between multiple independent variables in addition to the variable compared to itself (expected correlations of 1 which normally occur along the diagonal of the matrix). The sample size was adequate given that there was approximately a 1 to 10 ratio of cases for each item to be factor analyzed (21 items are included in the modified-FNAST X 10 cases per item = a sample size estimate of 210). The actual sample size included (n = 207, with n = 196 remaining in the sample for analysis even when listwise exclusion was executed in SPSS to ensure the stability of the Correlation Matrix). However, no further analysis could be performed due to the unreliable nature of correlation matrix which was generated from the specific required variables in the data set. The correlation matrix must be reliable and stable as it serves as the basis for all subsequent sub analyses necessary to perform an accurate factor analysis (including factor extraction, rotation,

interpretation of factor loadings, and reliability testing). Given that the correlational matrix was not reliable, no further analysis was performed.

Results of Aim 4

It was not possible to make any comparisons of the underlying structures of the interrelationships of the items of the modified-FNAST as determined by a series of exploratory factor analyses (EFA) in infants less than and greater than 28 days of life diagnosed with NAS experiencing acute drug withdrawal because the preliminary tests could not be reliably performed.

Results of Aim 5

The descriptive statistics for the total modified-FNAST scores on day 1, 3, 7, and weekly until discharge for the infants with NAS are reported in Table 6. The total modified-FNAST scores ranged from 0-21 on day 1 of life with a mean of 8.68 and a SD (4.127), and then gradually decreased over the length of the hospitalization until discharge.

Table 6. *Summary of the Descriptive Statistics for the Total Finnegan Scores by DOL (n = 207)*

			Descriptive Statistics			
Total Finnegan Score by DOL,	*n*	Range	Minimum	Maximum	Mean	SD
DOL 1	146	21	0	21	8.68	4.127
DOL 3	202	17	0	17	6.39	3.179
DOL 7	203	12	0	12	4.73	2.280
DOL 14	204	14	0	14	4.10	2.132
DOL 21	205	11	0	11	3.86	2.122
DOL 28	206	10	0	10	3.82	2.061
DOL 35	141	12	0	12	3.68	2.227
DOL 42	91	11	0	11	3.44	2.414
DOL 49	50	8	0	8	3.40	1.829
DOL 56	28	7	0	7	2.82	1.887
DOL 63	16	7	0	7	2.44	2.279
DOL 70	4	6	0	6	4.50	3.000
DOL 77	3	3	2	5	3.00	1.732
DOL 84	2	4	0	4	2.00	2.828
DOL D/C	198	10	0	10	2.38	1.792

Note: DOL=day of life, discharge= D/C

All medications used to treat the infants for NAS and are described in Table 7. Most of the infants received morphine as monotherapy or in combination with phenobarbital or clonidine consistent with the established JHACH NAS weaning protocol. The four most common medications used to treat the infants for NAS in relative rack order included, morphine (99.0%), phenobarbital (66.2%), clonidine (25.1%), and buprenorphine (1.9%).

Table 7. *Summary of the Descriptive Statistics of Medications Used to Treat NAS (n =207)*

	Descriptive Statistics			
Medications	*n* Treated	Percent	*n* Not Treated	Percent
Morphine	205	99.0%	2	1.0%
Buprenorphine	4	1.9%	203	98.1%
Clonidine	52	25.1%	155	74.9%
Phenobarbital	137	66.2%	70	33.8%

The minimum and maximum, and duration of treatment for each of the drugs are described in Table 8.

Table 8.
Summary of the Minimum-Maximum Dose and Treatment Length for the Medications Used to Treat NAS

	Descriptive Statistics n = 207					
Medications	Min Dose	Max Dose	Min Duration of Inpatient Treatment Days	Max Duration of Inpatient Treatment Days	Median Duration of Inpatient Treatment Days	SD Duration of Inpatient Treatment Days
Morphine (mg/kg/day)	0.33	2.170	14.00	81.00	32.00	11.69
Buprenorphine (mcg/kg/day)	7.00	61.30	4.00	30.00	8.00	11.82
Clonidine (mcg/kg/day)	3.97	28.93	16.00	87.00	32.00	14.77
Phenobarbital (mg/kg/day)	3.00	16.00	2.00	84.00	21.50	17.67

Note: Min = minimum; Max = maximum; SD = standard deviation; Exclude listwise was entered in SPSS to run the analyses.

Trajectory of Mean M-FNAST Scores and Medications Used to Treat NAS. The relationship between the medications used to treat the infants for NAS and the longitudinal trajectory of the Finnegan scores were further explored. Descriptive analyses were used to

describe the relationship between the means of the total modified-FNAST scores (on day 1, 3, 7, and then weekly) for two of the medications (clonidine and phenobarbital) used to treat the infants for NAS. The longitudinal trajectory of the mean total Finnegan scores on day of life 1, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, & 84, and the relationship between the treated and non-treated medication groups (including clonidine and phenobarbital) are reported in the run chart below (see Figure 4). These specific variable data were determined to be appropriate for analyses because they were collected as ordinal level, total modified-FNAST scores, and coded as scale variables which were normally distributed.

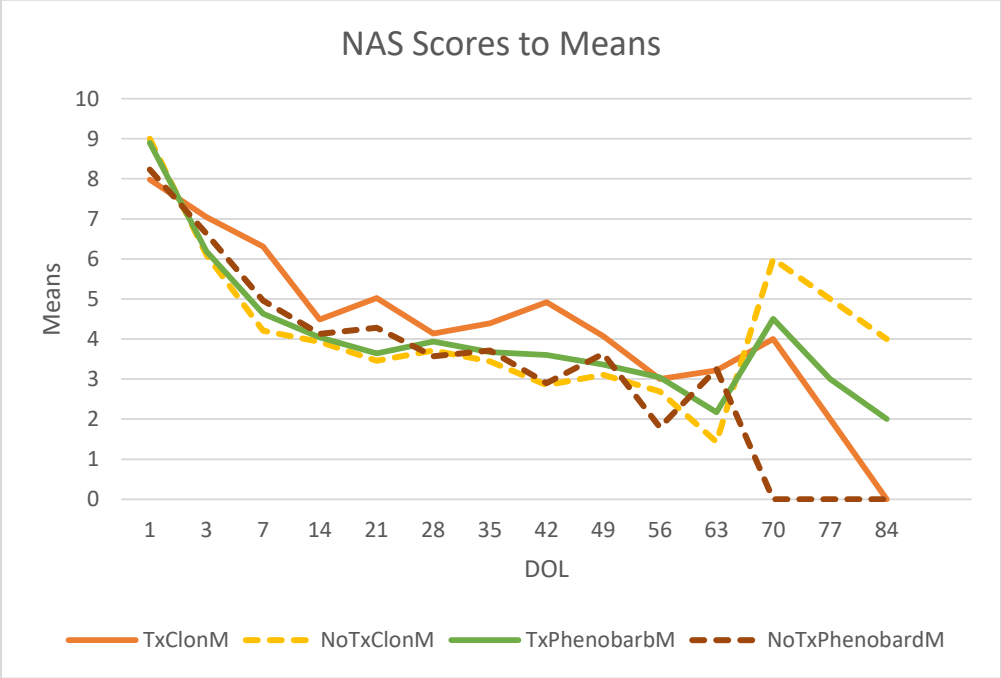

Figure 4. *Trajectory of Mean M-FNAST Scores and Medications Used to Treat NAS*

Mixed Effects Models. We performed a mixed effects models for the repeated measures of the TOTAL Finnegan score. SAS PROC MIXED was used with the total Finnegan score as the Dependent Variable and the two medications (clonidine and phenobarbital) as the primary Independent Variables controlling for infant birthweight, infant gender, estimated number of

cigarettes during pregnancy, infant gestational age (see Tables 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18 below which detail the mixed procedure performed using the SAS System).

Table 9. *Summary of the Mixed Effects Model Information*

Model Information	
Data Set	Work, Transposed
Dependent Variable	Total Finnegan Scores
Covariance Structures	Autoregressive, Variance Components
Subject Effects	ID, ID
Estimate Method	REML
Residual Variance Method	Parameter
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Table 10. *Summary of the Mixed Effects Model Class Level Information*

Class Level Information		
Class	Levels	Values
ID	124	2,3,4,6,7,8,9,11,14,1516,18,19,21,22,25,26,27,29,31,32,33,36,37,38,39,50,51,52,55, 56,58,59,60,62,63,64,66,69,71,72,73,74,76,77,79,80,82,85,88,89,90,92,93,95,96,97, 99,101,104,105,106,108,109, 110, 111, 113, 118, 120, 121, 122, 123, 126, 127, 128, 129, 131, 135, 137, 138, 139, 140, 141, 144, 145, 146, 147, 148, 149, 150, 152, 154, 155, 156, 157, 158, 161, 162, 164, 165, 167, 172, 173, 174, 175, 177, 180, 181, 185, 186, 188, 189, 190, 191, 193, 195, 196, 198, 200, 201, 202, 203, 204, 207
Gender_infant	2	0,1
tx_inf_nas_4	2	0,1
tx_inf_nas_5	2	0,1

Note: Tx = treat; inf = infant; and ID = participant unique identifier number..

Table 11. *Summary of the Mixed Effects Model Dimensions*

Dimensions	
Covariance Parameters	3
Columns in X	15
Columns in Z per Subject	1
Subjects	124
Maximum Observations per Subject	13

Table 12. *Summary of the Number of Observations for the Mixed Effects Model*

Number of Observations	
Number of Observations Read	2898
Number of Observations Used	907
Number of Observations Not Used	1991

Table 13. *Mixed Effects Model Iteration History*

Iteration History			
Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	4543.62193798	
1	2	4543.62253444	0.00000494
2	1	4543.62193801	0.00000000

Note: Convergence criteria met but final hessian is not positive definite.

Table 14. *Mixed Effects Model Covariance Parameter Estimates*

Covariance Parameter Estimates		
Covariance Parameter	Subject	Estimate
Variance	ID	0
AR(1)	ID	0
Residual	ID	8.6427

Note: AR = Auto regressive

Table 15. *Summary of Fit Statistics for Mixed Effects Model*

Fit Statistics	
-2 Res Log Likelihood	4543.6
AIC (Smaller is Better)	4547.6
AICC (Smaller is Better)	4547.6
BIC (Smaller is Better)	4553.3

Note: AIC = Akaike Information Criterion; AICc = Corrected Akaike Information Criterion; and BIC = Bayesian Information Criterion.

Table 16. *Null Model Likelihood Ratio Test for Mixed Effects Model*

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
1	0.00	1

Note: ChiSq = Chi-Square, and DF = degrees of freedom.

Table 17. *Summary of the Solution for the Fixed Effects Model*

Solution for Fixed Effects

Effect	Infant Gender	Tx Clonidine	Tx Phenobarbital	Estimate	SE	DF	*t*-value	Pr > |*t*|
Intercept				6.5199	3.6151	117	1.80	0.0739
Infant Gender	0			-0.09947	0.2038	781	-0.49	0.6257
Infant Gender	1			0	.	.	.	.
Birthweight				0.01880	0.2397	781	0.08	0.9375
Gestational Age				-0.01919	0.09777	781	-0.20	0.8444
Estimated number of cigarettes smoked per day during pregnancy				0.02730	0.07907	781	0.35	0.7300
DAY				-0.01991	0.004721	781	-4.22	<.0001
Tx_inf_nas_4 (Clonidne)		0		-0.8441	0.2847	781	-2.97	0.0031
Tx_inf_nas_4 (Clonidine)		1		0	.	.	.	.
Tx_inf_nas_5 (Phenobarbital)			0	0.1505	0.3712	781	0.41	0.6852
Tx_inf_nas_5 (Phenobarbital)			1	0	.	.	.	.
Tx_inf_na*tx_inf_nas		0	0	-0.2174	0.4663	781	-0.47	0.6412
Tx_inf_na*tx_inf_nas		0	1	0	.	.	.	.
Tx_inf_na*tx_inf_nas		1	0	0	.	.	.	.
Tx_inf_na*tx_inf_nas		1	1	0	.	.	.	.

Note: Tx = treat; inf = infant, DF = degrees of freedom, SE = standard error.

Table 18. *Summary of Type 3 Tests of Fixed Effects*

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F-value	Pr > F
Infant Gender	1	781	0.24	0.6257
Birthweight	1	781	0.01	0.9375
Gestational Age	1	781	0.04	0.8444
Estimated number of cigarettes smoked per day during pregnancy	1	781	0.12	0.7300
DAY	1	781	17.78	<.0001
Tx_inf_nas_4 (Clonidne)	1	781	16.60	<.0001
Tx_inf_nas_5 (Phenobarbital)	1	781	0.03	0.8579
Tx_inf_na*tx_inf_nas	1	781	0.22	0.6412

Tx = treat; inf = infant, Num = Numinator, Den = Denominator, DF = degrees of freedom.

Both the mean effects and the interaction of the two medications were tested. The effect of TIME was also tested by using the DAY variable which is the day a specific total Finnegan score was measured. The Akaike Information Model (AIC) criteria was used for model selection. The Auto Regression Model (AR) (1) correlation structure was used to model the serial correlations among the repeated measures of the total Finnegan scores. The Mixed Effects Model Analysis

revealed that there was an overall decline of total Finnegan scores over time ($p < 0.0001$). The mean total Finnegan scores showed a statistically significant difference in the groups treated and not with clonidine (tx_inf_nas_4) ($p = 0.0031$). The group treated with clonidine had higher mean Finnegan scores. The infants treated and not treated with phenobarbital (tx_inf_nas_5) did not show a significant association with the total Finnegan scores ($p = 0.6852$). All other control variables failed to show significant associations with the repeated measures of total Finnegan scores including gender ($p = 0.6257$), infant birth weight ($p = 0.9375$), gestational age ($p = 0.8444$) and estimated number of cigarettes smoked by the mother during the pregnancy ($p = 0.7300$). The interaction between the two medications (clonidine and phenobarbital) were not statistically significant either ($p = 0.6412$).

Summary

In summary, the chapter provided a detailed review of the study results. The chapter began with a description of the demographics of the study sample including critical characteristics on both the mother and the infants with NAS. In addition, the chapter provided a presentation of the study results with respect to each the five study aims according to the a priori data analyses plan.

CHAPTER FIVE:

DISCUSSION

The final chapter of this dissertation begins with an overview of the study findings. Exploration of how the study findings compare and contrast to the existing published literature will then be discussed. In addition, the limitations of the study will be examined. Finally, the implications for current practice and future research will be considered.

Discussion of Study Findings

It was not possible to determine which of the 21 items on the modified-FNAST were most predictive of the need for pharmacological treatment in infants less than and greater than 28 days of life, diagnosed with NAS, using logistic regression analysis. It was also not possible to explore the interrelationships among the 21 items of the modified-FNAST to determine the underlying structure in infants with NAS less than and greater than 28 days of life experiencing acute drug withdrawal using multiple exploratory factor analyses. As explained previously, the specific variables in the data set related to the 21 items of modified-FNAST were examined and found to have several limitations. Two of the modified-FNAST score items (myoclonic jerks and convulsions) were found to have been coded as dichotomized variables (with values of 0 or 1) indicating the absence or presence of the symptom respectively. In order for SPSS to accurately execute the analyses these items needed to have been obtained as raw score values and coded as scale variables and this was not done. All other modified-FNAST score items were coded correctly as scale variables, and reflected the mean score for that item over the 24 period (average of all scores documented in the EMR for the 24 hour period for that symptom). Infants

are assessed and scored for severity of drug withdrawal using the 21 item modified-FNAST every 3-4 hours after feeding. Further inspection of the data also revealed that the last 2 items on the modified-FNAST (loose and watery stools) were coded as one variable bowel movement (BM) according to how the instrument appears on the drop down screen in the EMR when the nurses document. The specific variables of the modified-FNAST data sets on day of life 1, 3, 7, and weekly were determined to be unsuitable for factor analyses. The data were not all ordinal level data approximating interval level data, and therefore were not normally distributed. This was evident from inspecting the Correlation Matrices which were produced from the data sets that revealed correlation coefficients as high as 0.995 between multiple independent variables in addition to the variable compared to itself (suggesting evidence of multicollinarity). The sample size was adequate given that there was approximately a 1 to 10 ratio of cases for each item to be factor analyzed (21 items are included in the modified-FNAST X 10 cases per item = a sample size estimate of 210). The actual sample size included 208 infants and 196 remained in the sample for analysis even after listwise exclusion was executed in SPSS (to ensure the stability of the Correlation Matrix). However, no further analysis could be performed due to the unreliable nature of correlation matrix which was generated from the specific required variables in the data set. The correlation matrix must be reliable and stable as it serves as the basis for all subsequent sub analyses necessary to perform an accurate factor analysis (including factor extraction, rotation, interpretation of factor loadings, and reliability testing). Given that the correlational matrix was not reliable, no further analysis was performed.

The relationship between the means of the total Finnegan scores (on day 1, 3, 7, and then weekly until discharge) and the medications used to treat the infants in the sample were explored using descriptive statistics. The results of the study revealed that the total modified-FNAST

scores ranged from 0-21 on day 1 of life with a mean of 8.68 and a SD (4.127), and then gradually decreased over the length of the hospitalization until discharge. Four medications were used to treat the infants for NAS. The medication used to treat the infants for NAS included morphine (99%), phenobarbital (66.2%), clonidine (25.1%), and buprenorphine (1.9%). The minimum to maximum dosage and minimum and maximum duration of inpatient treatment days for each of the medications were examined and revealed, morphine (dosage range, 0.33-2.170 mg/kg/day and duration of 14-81 days), buprenorphine (dosage range 7.00-61.30 mcg/kg/day and duration of 4.00-30.00 days), clonidine (dosage range 3.97-28.93 mcg/kg/day and duration of 16.00-87.00 days), and phenobarbital (dosage range 3.00-16 mg/kg/day and duration of 2.00-84.00 days). Most of the infants received morphine alone or in combination with phenobarbital or clonidine consistent with the established evidence-based JHACH NAS weaning protocol. The medications used to treat the infants with NAS in this study sample were consistent with the 2012 AAP guidelines which recommend that pharmacological management of infants with NAS due to prenatal exposure to an opioid include treatment with an opiate derivative (Hudak & Tan, 2012). According to the 2012 AAP recommendations, morphine and methadone are considered first line therapy, while phenobarbital and clonidine are considered adjunctive therapies for NAS infants with persisting signs despite treatment with an opiate derivative (Hudak & Tan, 2012).

The trajectory of the modified-FNAST scores and the medications used to treat the infants were consistent with the JHACH NAS established weaning protocol. According to the established JHACH protocol for weaning NAS infants greater than 35 weeks gestation, all infant admitted to the NICU with a diagnosis of NAS are treated with non-pharmacological interventions first. Infants are started on pharmacological treatment with oral morphine (0.04 mg/kg/dose every 3 hours with feedings) if their modified-FNAST scores are greater than 8

times two consecutive scores or greater than 12 at any time despite non pharmacological interventions. If the infant scores remain elevated (greater than 8 times two consecutive scores or greater than 12 times one) the dose of oral morphine is increased to a maximum dose of (0.08 mg/kg/dose every 3 hours with feedings). If the infant continues to demonstrate elevated scores (greater than 8 times two consecutive scores) on the maximum dose of morphine the infant may be started on oral clonidine (1 mcg/kg/dose every 6 hours) provided there are no contraindications. The dose of clonidine can be gradually increased to maximum dose of (2 mcg/kg/dose every 3 hours). If the infant continues to evidence persisting elevated modified-FNAST scores (greater than 8 times two consecutive scores) on maximum doses of morphine and clonidine, the infant may be treated with a loading dose of oral phenobarbital (20mg/kg/dose), followed 12 hours later by maintenance phenobarbital at a dose of (5 mg/kg/day divided every 12 hours). Phenobarbital may be increased by 0.5 mg/kg/dose (1mg/kg/day) for continued elevated scores (greater than 8 times two consecutive scores). Once the infant is stabilized with modified-FNAST scores less than six the infant is gradually weaned off pharmacological management according to the protocol. Morphine is weaned first, followed by clonidine, and then phenobarbital. Infants must be weaned completely off morphine and clonidine prior to discharge. However, infants may be discharged home on phenobarbital with continued weaning by protocol out patient at the pediatrician office based on scores.

A repeated measures Mixed Effect Model was used to compare the mean Finnegan scores between the different medication groups (clonidine and phenobarbital) (Tabachnick, & Fidell, 2013). The results revealed that treatment with clonidine vs. no treatment with clonidine was significantly correlated with higher total modified-FNAST scores over time. Treatment with phenobarbital vs. no treatment with phenobarbital was not significantly associated with higher

modified-FNAST scores. Infants who required treatment with clonidine in addition to morphine probably were experiencing more severe and persisting generalized autonomic related symptoms of acute drug withdrawal and potentially from a combination of both narcotic and nonnarcotic drugs. Phenobarbital was not significantly associated with higher modified-FNAST scores possibly because the symptoms infants in this group were experiencing were more easily controlled with phenobarbital and a greater number of infants were treated with phenobarbital when compared to clonidine. Phenobarbital has been shown to be effective for controlling drug withdrawal symptoms from narcotics related to irritability, hyper excitability, and seizures (Gomella, Cunningham, & Eyal, 2013). It is not effective in controlling gastrointestinal symptoms of drug withdrawal related to nonnarcotic agents (Gomella, Cunningham, & Eyal, 2013). All other controlled variables (including gender, birth weight, gestational age, and estimated number of cigarettes smoked per day by the mother) were not significantly associated with increased total modified-FNAST scores.

The traditional score based care model utilized at the study site is consistent with a recent national survey of management strategies used in the care of infants with NAS in US NICUs (response rate of 47%). According to the survey, the Finnegan or modified-FNAST were the most commonly used instruments to measure the severity of withdrawal across United States (US) NICUs (65-95.5%) (Mehta, Forbes, & Kuppala, 2013). In addition, the survey revealed that 95% of NICUs offered some aspect of non-pharmacological interventions, 26% relied primarily on non-pharmacological interventions, and 54.1% utilized a combination of pharmacological and non-pharmacological interventions (Mehta, Forbes, & Kuppala, 2013).

This traditional score-based model of care which includes hospitalization in the NICU and treatment based primarily on modified-FNAST scores is commonly used among US

hospitals (Marcellus, 2018; Wachman, et al., 2018). Concerns related to the complexity of scoring the instruments, training and maintaining staff reliability in scoring using an instrument, variability of scores related to subjectivity in scoring, and lack of reliability in scoring among staff have been reported (D'Apolito, & Finnegan, 2010; Timpson, Killoran, Maranda, Picarillo, & Bloch-Salsbury, 2018).The traditional approach to treating infants with NAS was originally described by Finnegan, et. al. (1975). Consistent with this model of care, infants with NAS are assessed after every feeding every 3-4 hours using a valid and reliable abstinence scoring instrument. According to the AAP 2012 guidelines, nonpharmacological interventions are implemented first, however, if the modified-FNAST scores remain elevated the infants are started on pharmacological treatment according to an established NAS weaning protocol (Hudak & Tan, 2012). This traditional model of care for infants with NAS and treatment approach based primarily on Finnegan scores has recently been questioned. The traditional model has been recently challenged because treatment decisions based primarily on total modified-FNAST scores may have the potential to result in overtreatment (including unnecessary or extended hospitalization in the NICU and or pharmacological treatment), escalating costs, and unnecessarily separating mother-infant dyads which can result in impairment in mother infant bonding (Marcellus, 2018; Wachman, et al., 2018).

In contrast to the traditional score based model, Grossman, et al. (2017) proposed the Eat, Sleep, and Console (ESC) functional infant model (as part of a quality improvement initiative) as a basis for making treatment decisions for infants with NAS. Family centered care and nonpharmacological interventions are implemented first. Nonpharmacological interventions include promoting breastfeeding, maternal rooming in, skin-to-skin, and reduction of environmental stimuli have empirical evidence to support reductions in modified-FNAST scores,

length of stay, and reduction in medication treatment dose and duration in infants with NAS (Edwards and Brown, 2016; Green & Goodman, 2003; Hodgson & Abrahams, 2012; Marcellus, 2007; Newman et al., 2015; Pritham, 2013; Ryan, Dooley, Finn, & Kelly, 2018; Velez & Jansson, 2008). Infants with NAS who are unable to perform essential functions characteristic of a healthy newborn (eat a minimum of at least 1 ounce per feeding or breastfeed, sleep greater than or equal to one hour, and be consoled within 10 minutes from a cry state) after maximizing the implementation of nonpharmacological interventions are considered for treatment with as needed doses of medication (Grossman, et al., 2018). The ESC instrument was developed to assess the functional status of the infant and reduce the potential for over treatment of infant drug withdrawal based solely on the total infant withdrawal score. Infants with NAS who are eating, sleeping, and easily consoled are considered to be stable. Infants with NAS who are unable to maintain their functional status according to the established criteria are provided additional support with nonpharmacological treatment. If nonpharmacological treatment alone is no longer sufficient in allowing the infant to maintain a reasonable functional status, the infant is treated with a dose of 0.05mg/kg of oral morphine and then reassessed (Grossman, et al., 2018). Grossman, et al. (2017) conducted a retrospective chart review to compare the treatment decisions of 50 infants with NAS who were clinically assessed using the ESC approach. The findings suggest that using the ESC criteria resulted in only 6 (12%) of the infants requiring treatment with morphine compared to 31 infants (62%) predicted to require treatment using the Finnegan Neonatal Abstinence Scoring System (which was statistically significant, $p < .001$). In addition, the overall average length of stay was reduced to 5.9 days compared to an estimated 10 days longer if the infants were managed using the traditional score based approach, and the average length of stay was also reduced in the infants who required treatment with morphine to

control withdrawal symptoms from 16.9 to 12.3 days (Grossman, et al., 2018). There were no reported adverse events (such as seizures or failure to thrive) or readmissions during the study period (Grossman, et al., 2018).

The findings from this retrospective chart review revealed that mothers in this sample had experienced mental health related problems (including anxiety, depression, panic and bipolar disorders) and trauma related events (including domestic violence, rape, baker acted, suicide attempt, and incarceration). This is consistent with the literature which suggests that advocacy, respectful, non-judgmental, harms reduction, and trauma-informed care models need to be integrated in any model of care for this high-risk population of mother-infant dyads to provide a safe, therapeutic environment to reduce unnecessary stress and anxiety for women who have experienced or are at risk for facing trauma (Marcellus, 2014; Marcellus, 2018). Comprehensive care models that ensure collaboration between psych-mental health professionals, addiction specialists, obstetricians, neonatologists, nursing, lactation, social work, drug court and child protective services are also recommended to prepare the mother to safely care for her infant, and link her with essential community resources (access and transportation to access prenatal, safe housing, and job skills) in order to promote the long term recovery of the mother and improve the neurodevelopmental outcomes for the infant (O'Connor et al., 2013).

Future studies need to examine the modified-FNAST to determine if further modification will be necessary to ensure the validity and reliability of the drug withdrawal severity scores generated in critical subpopulations of infants with NAS for whom there are no valid and reliable instruments including preterm infants and infants greater than 28 days of life.

Limitations

This was a retrospective study designed to analyze existing hospital data collected from January 1, 2010 to May 18, 2018. As a result the study is subject to many possible biases and threats to the internal and statistical conclusion validity. Other risk factors or confounding variables may have been present that were not measured. The accuracy of the data is only as reliable as what was documented in the electronic medical record, which may lead to ascertainment bias and/or missed cases. The data were collected over an 8 year time period in which maternal drug dependence patterns, and NAS weaning protocols have changed which were not accounted for.

Multiple variables related to maternal demographics (including race, ethnicity, highest level of education achieved) could not be reported for most of the women because they were not documented in the EMR as part of the NICU medical admission or discharge notes, and the mothers were not inpatients of the study hospital. This posed limitations on the description of the demographics of the sample of mothers. In addition, although the study team members who completed the data extraction from the EMR were trained, monitored, and used standardized abstraction forms (based on the a priori coding rules and definitions), they were not blinded to the hypotheses being tested which may have introduced bias. The study population included infants with NAS from a single study site which may also pose limitations to the generalizability of the study findings.

Implications for Clinical Practice and Future Research

The traditional model of care for infants with NAS utilizing primarily an abstinence score based approach may need to be re-examined in light of the promising clinical outcome results (reduction in need for pharmacological treatment and reduced length of hospital stay) reported in

recent quality improvement initiatives utilizing functional assessment based approach (ESC approach) (Grossman, et al., 2018). Respectful, non-judgmental, harms reduction, and trauma based care models need to be considered and empirically tested. Finally, care models that ensure collaboration between psych-mental health professionals, addiction specialists, obstetricians, neonatologists, lactation specialists (to support breastfeeding), nursing (to provide maternal education regarding infant care), social work, child protective services, and community services (access to medical and dental care, housing, and job training) are also recommended to break the cycle of addiction and promote long term recovery in the mother (O'Connor et al., 2013). Combined inpatient and outpatient weaning programs such as the Managing Abstinence in Newborns (MAiN) program for carefully selected mother-infant dyads need to be further developed and tested (Summey, et al., 2018). These different models of care and assessment approaches need to be tested using large scale randomized controlled trials to determine which approach or combination are most efficacious, cost effective, support the mother in her recovery, treat the infant for NAS, and are shown to improve the long-term neurodevelopmental outcomes for this high-risk population of infants. In addition, large scaled randomized controlled trials are necessary to determine which opioid derivatives are the most safe and efficacious and are shown to have best neurodevelopmental outcomes. Commonly prescribed opioids (including methadone, morphine, buprenorphine, alone and in combination with phenobarbital and clonidine) need to be tested side by side in multiple arms of randomized controlled trials to provide reproducible empirical evidence, potentially leading to the development of standardized national medication treatment protocols for this high-risk population of NAS infants. Infants with NAS who have been exposed prenatally to opioids and benzodiazepines must be included in these studies as this sub-population of high-risk infants has historically been excluded from

previous drug studies and represents an increasing number of infants. The modified-FNAST needs to undergo additional psychometric testing and potentially modification to ensure the validity and reliability of the drug withdrawal severity scores generated in critical subpopulations of infants with NAS for whom there are no valid and reliable instruments including preterm infants and infants greater than 28 days of life.

Summary

The final chapter of this dissertation provided an overview of the important study findings. In addition, an exploration of how the study findings from this retrospective chart review validated or conflicted with the existing published literature was discussed. The limitations of the study were presented and implications for current practice and future research were explored.

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APPENDIX A:

SYNTHESIS TABLE

Synthesis of the Empirical Referents & Evidence on the Care and Treatment of Infants with NAS

Screening and Measurement Instruments for Infants at Risk for NAS		
Author, year, and location	Design, sample size, purpose, and instruments	Findings and limitations of the study
Murphy-Oikonen, et al., 2010 Canada	Retrospective chart review; *n* = 21 pre implementation of the protocol compared to *n* = 70 in the post group *Purpose:* To determine if the use of standardized screening protocol (combining maternal self-report, with mother and infant urine and meconium drug testing) could accurately detect infants at risk for NAS. *Instruments:* Modified- Finnegan Neonatal Abstinence Scale Tool (M-FNAST)	*Findings:* The use of the protocol resulted in 29% more infants being identified with NAS. There were discrepancies between the maternal self-report and the urine and meconium drug screen results. Urine drug screen results available within 24-72 hours. Meconium drug screen results took longer to get back, but more accurately reflected drug use over the course of the pregnancy. Therefore the authors recommended using all three methods to improve screening accuracy. *Limitations:* This study was a retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete.
Finnegan, et al., 1975 United States	Psychometric Testing; *n* = 37 term and near term infants born to drug dependent mothers in Philadelphia were assessed using the instrument. *Purpose:* To assess the validity of the inferences of the scores using the Finnegan to assess the severity of drug withdrawal in infants with NAS. *Instruments:* Finnegan Neonatal Abstinence Scoring Tool (FNAST)	*Findings:* NAS infants with score ranges up to 7 were provided with non-pharmacological measures. Score values above 8 were determined to be pathological, requiring treatment with phenobarbital or paregoric. A significant reduction in the treatment time was noted for exposed infants treated based on the scores generated from the instrument compared to infants assessed without an instrument (current standard of care). The study provided the initial evidence to support face validity, and construct validity of the original Finnegan instrument to assess the severity of drug withdrawal in infants with NAS. *Limitations:* Only 37 infants with NAS were included in the sample which poses a limitation to the study findings.
Zimmermann-Baer, et al., 2010 United States	Psychometric testing; *n* = 102 healthy newborns greater than 34 weeks gestation whose mothers denied illicit drug use during the pregnancy. Meconium and urine testing was done on the infants scoring	*Findings:* The investigators reported that for the first 3 days of life the median M-FNAST scores remained stable at 2, but the variability increased with 95th percentile rising from 5.5 on day 1 to 7 on day 2. At weeks 5-6 median values were higher

	high and confirmed that they did not have any prenatal drug exposure. *Purpose:* To assess the variability of the scores in healthy newborns not exposed to illicit drugs. To assess the divergent validity of the Finnegan Score. *Instruments:* Modified- Finnegan Neonatal Abstinence Scale Tool (M-FNAST)	during the daytime (50^{th} percentile = 5, and 95^{th} percentile = 8). Healthy infants never exceeded a score of 8. The score in healthy newborns increases with age related to brain maturation and circadian rhythms. Values above 8 are pathological, requiring treatment for NAS. Provided evidence for the divergent validity of the Finnegan in healthy newborn infants. *Limitations*: Different nurses scored the infants at the two points in time and the parents also assigned infant drug withdrawal scores at weeks 5 or 6. Drugs screens were only analyzed on the infants with elevated scores.
D'Apolito & Finnegan, 2010 United States	An Inter-Observer Reliability Program for Scoring the M-FNAST; *Purpose:* An Inter-Observer Reliability Program for Scoring the M-FNAST. The educational program is available on CD. The program provides didactic on NAS, pharmacological and non-pharmacological interventions used to treat infants with NAS. The program also provides an overview of the M-FNAST. The definitions for scoring are reviewed and then the learner is guided through a videotaped example of an NAS infant being scored using the instrument. Then the participant is asked to score another NAS infant video and achieve 90% reliability with the instructor. *Instruments:* 90% reliability scoring the M-FNAST to achieve inter-observer reliability.	*Findings:* Provided a program for nurses to achieve reliability in scoring the M-FAST. The program is targeted for use in NICU's, Mother-Baby Units, and Newborn Nursery to improve the accuracy of the nurses scoring the degree of withdrawal in NAS infants using the M-FNAST. *Limitations:* The medication dosing protocol presented in the program is no longer current, as many centers are now using buprenorphine and clonidine in addition to morphine and phenobarbital.
Maguire, et al., 2013 United States	Retrospective chart review; 33 856 M-FNAST assessments obtained from the electronic medical records of N = 171 infants admitted to an NICU were analyzed. *Purpose:* To complete a factor analysis of the M-FNAST instrument to provide additional psychometric testing to support the validity of the inferences of the accuracy of this instrument to assess the degree of withdrawal in NAS infants hospitalized in an NICU. *Instruments:* Principle axis factoring (PAF) extraction with Varimax rotation was performed on 33 856 M-FNAST assessments obtained from the electronic medical records of 171	*Findings:* Provided further evidence for the construct validity of the M-FNAST scores to assess the severity of drug withdrawal of NAS infants 0-28 days of life. The finding also suggested that the 2-factor solution explained 23.74% of the total variance. Mild/early (crying, duration of sleep, increased muscle tone), and moderate/advanced signs (tremors, respiratory rate, sweating and excessive sucking). The 2-factor solution short form FNAST was significantly correlated with the total score on the M-FNAST. *Limitations:* The short form has not been tested clinically. May not accurately assess the severity of acute drug withdrawal in NAS infants with rapidly escalating symptoms due to the limited number of items.

	infants admitted to an NICU were analyzed.	
Grossman, et al., 2018 United States	Retrospective chart review; *Purpose:* Compared treatment decisions of *n* = 50 consecutive opioid exposed infants assessed using the Eat, Sleep, Console (ESC) approach vs. modified FNAST to determine how many infants met the criteria and were treated with morphine.	*Findings:* Use of the ESC method resulted in only 6 infants (12%) requiring treatment with morphine (as needed) compared to 31 (62%) who would have met the treatment criteria if the modified-FNAST would have been used (prior clinical practice) The infants assessed using the ESC criteria were hospitalized less days and there were no readmissions or adverse events reported. *Limitations:* This study was a retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete.

Pharmacological Treatment of NAS

Author, year, and location	Design, sample size, purpose, and instruments	Findings and limitations of the study
Osborn, et al., 2010a Australia	Meta-Analysis; *n* = 9 studies (randomized and quasi-randomized trials). N = 645 infants met the inclusion criteria. Included trials with opiates vs placebo or no treatment, comparisons of opioid drugs used to treat this population, opioids vs sedatives (clonidine, a benzodiazepine, barbiturates, or neuroleptic agents, and opioids vs non-pharmacological interventions. *Purpose:* The purpose of the study was to determine the level and quality of the evidence (from random and quasi-random control trials) that an opiate is more effective than a sedative or non-pharmacologic treatment of clinical significant NAS due to opioid withdrawal. *Instruments:* N/A	*Findings:* Use of opioids (illicit or prescribed as part of a drug treatment program) in pregnant women may result in NAS. An opioid should be used as initial treatment for withdrawal symptoms in infants with NAS exposed to opioids in utero. This review is consistent with the AAP (1998) that NAS should be treated with the same class of drug of exposure in utero. *Limitations:* The results are limited by the relative quality and variability of the methods used in the studies included.
Osborn, et al., 2010b Australia	Meta-Analysis; *n* = 7 studies, *n* = 385 NAS infants *Purpose:* To assess the safety and efficacy of using a sedative compared to a non-opioid control for NAS secondary to withdrawal from opiates, and determine which sedative is the safest and most effective. The meta-analysis included seven trials enrolling infants diagnosed with NAS who were born to opioid dependent mothers with > 80% follow-up and using quasi-	*Findings:* The use of opioids by pregnant women may result in withdrawal symptoms in their newborn infants. Infants treated for NAS are at risk for alterations in maternal-infant bonding, difficulties with feeding and sleeping, weight loss, and seizures. Individual studies have reported that phenobarbital compared to supportive care alone reduces the time the infant needs supportive care, and is better compared to diazepam. Phenobarbital is preferred when a sedative is needed to control

	random or random allocation to sedation or control group. Control could include other sedatives or non-pharmacological treatment. *Instruments:* N/A	persisting CNS symptoms in newborns with opioid withdrawal due to in utero exposure to opioids. *Limitations:* The results are limited by the relative quality and variability of the methods used in the studies included.
Brown, et al., 2015 United States	Single site, prospective, double-masked, randomized trial. *n* = 15 were randomized into the methadone group and *n* = 16 were randomized into the morphine group. *Purpose:* The purpose of the study was to test the hypothesis that the length of treatment for NAS in the methadone group would be shorter than the length of treatment required for the morphine group. *Instruments:* Finnegan scores	*Findings:* The results revealed that length of opioid treatment was shorter for the methadone group (median = 14 days) as compared to the morphine group (median = 21days) which was statistically significant (*p* = 0.008). *Limitations:* The sample size was small and limited to one unit.
Davis, et al., 2018 United States	Single site, randomized, double-blind, intention-to-treat trial. *n* = 59 were randomized into the methadone group and *n* = 58 were randomized into the morphine group. *Purpose:* The purpose of the study was to test the hypothesis that the length of hospital stay and length of treatment in the methadone group would be shorter than the length of hospital stay and length of treatment required for the morphine group.	*Findings:* The results revealed that the length of hospital stay was 14% shorter (by 2.7 days) and a 16% reduction in the length of treatment (by 2.3 days) for the methadone group as compared to the morphine group which were both statistically significant *p* = .01, and *p* = .02 respectively. *Limitations:* The sample size was small and limited to one unit.
Kraft et al., 2008 United States	Single site, randomized, phase I, open-label, placebo controlled trial comparing sublingual buprenorphine to oral morphine. Term infants *n* = 26 requiring pharmacological treatment for NAS were randomized *n* = 13 to buprenorphine and *n* = 13 to neonatal opium (NOS) group. *Purpose:* To determine the safety and efficacy of buprenorphine compared to NOS for the treatment of infants with NAS born to mothers with opioid dependence. *Instruments:* Pharmacological treatment for NAS, and length of hospital stay. Withdrawal scores assessed using the MOTHER NAS score.	*Findings:* Buprenorphine administered (at a dose of 13 mcg to 39 mcg/kg/day in three divided doses every 8 hours) sublingually is feasible and safe for the treatment of NAS. The investigators reported that 98% of the plasma concentrations were reported to be undetectable to 0.6 ng/ml, which is less than what is required to treat adults with abstinence syndrome. The mean length of treatment for infants treated with buprenorphine was 22 days compared to 32 days in the infants treated with NOS (standard of care). The mean length of stay for the buprenorphine group was 27 days compared to 38 days in the NOS group. *Limitations:* The small sample size did not provide adequate power to support the study findings reported. Infants with exposure to both opioids and benzodiazepines were excluded from the study.
Kraft et al., 2011 United States	Single site, randomized, phase I, open-label, placebo controlled trial comparing sublingual buprenorphine to oral morphine. Term infants *n* = 24	*Findings:* Buprenorphine administered (at a dose of 15.2 mcg/kg/day to 60 mcg/kg/day in three divided doses every 8 hours) sublingually is feasible and safe for the treatment of NAS. Infants treated with

	requiring pharmacological treatment for NAS were randomized *n* = 12 to buprenorphine and *n* = 12 to neonatal opium (NOS) group. *Purpose:* To determine the safety and efficacy of buprenorphine compared to oral morphine in the treatment of infants with NAS born to mothers with opioid dependence. Dose optimized treatment plan: increasing the initial dose, increasing the rate of dose escalation to control symptoms, and increasing the maximum total dose. *Instruments:* Pharmacological treatment for NAS, and length of hospital stay. Withdrawal scores were assessed using the MOTHER NAS score.	buprenorphine required a 23-day length of treatment compared to 38-days in the morphine treated group (*p*= 0.01) which represented a 40% reduction in the length of treatment. Length of hospital stay was reduced from 42-days in the buprenorphine group to 32-days (*p* = .05), representing a 24% reduction in length of hospital stay. Three infants in the buprenorphine group required phenobarbital, compared to one in the morphine group. *Limitations:* The small sample size did not provide adequate power to support the study findings reported. Infants with exposure to both opioids and benzodiazepines were excluded from the study.
Kraft & van den Anker, 2012 United States	Secondary data analysis, combined the data from two randomized, phase I, open-label, placebo controlled trial comparing sublingual buprenorphine to oral morphine. The sample consisted of *n* = 50 term infants requiring pharmacological treatment for NAS. *Purposes:* To determine the optimal dose of sublingual buprenorphine necessary to treat NAS in infants exposed to opioids in utero. The dose optimized treatment plan consisted of: increasing the initial dose, increasing the rate of dose escalation to control symptoms, and increasing the maximum total dose. *Instruments:* Pharmacological treatment for NAS, and length of hospital stay. Withdrawal scores were assessed using the MOTHER NAS score.	*Findings:* Infants treated with buprenorphine required a mean 23-day length of treatment compared to 34-days in the morphine treated group (*p*= 0.001) representing a 36% reduction in the length of treatment. Length of hospital stay was reduced in the buprenorphine group by 29% (*p* = .006). Six of the 25 infants in the buprenorphine group required phenobarbital, compared to two in the morphine group. *Limitations:* The small sample size did not provide adequate power to support the study findings reported. Infants with exposure to both opioids and benzodiazepines were excluded from the study.

Agthe et al., 2009 United States	Randomized control trial of clonidine compared to placebo as an adjunct to morphine treatment for patients with NAS. The sample consisted of *n* = 40 infants with NAS with in utero exposure to opioids. *Purpose:* The purpose of this study was to determine the effectiveness of clonidine compared to placebo combined with morphine as an adjunct medication on total morphine dose and length of hospital stay in infants with NAS with in utero exposure to opioids. *Instruments:* Pharmacological treatment for NAS (total dose of morphine), and length of hospital stay.	*Findings:* Clonidine was tolerated well without reported significant hypotension or bradycardia in the infants. The morphine/clonidine group had statistically significant shorter lengths of hospital stay of 11 days (95% CI: 8-15) compared to 15 days in the morphine/placebo group (CI: 13-17). The total morphine dose was 7.7 mg with combined morphine/clonidine compared to 19.2 mg morphine/placebo, (*p*=.03). An incidence of SVT was reported in one infant 3 days post discontinuation of the clonidine. Three infants in the clonidine group died with autopsy verified findings of (myocarditis, SIDS, and homicide (methadone overdose). Each of the infant deaths occurred at least 22 days after discontinuation of the study drug and was assessed to be unrelated. The authors concluded that rapid clearance of clonidine by neonates in the first month of life may be causally associated with the infant adverse events reported with the drug in this study. Therefore, they cautioned that dosage and weaning needs further study to better understand the pharmokinetics and long term safety of the drug in this high-risk population of infants. *Limitations:* Small sample size was a limitation in this study.
Surran, B., et al., 2013 United States	Prospective, non-blinded, block randomized trial at a single level III NICU; The sample consisted of *n* = 82 infants > 35 weeks requiring treatment (methadone or morphine for in utero exposure to opioid) were eligible, of which *n* = 68 were randomized into each group. *Purpose:* The purpose of this study was to compare the efficacy of clonidine vs phenobarbital in reducing morphine sulfate treatment days for NAS. *Instruments:* Pharmacological treatment for NAS (total dose of morphine), and length of hospital stay.	*Findings:* Adjusting for covariates phenobarbital as compared with clonidine was shown to have shorter morphine treatment days, with no difference in average morphine dose. Post- discharge phenobarbital was continued for an average of 3.8 months. There were no differences in both groups related to total morphine dose suggesting that both drugs were equally effective in controlling NAS symptoms. Phenobarbital as adjunct therapy had clinically nonsignificant shorter inpatient but significant overall longer therapy time as compared with clonidine. The infants on clonidine had the medication discontinued prior to discharge. These results are significant given the concerns about the long-term outcomes from prolonged phenobarbital exposure on the developing brain. This study provides further support for the use of clonidine as an alternative to phenobarbital. *Limitations:* Included the inability to blind the two groups for the study medications due to different dosing units, intervals, and clinical monitor required.
Burke, & Beckwith, 2017	Retrospective chart review; 36 Infants with NAS (*n* = 17 treated with	*Findings:* Infants treated with morphine were noted to have higher mean scores on the Bayley-III on the Cognitive Composite (91.3 compared to 83 with a *p*

United States	methadone, and *n* = 19 treated with morphine). *Purpose:* The purpose of this study was to compare the neurodevelopmental outcome of infants treated for NAS with methadone compared to morphine. *Instruments:* Bayley Scales of Infant and Toddler Development- Third Edition (Bayley-III) at 3 to 7 days prior to discharge.	= 0.03410), and total Motor Composite (96.3 compared to 89.6 with a *p* = 0.0149) when compared to infants who were treated with morphine monotherapy. Mean age at the time of neurodevelopmental testing was 50 days in the morphine group and 46 days in the methadone group. *Limitations:* This study was a retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete. The small sample size may also be a limitation in this study. The infants were not followed over time.
Gullickson, et al., 2018 Canada	Retrospective chart review; 174 Infants with NAS (*n* = 22 treated with morphine alone, and *n* = 100 treated with morphine combined with clonidine). *Purpose:* The purpose of this study was to determine whether treating infants diagnosed with NAS with clonidine combined with morphine would result in a reduction in the length of treatment compared with morphine alone. *Instruments:* Pharmacological treatment for NAS (maximum dose of morphine), and length of treatment.	*Findings:* Infants treated with a combination of morphine and clonidine were noted to have statistically significant longer lengths of treatment (*p* = 0.004), and higher peak morphine doses (*p* = 0.045) when compared to infants who were treated with morphine monotherapy. *Limitations:* This study was a retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete. The small sample size in the morphine only group may also be a limitation in this study.
Hall, et al., 2015 United States	Retrospective chart review; Infants with NAS (> 35 weeks requiring treatment (methadone or morphine for in utero opioid exposure) who were treated at the 3 sites with existing weaning protocols (controls) *n* = 813 infants (454 before adoption and 359 after). Infants with NAS treated at the 3 sites without prior weaning protocols (treatment) *n* = 168 infants (75 before, and 93 after). *Purpose:* The purpose of this study was to evaluate the generalizability of stringent protocol-driven pharmacological weaning to reduce the total duration of opioid treatment and length of inpatient hospital stay in infants treated for NAS. *Instruments:* Pharmacological treatment for NAS (duration of opioid), and length of hospital stay.	*Findings:* After adoption of the multicenter weaning protocol for infants with NAS, the 3 groups previously without a strict protocol noted a statistically significant reduced duration of opioid treatment length (23 vs 34 days, *p* < .001) and a reduction in hospital length of stay (23.7 vs 31.6 days, *p* < .001). Outcomes were sustained in the 3 hospital groups that previously were following the strict weaning protocol (duration of treatment = 17 days, and length of stay = 23.3 days). Implementation of a standard weaning protocol for infants treated for NAS reduced duration of opioid exposure and length of hospital stay in 6 children's hospitals in Ohio. *Limitations:* Study limited to 6 centers from one Ohio health system which reduces the generalizability of the findings.

Non-Pharmacological Treatment of NAS

Author, year, and location	Design, sample size, purpose, and instruments	Findings and limitations of the study
Frazer, et al., 2007 Australia	Interpretative methods descriptive study; *n* = 8 nurses from four Special Care Nursery Units *Purpose:* The purpose of this study was to explore neonatal nurses' experiences of providing care to drug-exposed newborns and their parents over the duration of hospitalization for NAS. *Instruments:* Group Interviews	*Findings:* Supported the use of cuddlers to provide comfort care to the infants and lessen the workload on the nurses. Five themes emerged from the data: the relationship with the baby; response to the family; tensions within the care environment; nurse's needs; and making a difference. The results of this study indicated that management of these babies and their parents is compromised by a range of attitudinal and organizational factors. The investigators concluded that there is a need to address these barriers in order to optimize patient care delivery, and improve neonatal nurse's impact on promoting parent infant bonding. *Limitations*: Only 8 nurses were included in the sample which poses a limitation to the study findings.
Green, & Goodman, 2003 United States	Case series, descriptive; included studies related to the care of infants with NAS. *Purpose:* Description of the state of the art care for in utero drug-exposed infants. *Instruments:* Descriptive review of empirical evidence on non-pharmacological interventions to support infants with NAS.	*Findings:* The study provided limited empirical evidence for the use of multiple non-pharmacological interventions in the care of infants with NAS. Quiet environment, non-nutritive sucking, vestibular stimulation (gentle vertical rocking), minimal handling was used to provide non-pharmacological support for infants with NAS, and was reported to be beneficial in this descriptive case series. *Limitations:* Descriptive case series study, therefore, the generalizability of the findings are limited.
Marcellus, 2007 United States	Case series, descriptive; included studies related to the care of infants with NAS. *Purpose:* Description of the state of the art care for in utero drug-exposed infants. *Instruments:* Descriptive review of empirical evidence on non-pharmacological interventions to support infants with NAS.	*Findings:* The study provided limited empirical evidence for the use of multiple non-pharmacological interventions in the care of infants with NAS. Holding, swaddling, and minimal stimulation was used to provide non-pharmacological support for infants with NAS, and was reported to be beneficial in this descriptive case series. *Limitations:* Descriptive case series study therefore the generalizability of the findings are limited.
Valez, & Jansson, 2008 United States	Case series, descriptive; included studies related to the care of infants with NAS. *Purpose:* Description of the state of the art care for in utero drug-exposed infants. *Instruments:* Descriptive review of empirical evidence on non-	*Findings:* The study provided limited empirical evidence for the use of multiple non-pharmacological interventions in the care of infants with NAS. Pacifier, quiet or low stimulation environment, positioning supine, slow vertical rocking, gentle pressure to posterior head was used to provide non-pharmacological support for infants with NAS, and was reported to be beneficial in this descriptive case series.

	pharmacological interventions to support infants with NAS.	*Limitations:* Descriptive case series study therefore the generalizability of the findings are limited.
White-Trout et al., 2002 United States	Prospective randomized clinical trial; n = 45 drug exposed infants were enrolled in the treatment group, and n = 72 non-exposed infants in the control group. *Purpose:* The purpose of this study was to compare the responses of non-exposed and drug-exposed newborns to an auditory, tactile, visual, and vestibular (ATVV) intervention. *Instruments:* Infant behavior state (IBS), and pulse rate (PR) were measured.	*Findings:* The investigators reported that the non-exposed and drug-exposed control groups (p = 0.021) differed on the distribution of IBS. However, they found no differences between the two experimental groups. Non-exposed and drug-exposed infants in the treatment group experienced greater alertness and decreased quiet sleep when compared to controls ($p < 0.05$). PR and IBS were significantly correlated for all but the drug- exposed control group (non-exposed control, r = 0.938, p = 0.006; non-exposed experimental, r = 0.979, p = 0.001; drug- exposed experimental, r = 0.955, p = 0.003). Within the combined (experimental and control) drug-specific groups, only polydrug-exposed infants demonstrated such a correlation (r = 0.584, p = 0.046). A significant correlation was also identified within the cocaine-exposed group for the experimental only (r = 0.992, $p < 0.001$). The investigators therefore concluded that the ATVV promoted normal physiologic and behavioral function. *Limitations:* The sample size was small and the infants were observed over a 12 hour time frame in the early postnatal when many behavioral and physiological adjustments are normally taking place. Lastly, the mothers who agreed to participate in the study may be different (with respect to critical characteristics) from the mothers who decided not to participate.
Oro, & Dix, 1988 United States	Quasi experimental study; n = 30 narcotic exposed infants with confirmed urine toxicology studies were enrolled in the study. All were full term except for two preterm (34-35 weeks gestational age) infants who served as matched pairs. The infants were matched (type of drug exposure, methadone dose when appropriate, ethnicity, gestational age, birth weight, medication, and initial M-FNAST score) n = 15 to non-oscillating waterbed or n = 15 traditional bassinette. *Purpose:* The purpose of this study was to assess the efficacy of non-oscillating waterbeds compared to traditional bassinette for supportive care of NAS infants, M-FNAST scores, amount of pharmacological	*Findings:* The investigators reported that the matching process was successful in assuring the comparability of treatment and control groups. The infants in the waterbed group had a less severe course of NAS, their CNS sub-scores were lower, they required less pharmacological treatment (required less phenobarbital dosage, and a greater number of infants weaned of pharmacological treatment prior to discharge), and had improved weight gain compared to control group. *Limitations:* Only 30 narcotic exposed infants with NAS were included in the sample which poses a limitation to the study findings.

	treatment required, and pattern of weight gain. *Instruments:* M-FNAST scores, amount of pharmacological treatment required, and pattern of weight gain.	
D'Apolito, 1999 United States	Repeated measure experimental design; *n* = 14 infants exposed to methadone and other illicit drugs in utero. *Purpose:* The purpose of this study was to determine if the use of a mechanical rocking bed with maternal intrauterine sounds would decrease symptoms of withdrawal and promote neurobehavioral adaptation in infants with NAS exposed to methadone and other illicit drugs in utero. *Instruments:* Neonatal Abstinence Scoring System – was used to measure the degree of drug withdrawal. Braselton Neonatal Behavioral Assessment Scale (BNBAS)	*Findings:* The infants in the treatment group (mechanical rocking bed) had higher NAS withdrawal scores (p = .05), and increased sleep disturbances (p = .05). The results suggest that rocking beds may be too stimulating for infants with NAS in the acute phase of withdrawal from methadone or other illicit drugs. Therefore, the investigator concluded that mechanical rocking beds should not be used in this fragile population of infants until further studies have been conducted. *Limitations:* Only 14 infants with NAS were included in the sample which poses a limitation to the study findings.
Wolfgang, et al., 2015 Austria	Prospective, randomized controlled, blinded, single-center trial; *n* = 14 were randomized to the treatment group (laser acupuncture combined the pharmacological therapy), and *n* = 14 were randomized to the control group (pharmacological therapy alone). *Purpose:* The purpose of this study was to determine if infants randomly allocated to laser acupuncture (combined with pharmacological therapy of morphine and phenobarbital) or control group (pharmacological therapy alone) would reduce the duration of treatment required in NAS infants. Infants born to mothers with polydrug abuse were excluded. *Instruments:* Measured the duration of pharmacological (morphine) therapy. Highest Finnegan score, time to highest Finnegan score, and length of hospital stay.	*Findings:* The infants in the treatment group (combination of laser acupuncture and pharmacological management) had shorter duration of oral morphine treatment when compared to infants in the control group (pharmacological management only). The acupuncture group required oral morphine for 28 days vs. 39 days in the control group. *Limitations:* Only 28 infants with NAS were included in the sample which poses a limitation to the study findings.
Jansson, et al., 2004 United States	Systematic review of the literature; *n* = 8 studies were included *Purpose:* Comprehensive review of the literature on methadone maintenance and lactation to assess the amount of methadone in breastmilk to determine if it is safe to feed infants with NAS.	*Findings:* The American Academy of Pediatrics (AAP) 2012 guidelines support breastfeeding in methadone treated mothers, provided they are in a drug treatment program, HIV negative, and not using other illicit drugs (heroin, phencyclidine (PCP), cocaine, and amphetamines). There are additional contraindications for mothers of NAS infants with psych mental health problems requiring

	Instruments: Included studies on methadone maintenance and lactation to assess the amount of methadone in breastmilk to determine if it is safe to feed infants with NAS.	pharmacological treatment (lithium, fluoxetine, and Haldol). Hepatitis C is not a contraindication to breastfeeding; however, the CDC recommends mothers who are positive for hepatitis C consider abstaining from breastfeeding if their nipples are cracked or bleeding. Based on their review of the literature the investigators concluded that the amount of methadone in the breastmilk is low and that breastfeeding is safe in this population. In addition, the investigators suggested that to be successful with breastfeeding mothers of NAS infants need lactation consultants with additional training on NAS. *Limitations:* The 8 studies included had small sample sizes, and therefore the short and term developmental effects of methadone in breastmilk are inconclusive in this population.
McQueen, et al., 2011 Canada	Retrospective chart review; *n* = 28 infants were exposed to methadone in utero and developed NAS. *n* = 8 mostly breastfed (75% or more feedings), *n* = 11 combination of breastmilk and formula, *n* = 9 mostly formula fed. *Purpose:* The purpose of the study was to determine whether NAS scores as measured by the M-FNAST would differ based on whether the infant was the infant was feed primarily breastmilk, a combination of breastmilk and formula, or formula only *Instruments:* Measured the effect of the type of feeding on the number of M-FNAST scores, and mean M-FNAST scores of the infants	*Findings:* There were statistically significant differences between the groups in relationship to the number of M-FNAST scores obtained on the infants. The infants in the mostly breast fed group had the lowest, and the lowest mean scores compared to the combination breastmilk and formula, and formula only groups. The investigators therefore concluded that provided there are no contraindications (HIV and/or illicit drug use), mothers of NAS infants in methadone treatment programs should be encouraged to breastfeed. The investigators also recommended education on benefits of breastfeeding and practical advice on how to successfully breastfeed NAS infants (early initiation of breast feeding, skin-to-skin, rooming in). *Limitations:* This study is a retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete. In addition, the mothers self-selected their feeding group, which limits the generalizability of the study findings.
Pritham, et al., 2012 United States	Retrospective chart review; *n* = 136 mothers of NAS infants on methadone maintenance, and *n* = 16 mothers of infants on buprenorphine maintenance. *Purpose:* The purpose of this study was to examine opioid maintenance therapy in pregnancy and its effects on neonatal outcomes, and length of stay. *Instruments*: Measured the length of hospital stay.	*Findings:* Exposure to methadone and benzodiazepines was associated with increased length of stay of 8.6 days for infants with NAS. Length of stay was decreased in breastfed infants compared to partial breastfed and only formula fed infants. The number of days spent in the hospital for treatment of NAS was shorter 14 days in the buprenorphine group compared to 21 days in the methadone group. *Limitations:* This study is a retrospective chart review therefore the data extracted from the documentation in the medical records may not be

		complete. In addition, there are many unmeasured confounders (maternal length of time in drug treatment program and the number of relapses). The methadone and buprenorphine group sizes were non-equivalent.
O'Connor, et al., 2013 United States	Retrospective chart review; *n* = 88 NAS mother infant dyads were identified and of these, *n* = 65 or 76% chose to breastfed. *Purpose:* The purpose of this study was to examine the rates of breastfeeding in opioid dependent mothers of NAS infants treated with buprenorphine, and determine how many continued to breastfeed at 6-8 weeks post initiation. The study also sought to describe the relationship between breastfeeding and the duration and severity of NAS in this sample. *Instruments:* Measured the need for pharmacological treatment, and M-FNAST scores	*Findings:* The investigators reported that 76% of the opioid dependent mothers in the integrated medical and behavioral health program treated with buprenorphine chose to breastfeed their infants, and 66% were still breastfeeding at 6-8 weeks postpartum. The results suggested that breastfeeding may reduce the symptomatology in infants with NAS. The breastfeed infants were less likely to require pharmacological treatment (15 of 65 or 23.1% vs 6 of 20 or 30% in the non-breastfeeding group, and had lower peak NAS scores as measured by the Finnegan Scoring System (8.83 vs 9.65) compared to infants who were not breastfed. *Limitations:* Retrospective chart review therefore results cannot be used to establish cause and effect. It is not possible to determine the effects of other modifying variables such as skin-to-skin care, swaddling, and increased maternal contact due to the study design. The reasons mothers initiated breast feeding or discontinued breastfeeding was not available on the mothers in the historical controls.
Wachman, et al., 2010 United States	Retrospective chart review; *n* = 276 mother infant dyads were born July 2003-January 2009 with a diagnosis of NAS were assessed for inclusion. The mothers were eligible to breastfeed if their urine drug screen was negative on admission for illicit drugs; the mother had no reported illicit drug use during the last trimester, and was HIV negative. *Purpose:* The purpose of this study was to determine breastfeeding rates among opioid dependent pregnant women delivering at a Baby-Friendly Hospital. *Instruments:* Measured the number of eligible opioid dependent mother who initiated breastfeeding, and the total number of days they actually breastfed their infants.	*Findings:* The investigators reported that of the 276 dyads, 68% of the mothers met the eligibility criteria to breastfeed. Of the 68% of mothers who were eligible to breastfeed, 24 % actually breastfed their infants to some extent. 60% of the mothers who initiated breastfeeding stopped after 5.88 days. *Limitations:* Retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete.
Hodgson, & Abrahams, 2012 Canada	Retrospective chart review; *n* = 295 mother infant dyads were born October 1, 2003-December 31, 2009 with a diagnosis of NAS who received	*Findings:* The study suggested that rooming-in could play a useful role in mitigating the relationship between maternal methadone dose and the need to treat the newborn for opiate withdrawal.

	care in the rooming in program were enrolled. *Purpose:* The purpose of this study was to explore the effect of a rooming-in program protocol on the need for pharmacological treatment of opioid exposed newborns. *Instruments:* Collected data on the type of drug used by the mother, maternal methadone dose at delivery, morphine treatment if required on the newborn, and perinatal outcomes.	Rooming-in appears to be a safe alternative to the current standard of care which frequently results in the separation of mother and newborn in substance-dependent populations. Limitations: Retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete.
Brackets, et al., 2012 United States	Retrospective chart review from January 2007 and January 2009; *n* = 121 infants born to opiate dependent mothers and treated for NAS. Of the 121 infants, *n* = 75 received traditional pharmacological treatment and weaning entirely in the NICU. A sub set of carefully selected infants, N = 46 were initially treated with methadone as inpatients and then completed their weaning process outpatient. *Purpose:* The purpose of this study was to compare the safety and efficacy of a traditional inpatient only approach to a combined inpatient and outpatient weaning strategy for infants with NAS. *Instruments:* Collected data on the type of drug used by the mother, duration of methadone treatment, breastfeeding rates, readmission and child protective services/social services referral rates.	*Findings:* The investigators reported that in carefully selected infants, combined inpatient/outpatient weaning compared to traditional inpatient only was associated with reduced hospital length of stay, treatment duration, and increased rates of breastfeeding. Breast feeding rates improved: (24% in the combined group vs. 8% in the traditional group, *p* value < .05). Length of hospital stay was reduced ranging from 25 $\pm$ 15 days for the traditional group, and 13 $\pm$ 5 days for the combined group. Duration of methadone treatment was longer 37 $\pm$ 20 days vs 21 $\pm$ 14 day, *p* = <0.001). The cumulative dose was similar (3.6 $\pm$ 3 vs 3.1 $\pm$ 5 mg kg/day, *p* = < 0.42). Concerns regarding infant neglect or abuse, and readmission rates were similar between the two groups (5% traditional, 7% combined). Average cost for infant in the combined group was $13 729, compared to $27 546 in the traditional group. The investigators reported an estimated cost reduction of $635 000 in a 2 year period. *Limitations:* Retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete.
Smirk, et al., 2014 Australia	Retrospective chart review; *n* = 38 > 35 weeks gestational age infants with NAS who were admitted to the NICU and treated for opioid dependence (methadone or buprenorphine) were selected to be transitioned to home based therapy. *n* = 80 were treated as traditional inpatients and their outcomes were compared. *Purpose:* The purpose of this study was to explore the effect of a transition program from inpatient to an outpatient setting for the treatment of opioid exposed newborns.	*Findings:* In selected infants, home-based detoxification is associated with reduced hospital stays and increased rates of breastfeeding, without prolonging therapy. Safety of the infants is critical which precludes many from entering such a program. The investigators reported that the infants in the home based detoxification group had shorter hospital stays (mean 19 days vs. 41 days). The infants in the detoxification group were more likely to be breastfeeding on discharge from hospital care (45% vs. 22%). *Limitations:* Retrospective chart review therefore the data extracted from the documentation in the medical records may not be complete.

	Instruments: Collected data on the type of drug used by the mother, infant length of stay, cumulative infant morphine doses, duration of morphine treatment, breastfeeding rates, and safety (need for protective services, and foster care placement, serious adverse events (missed medication doses, missed appointments, readmissions).	

APPENDIX B:

JHACH & USF IRB APPROVAL LETTERS

JOHNS HOPKINS
MEDICINE

Office of Human Subjects Research
Institutional Review Boards

1620 McElderry Street, Reed Hall, Suite B-130
Baltimore, Maryland 21205-1911
410-955-3008
410-955-4367 Fax
e-mail: jhmeirb@jhmi.edu

Date: March 21, 2018

APPLICATION APPROVAL

Review Type:	Expedited
Principal Investigator:	Genieveve Cline
Number:	IRB00153777
Title:	Assessing Abstinence in Infant Greater Than 28 Days Old
Committee Chair:	Verena Jorgensen
IRB Committee:	JHM ACH IRB

Date of approval: March 21, 2018

Date of Expiration: March 20, 2019

The JHM IRB approved the above-referenced Application.

45CFR46.404 and/or 21 CFR 50.51: This study has been approved for the inclusion of children as 'research not involving greater than minimal risk'. The permission of parents/guardians is waived.

Assent is waived for all children.

Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

Date of Approval and Expiration Date: The approval and expiration date for this research are listed above. If the approval lapses, the research must stop and you must submit a request to the IRB to determine whether it is in the best interests of individual participants to continue with protocol-related procedures.

Changes in Research: All proposed changes to the research must be submitted using a Change in Research application. The changes must be approved by the JHM IRB prior to implementation, with the following exception: changes made to eliminate apparent immediate hazards to participants may be made immediately, and promptly reported to the JHM IRB.

Continuing Review: Continuing Review Applications should be submitted at least 6 weeks prior to the study expiration date. Failure to allow sufficient time for review may result in a lapse of approval. If the Continuing Review Application is not submitted prior to the expiration date, your study will be terminated and a New Application must be submitted to reinitiate the research.

Unanticipated Problems: All unanticipated problems must be submitted using a Protocol Event Report.

If this research has a commercial sponsor, the research may not start until the sponsor and JHU have signed a contract.

The JHMIRB is constituted to meet the requirements of the Privacy Rule at section 45 CFR 164.512(i)(1)(i)(B) and is authorized and qualified to serve as the Privacy Board for human subjects research applications conducted by Hopkins' faculty members. The JHM IRB reviewed your request to waive authorization the above-referenced project. The IRB determined that all specific criteria for a waiver of authorization were met, as follows:
(A) The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of the following elements;
(1) An adequate plan to protect the identifiers from improper use and disclosure;
(2) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
(3) Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted;
(B) The research could not practicably be conducted without the waiver or alteration; and
(C) the research could not practicably be conducted without access to and use of the protected health information.

Study documents:

HIPAA Form 4:
HIPAA form

Additional Supplemental Study Documents:
Demographic Data..xls
Use of Data Agreement.pdf
Key Code, Cline, G..xls

Protocol:

Protocol

Johns Hopkins Study Team Members:
Andrea Shimko, Aaron Germain

USF
UNIVERSITY OF
SOUTH FLORIDA

RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799
(813) 974-5638 • FAX (813) 974-7091

4/17/2018

Genieveve Cline, DNP, ARNP, NNP-BC, CNE, RN-BC
College of Nursing
12901 Bruce B Downs Blvd, MDC22
Tampa, FL 33612

RE: **Expedited Approval for Initial Review**
IRB#: Pro00032766
Title: Assessing Abstinence in Infant Greater Than 28 Days Old

Study Approval Period: 4/17/2018 to 4/17/2019

Dear Dr. Cline:

On 4/17/2018, the Institutional Review Board (IRB) reviewed and **APPROVED** the above application and all documents contained within, including those outlined below.

Approved Item(s):
Protocol Document(s):
Protocol version 1

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR 56.110. The research proposed in this study is categorized under the following expedited review category:

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

Your study qualifies for a waiver of the requirements for the informed consent process for this retrospective chart review as outlined in the federal regulations at 45CFR46.116 (d) which states that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that (1) the research involves no more than minimal risk

to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Your study qualifies for a waiver of the requirement for signed authorization as outlined in the HIPAA Privacy Rule regulations at 45CFR164.512(i) which states that an IRB may approve a waiver or alteration of the authorization requirement provided that the following criteria are met (1) the PHI use or disclosure involves no more than a minimal risk to the privacy of individuals; (2) the research could not practicably be conducted without the requested waiver or alteration; and (3) the research could not practicably be conducted without access to and use of the PHI. A waiver of HIPAA Authorization is granted for this retrospective chart review of infants diagnosed with NAS who were admitted to the NICU at Johns Hopkins All Children's Hospital between January 1, 2010 and January 1, 2017. This waiver allows the study team and/or its honest broker to obtain PHI of patients in this cohort and their mothers from the infants' Johns Hopkins All Children's Hospital medical record.

This study involving child participants falls under the minimal risk category 45 CFR 46.404: Research not involving greater than minimal risk.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval via an amendment. Additionally, all unanticipated problems must be reported to the USF IRB within five (5) calendar days.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

V Jorgensen MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board