SCHOOL of GRADUATE STUDIES
EAST TENNESSEE STATE UNIVERSITY

East Tennessee State University
Digital Commons @ East Tennessee State University

Electronic Theses and Dissertations | Student Works

5-2020

A Replication and Extension of a Prediction Tool Identifying Need for Treatment Among Opioid Exposed Infants

Loni Parrish
East Tennessee State University

Follow this and additional works at: https://dc.etsu.edu/etd

 Part of the Congenital, Hereditary, and Neonatal Diseases and Abnormalities Commons

Recommended Citation

Parrish, Loni, "A Replication and Extension of a Prediction Tool Identifying Need for Treatment Among Opioid Exposed Infants" (2020). *Electronic Theses and Dissertations.* Paper 3758. https://dc.etsu.edu/etd/3758

This Thesis - unrestricted is brought to you for free and open access by the Student Works at Digital Commons @ East Tennessee State University. It has been accepted for inclusion in Electronic Theses and Dissertations by an authorized administrator of Digital Commons @ East Tennessee State University. For more information, please contact digilib@etsu.edu.

www.manaraa.com

A Replication and Extension of a Prediction Tool Identifying Need for Treatment Among Opioid Exposed Infants

---

A thesis

presented to

the faculty of the Department of Psychology

East Tennessee State University

In partial fulfillment

of the requirements for the degree

Master of Arts in Psychology

---

by

Loni Parrish

May 2020

Alyson Chroust, Chair Ph.D.

Andrea Clements, Ph.D.

Meredith Ginley, Ph.D.

Keywords: Opioid, NOWS, Development

www.manaraa.com

ABSTRACT

A Replication and Extension of a Prediction Tool Identifying Need for Treatment Among Opioid Exposed Infants

by

Loni Parrish

The incidences of maternal opioid use and neonatal opioid withdrawal syndrome (NOWS) have increased by nearly 400% over the past decade. Isemann and colleagues (2017) developed prediction tools (TiTE/TiTE$_2$) to differentiate, within the first two days of life, between infants who will require pharmacotherapy for NOWS from those infants who will not require pharmacotherapy for NOWS. The goal of the current experiment was to replicate and extend their prediction model. The present experiments successfully replicated Isemann et al. (2017) results and also established alternative cutoff values for requiring treatment that provide better balance between all four metrics. Moreover, new prediction models (TEN/TEN$_2$) were proposed based on a factor analysis of modified Finnegan scores across the first 48 hours of life. Area Under the Curve-Receiver Operating Characteristic curve analyses indicated that the TEN$_2$ was the best prediction model compared to the TiTE$_2$ and the TEN.

www.manaraa.com

Copyright 2020 by Loni Parrish

All Rights Reserved

www.manaraa.com

TABLE OF CONTENTS

www.manaraa.com

LIST OF TABLES

www.manaraa.com

LIST OF FIGURES

www.manaraa.com

Chapter 1. Introduction

Within the last few years, the number of women using opioids has increased dramatically (Stover & Davis, 2015). Additionally, there has been a rise in the number of women using opioids during pregnancy (Bateman et al., 2014; Handal, Engeland, Ronning, Skurtveit, & Furu, 2011; Lind et al., 2017). For example, the number of reported cases of opioid use during pregnancy increased from 1.5 cases to 6.5 cases per 1000 delivery hospitalizations from 1999 to 2014 (Haight, Ko, Tong, Bohm, & Callaghan, 2018). The high rates of prescription and illicit opioid use during pregnancy is a significant public health concern, not only for pregnant women, but also for their fetuses. Opioids cross the placental and blood-brain barriers; thereby, posing increased risk for fetuses who are exposed to such drugs in utero (Hudak & Tan, 2012). Some of the common risks associated with prenatal opioid exposure include smaller head circumference (Greig, Ash, & Douiri, 2012), premature birth (Azuine et al., 2019), and higher rates of developing neonatal opioid withdrawal syndrome, or NOWS (Patrick, Davis, Lehman, & Cooper, 2015). NOWS refers to the withdrawal symptoms that opioid-exposed neonates may experience shortly after birth (Conradt et al., 2019). Similar to the rise in number of women using opioids during pregnancy, the number of infants diagnosed with NOWS has increased. Between 2000 and 2013, NOWS diagnoses increased from 1.2 cases to 5.8 cases per 1,000 hospital births (Conradt et al., 2019). The incidence rates of NOWS varies across the United States with rates almost three times above the national average in Southern Appalachia (i.e., Kentucky, Tennessee, Mississippi, and Alabama) with approximately 16.2 cases of NOWS per 1,000 births (Patrick et al., 2015).

Not all infants with prenatal opioid exposure are diagnosed with NOWS. Research indicates that between 50 – 80% of infants with prenatal opioid exposure are diagnosed with NOWS

www.manaraa.com

(Conradt et al., 2019). Consequently, it is important to predict which infants with prenatal opioid exposure will be diagnosed with NOWS and require pharmacotherapy from those infants with prenatal opioid exposure that will not be diagnosed with NOWS and thus not require pharmacotherapy. This paper replicates a prediction tool for requiring and for not requiring pharmacological treatment in a sample of infants at-risk for NOWS. Additionally, the current paper extends and improves upon the prediction tool by teasing apart the impact of polydrug exposure on the requirement of pharmacotherapy. Furthermore, a factor analysis was conducted to see which items loaded together in this dataset and to improve the sensitivity of the prediction tool.

Developmental Outcomes Associated with NOWS

The prenatal period is a critical time for brain development. When the fetus is exposed to a teratogen, like an opioid, it can adversely affect brain development (Caritis & Panigrahy, 2019). For instance, opioids can alter maturation in the connective tracts of the inferior and superior fasciculi (Walhovd, Watts, CandPsychol, & Woodward, 2012), impair brain growth, and promote neuronal death by apoptosis and necrosis (Yuan et al., 2014). These alterations in neurodevelopment may contribute to cognitive and behavioral difficulties later in life.

Neonates with prenatal opioid exposure are at-risk for several adverse birth outcomes. For example, neonates with prenatal opioid exposure are more likely to be born premature (Azuine et al., 2019), have a longer stay in the hospital (Devlin, Lau, & Radmacher, 2017), have lower birth weights (Ludlow, Evans, & Hulse, 2004), have higher NOWS rates (Patrick et al., 2015), have more respiratory issues, feeding difficulties, and seizures (Patrick, Schumacher, & Benny-Worth, 2012), have smaller head circumferences (Greig et al., 2012; Towers et al., 2019),

www.manaraa.com

and have a higher likelihood of fetal death (Kahila, Saisto, Kivitie-Kallo, Haukkammaa, & Halmesmäki, 2007) than neonates without prenatal opioid exposure.

Research on the short- and long-term developmental outcomes associated with prenatal opioid exposure has seen a recent increase but still remains limited and conflicting. There is data that support that exposure to opioids in utero is associated with adverse developmental outcomes (Yeoh, Eastwood, Wright, 2019), and there is data that support that prenatal opioid exposure is not related to adverse outcomes (Kaltenbach et al., 2018). Research examining developmental outcomes following a NOWS diagnosis is often muddled by the difficulty of properly defining the population, finding an appropriate control group, and lack of strictly controlled data (i.e., consideration and inclusion of information on the home environment, SES, polysubstance use, maternal characteristics, genetics, sex of newborn, prenatal care, and ethnicity) (Jones et al., 2016).

Following prenatal opioid exposure, some research suggests that infants may experience poor neurobehavior outcomes and motor delays (Bernstein, Jeremy, Hans, & Marcus, 1984; Hans & Jeremy, 2001; McGlone & Mactier, 2015; Merhar et al., 2018). Specifically, opioid-exposed infants have shown deficits in regulation, quality of movement, and excitement (Bernstein et al., 1984; Velez et al., 2018) and delays in developmental milestones such as sitting independently or crawling (Logan, Brown, & Hayes, 2013). In contrast, other research indicates that there are no statistically significant differences between opioid-exposed infants' motor scores on the PDI compared to the standardized scores (Beckwith & Burke, 2014; Messinger et al., 2004). An interesting pattern emerged in Hunt and colleagues' (2008) investigation. They found that there was no significant difference between opioid exposed infants and non-opioid

www.manaraa.com

exposed infants at 18 months but reported difference in motor performance around 3 years of age (Hunt, Tziomi, Collins, & Jeffry, 2008).

In addition to motor development, research efforts have also investigated prenatal opioid exposures association with cognitive performance. There is data suggesting that prenatal opioid exposure is related to deficits in cognitive performance (Hans & Jeremy, 2001; Hunt et al., 2008; Nygaard, Moe, Slinning, & Walhovd,2015). For example, researchers found that opioid-exposed children, ranging from 18-28 months-old, had significantly lower scores on the cognitive and language subscales of BSID-III compared to the normative population. This difference remained even after consideration of the different types of opioid exposure (i.e., methadone, buprenorphine, morphine), polysubstance use, length of hospital stay, gestational age, and birth weight (Merhar et al., 2018). These cognitive differences may persist into older ages. For example, Nygaard, Slinning, Moe, and Walhovd (2016) assessed children longitudinally at 4.5 and 8.5 years of age and found that children in the exposed group had scores that were more predictive of attention difficulties in comparison to the control group at both ages. Moreover, children with opioid exposure had lower test scores in reading, writing, numeracy, spelling, and grammar than children without prenatal opioid exposure. Critically, children in 7th grade who were diagnosed with NOWS as infants scored significantly lower than the controls in the 5th grade (Oei et al., 2017). Collectively, these results suggest that a NOWS diagnosis and its relation to lower cognitive performance in the first few years of life may continue later in life and impact school performance.

In contrast, there are other researchers who have no found empirical support for differences in cognitive performance following prenatal opioid exposure. For instance, Kaltenbach and colleagues (2018) longitudinal study assessed child growth parameters, cognition, language

www.manaraa.com

abilities, sensory processing, and temperament between 0 and 36 months. There was insufficient evidence to indicate that prenatal opioid exposure is associated with deficits in physical or mental development. Moreover, Salo and colleagues (2010) found that, after controlling for birth weight and height, gestational age, maternal age, SES, and number of foster placements, differences on the cognitive scale of the Bayley-III between children exposed to opioids and children not exposed to opioids were no longer significant. Finally, Bakhireva and colleagues (2019) reported no neurodevelopmental delays (e.g., Bayley-III, IBQ-R) between infants with prenatal opioid-exposure and infants without prenatal opioid exposure at 5-8 months of age.

The conflicting research on the developmental outcomes associated with prenatal opioid exposure in the domains of motor and cognitive development could be due to difficulty classifying infants as to whether they have NOWS. Current literature indicates that 50-80% of infants with prenatal opioid exposure will be diagnosed with NOWS and require pharmacotherapy to manage their withdrawal symptoms (Conradt et al., 2019). The use of pharmacotherapy is subsequently related to longer hospital stays and increased cost of hospital stays. If researchers can predict which opioid-exposed infants will require pharmacotherapy from the opioid-exposed infants that will not require pharmacotherapy, then health care providers can intervene earlier and potentially decrease the severity of the infants' withdrawal symptoms and length of stay in the hospital.

The American Academy of Pediatrics recommends that newborns with suspected prenatal opioid exposure be observed in the hospital for 5-7 days for the development of withdrawal symptoms. The Finnegan Neonatal Abstinence Scoring Tool (Finnegan, Connaughton, Kron, & Emich, 1975; Jansson, Velez, & Harrow, 2009) is the most widely used measure for tracking and quantifying the severity of the infant's withdrawal symptoms over time. The Finnegan was first

www.manaraa.com

published in 1975. The Finnegan has been modified since the original publication in an effort to remove components that were no longer relevant (Finnegan et al., 1992). For example, individual scores for excoriation on multiple body parts (i.e. nose, knees and toes) was revised to just a single item called excoriation. The Modified Finnegan Neonatal Scoring System (MFNSS) also organized items into three categories to help providers identify the most appropriate treatment plan (Maguire, Cline, Parnell, & Tai, 2013). Most hospitals use the Modified Finnegan Neonatal Scoring System (MFNSS), but it is commonly still referred to as "the Finnegan". The MFNSS consist of three sections with 21 items and 32 scoring options. The three sections are central nervous system disturbances (CNS), metabolic vasomotor respiratory disturbances, and gastrointestinal disturbances. Some of the CNS items consist of high-pitched cry, tremors, moro reflex, and excoriation. Example items from the metabolic disturbances include sweating, hyperthermia, nasal stuffiness, and respiratory rate. Lastly, a few items under gastrointestinal disturbances are excessive sucking, poor feeding, loose stools, and vomiting. Most hospital protocols dictate that if a newborn has three consecutive scores of greater than or equal to 8 or two consecutive scores of greater than or equal to 12, then the provider should start pharmacological treatment (Pomar et al., 2017). If the infant scores less than 8, then that indicates that the infant's withdraw is not severe enough for pharmacotherapy or the infant is ready to be weaned off of the treatment drug (Pomar et al., 2017). One difficulty researchers encounter when studying the relationship between MFNSS and treatment outcomes is that clinicians also use their clinical decision-making skill set to guide treatment decisions. This critical information is often not recorded in electronic medical records and thus a source of unmeasured variability for retrospective chart reviews.

www.manaraa.com

Although the MFNSS is the most commonly used tool to assess the severity of neonatal opioid withdrawal symptoms, it is not without limitations. First, the MFNSS was originally designed as a standardized scoring tool for researchers not for guiding clinical treatment decisions. Second, there has been very little empirical examination into the effectiveness of using the common cutoff score of 8 to guide pharmacological treatment decisions. Zimmerman-Baer, Notzli, Rentsch, and Bucher (2010) suggest that scores of 8 can differentiate between exposed and non-exposed infants, but it does not provide any validation for the need for pharmacological treatment following scores of 8 or greater (Gomez-Pomar & Finnegan, 2018). Finally, the MFNSS contains several items that do not have a strong pathological significance to opioid withdrawal in neonates (i.e., sneezing, yawning, and nasal stuffiness).

There are quite a few limitations associated with the MFNSS and its ability to quantify the severity of an infant's withdrawal symptoms. A recent alternative to the MFNSS has been introduced in a few hospitals in the United States. Grossman, Minear, Whalen and Wachman (2017) developed the Eat, Sleep, Console (ESC) approach because they believe that the start of medication should not depend on the newborns Finnegan score, but rather on how well the newborn is eating, sleeping and the newborns overall comfort level. This function-based assessment tool continues to assess the newborns withdrawal symptoms, but the use of any type of treatment depends on the overall comfort of the newborn (Grossman et al., 2017). ESC assessments are initiated within 4-6 hours after birth and performed every 3-4 hours during routine infant care. The ESC incorporates input from all of the newborn's caregivers (e.g. mother/parent, nurse, cuddler). Moreover, ESC assessments consist of a few questions that are answered with a Yes or No. There are certain guidelines that help physicians choose the right answer: Does the infant have poor feeding due to NAS?, Did the infant sleep for less than 1 hour

www.manaraa.com

after feeding due to NAS?, Is the infant unable to be consoled within 10 mins due to NAS. The physician also rates the newborns ability to be consoled on a scale of 1 to 3. If the newborn receives one "Yes" on any of the items, then a team huddle (i.e. parent, nurse, physician) is required to look for next steps in non-pharmacologic care (e.g. skin to skin contact, swaddling, quiet room, breastfeeding). If non-pharmacologic care does not work and the newborn continues to score "Yes" on the ESC, then pharmacologic treatment will be considered (Grossman et al., 2017).

Despite other models being created, the MFNSS is still the "gold standard" when it comes to quantifying the severity of the newborn's withdrawal symptoms and determining when pharmacotherapy is prescribed by the provider. Currently, the MFNSS is not used to *predict* which infants will require pharmacological treatment and which infants will not. However, there are several prediction models available and they are discussed below.

Predicting Pharmacologic Treatment

Researchers have been working on developing a way to predict whether an infant will require pharmacological treatment for their withdrawal or not. These predictions are important because they could significantly reduce the length of the hospital stay for the infants, reduce hospital stay cost, and enhance the caregiver-infant bond.

Oji-Mmuo and colleagues (2019) looked at the MFNSS to see whether it guided early discharge for infants at-risk for NOWS before providing pharmacologic treatment. Researchers examined hourly percentile curves of mean MFNSS scores in newborns being monitored for NOWS over the first seven days of life. They found that higher percentile curves of the mean MFNSS score were more likely to require pharmacologic treatment. Results showed that newborns with mean MFNSS scores less than the 25th percentile at three days did not require

www.manaraa.com

pharmacologic treatment, suggesting that these newborns could be safely discharged without further observation or intervention. Only a small percentage of newborns with MFNSS scores less than the 50th percentile required treatment at three days, leading researchers to suggests these newborns could also be safely discharged if families commit to close outpatient follow-up (Oji-Mmuo, Schaefer, Liao, Kaiser, & Sekhar, 2019). One consideration that limits the generalizability and practicality of this prediction tool is that it does not factor polysubstance exposure into the calculation of percentiles.

A second prediction model examined heart rate variability (HRV) parameters and their relation to Finnegan scores and the need for pharmacotherapy for infants at-risk for NOWS (Naguib, Alton, Avula, Hagglund, & Anne, 2014). HRV is a non-invasive way to look at automatic cardiovascular function. Thus, Naguib and colleagues (2014) assessed HRV and Finnegan scores in opioid-exposed newborns. Researchers compared HRV parameters of opioid-exposed newborn to jaundice controls because newborns diagnosed with jaundice and opioid-exposed newborns are placed in a similar hospital environment for observation. They found lower HRV in the first 2 days of life in opioid-exposed newborns. Additionally, they found that, in a span of three days, HRV parameters were cumulatively lower in the opioid-exposed group. Furthermore, one HRV parameter was able to differentiate opioid-exposed newborns with Finnegan scores greater than or equal to 8, from opioid-exposed newborns with Finnegan scores less than 8. This is a critical finding because Finnegan scores of 8 are often used clinically to start pharmacological treatment for withdrawal. Limitations of this study include the potential for error in calculating HRV parameters and the manual labor and time intensiveness that are required for calculating the HRV parameters. It is possible for neonates to wear a special monitor that could automate this process, but it is in need of pilot testing.

www.manaraa.com

Finally, Isemann and colleagues (2017) developed a pair of tools (i.e., TiTE and TiTE²) to predict the need for pharmacotherapy within the first 36 hours of life. The TiTE measures the average score of three symptoms from the Finnegan (e.g., increased muscle tone, tremors when disturbed, and excoriations) around 36 hours of life. The TiTE² incorporates exposure type into the prediction model to enhance the predictive value. The TiTE tool predicted infants who would require pharmacological treatment with positive predictive values of 90% and 100%. When predicting infants who would receive pharmacotherapy, the TiTE² was able to accurately predict infants who would receive pharmacological treatment with positive predictive values of 94% and 86% (Isemann, Stoeckle, Taleghani, & Mueller, 2017). Both prediction tools have high positive predictive values but low sensitivity. The distribution of infants receiving treatment and those not receiving treatment were analyzed to maintain thresholds that produced the highest positive predictive value while maintaining greater than 25% sensitivity (Isemann et al., 2017).

Sensitivity and specificity metrics are related to the accuracy of a screening test relative to a reference standard. In contrast, positive and negative predictive values assess the people. Trevethan (2017) proposed that it is the positive predictive value that is most important for the clinician. Sensitivity is the ability of a test to correctly classify people with the disease that will have a positive result. If a test is highly sensitive and the test result is negative, you can be nearly certain that they do not have the disease. A sensitive test helps "rule out" a disease (Parikh, Mathai, Parikh, Sekhar, & Thomas, 2008). Specificity is the ability of a test to correctly classify people without the disease that will have a negative test result. If a test is highly specific and the test result is positive, you can be nearly certain that they have the disease. A specific test helps "rule in" a disease (Parikh et al., 2008). Sensitivity and specificity are important for deciding what diagnostic screener to use but mean very little to a patient who test positive or negative. On

www.manaraa.com

the other hand, positive predictive values present the probability of correctly identifying, *from among people who might or might not have a condition, all people who do actually have that condition*. Negative predictive values present the screening test's probability of correctly identifying, *from among people who might or might not have a condition, all people who indeed do not have that condition* (Trevethan, 2017).

A high positive predictive value (minimizing false positives) is desirable because the subsequent risks of starting pharmacological treatment are high (increased length of stay, increased hospital cost, environmental stresses (NICU). However, it is also important to consider the sensitivity of the test. With only 25% sensitivity that means 75% of cases may be false positives. This is problematic because the test is designed to identify patients that can be sent home early because their withdrawal symptoms are minimal. These patients may exhibit withdrawal symptoms once home and the caregiver may not be prepared or know how to handle those symptoms. Therefore, we aimed to modify the prediction tool to create a better balance between the four metrics (i.e., sensitivity, specificity, positive predictive values, and negative predictive values). Moreover, this study excludes cannabinoids from potential influence and has oversimplified categories of polysubstance exposure. However, the current manuscript aims to rectify these limitations by considering the influence of marijuana on the need for pharmacological treatment and the inclusion of an additional polysubstance category.

www.manaraa.com

Chapter 2. Experiment 1A

Experiment 1A examined whether Isemann and colleagues' (2017) TiTE and TiTE² prediction tool's sensitivity, specificity, positive predictive values, and negative predictive values would replicate in an independent, retrospective, rural sample from the Appalachian Region. The TiTE/TiTE² prediction model was selected over the other previously discussed prediction models because it specifically investigates withdrawal symptoms that fall under the central nervous system (CNS). Function of the CNS is of specific interest in the case of opioid-exposure because opioid receptors are more concentrated in the CNS and gastrointestinal tract than other parts of the body. As a result, withdrawal symptoms generally reflect CNS irritability, over reactivity, and gastrointestinal tract dysfunction (Hudak & Tan, 2012). Additionally, this model lends itself to easy adoption by hospitals as it would reduce the time to administer and score the Finnegan as it only involves three items.

The TiTE and TiTE² were created and validated in single-center sample from an urban area (University of Cincinnati Medical Center). The creation and validation were completed on different samples of infants, but the validation sample only consisted of 121 infants. Applying the prediction models to an independent sample nearly four times the size of the original sample, from a different region of the United States, increases the generalizability of the prediction tools. Experiment 1A served as a replication of Isemann and colleagues (2017) prediction model and created the foundation for Experiment 1B in which the TiTE² exposure categories were adjusted in attempt to better understand the effects of polysubstance exposure.

Methods

This retrospective chart review was approved by the East Tennessee State University Medical IRB (0616.6sw-MSHA). An electronic medical record search for all deliveries between

www.manaraa.com

July 1, 2011 through June 20, 2016 was conducted. A total of 18,728 cases were returned. All newborns with an ICD 9/10 code for NOWS or with prenatal opioid exposure (as determined by a positive UDS or maternal report at delivery) were identified (n = 2638).

This is a unique research sample because the data was collected in the Appalachian Region were the opioid epidemic is highly prevalent and, some areas, have approximately 50 cases of NOWS per 1000 hospital births (Miller, McDonald, & Warren, 2016). The mother's and infant's medical records were used for data collection. Infant characteristics included in this study are birth weight, gestational age, in utero opioid exposure, toxicology results, pharmacological treatment, and individual symptoms scores that compose each of the Finnegan scores collected during 0, 1, and 2 days of life. Maternal characteristics included drug use history, drug toxicology results and socio-demographic information. For a complete summary of infant and maternal characteristics of the sample see Table 1.

Table 1.

Summary of Infant and Maternal Characteristics

Variable	n	Mean (SD)/Frequency (%)
Maternal Age (years)	384	26.89 (4.89)
Number of Prenatal Care Visits	226	8.68 (4.16)
Used tobacco during pregnancy	385	326 (84.7%)
Mother White	378	368 (95.6%)
Mother Unmarried	376	275 (71.4%)
Mother Graduated High School or Higher	360	251 (69.7%)
WIC	365	285 (74.0%)
Male Infants	385	203 (52.7%)
Gestational Age (weeks)	363	38.18 (1.29)
Infant Length of Stay (days)	385	11.50 (10.97)
Infant Birthweight (grams)	385	2997.56 (435.88)
Infant Head Circumference (cm)	380	13.24 (0.63)
APGAR 1 minute	375	8.10 (0.86)
APGAR 5 minutes	375	8.96 (0.50)
Breastfeeding	309	194 (50.4%)

www.manaraa.com

TiTE scores were calculated for each infant. Multiple MFNSS were charted during the first 48 hours of life. Therefore, all charted Finnegan scores within the first 48 hours were incorporated into the infant's TiTE score. For each instance of a detailed score in the infant's chart within the first 48 hours of life, scores on three individual items from the Finnegan (increased muscle tone, tremors when disturbed, and excoriation) were summed. For increased muscle tone infants could receive a score of zero or two. For tremors when disturbed infants could receive a score of zero, one, or two. For excoriation infants could receive a score of zero or one. Then, an average TiTE score was calculated for each infant. Each TiTE score was summed and divided by the total number of observations for that infant. Average TiTE scores ranged from 0 to 5. Additionally, a treatment variable was created to indicate whether the infant received pharmacological treatment (1) for their withdrawal or not (0) during their hospital stay.

TiTE^2 scores were calculated for each infant according to the exposure categories described in Isemann et al., (2017), which included buprenorphine only, methadone only, opioids other than buprenorphine or methadone, and polysubstance (i.e., buprenorphine or methadone plus additional opioids *or* the addition of any amphetamine, barbiturate, benzodiazepine, or cocaine to any opioid). This experiment was unable to replicate the methadone only category because only two infant participants were categorized as methadone exposed. Thus, these two participants were categorized in to the "opioids other than buprenorphine" group. A chi-square test of independence was performed to compare the proportion of infants who received pharmacotherapy or not for each category of exposure. Post hoc, a value of 0 (associated with no treatment), 1 (no statistical difference), or 2 (associated with treatment) was assigned based on the exposure categories' association with treatment (see Table 2). The TiTE score plus the exposure "points" reflect the TiTE^2 score. For example, using the values provided in Table 2, if

www.manaraa.com

an infant had a TiTE score of 3 and was exposed to an opioid other than buprenorphine they would receive one additional $TiTE_2$ point and a resultant $TiTE_2$ score of 4.

Table 2.

Category of In Utero Opioid Exposure and Association with Pharmacological Treatment Experiment 1A.

	Treated	Not Treated	*p*-value from Chi Square	$TiTE_2$ "Points"
Experiment 1a				
Buprenorphine only	32	115	$p < .001$	0
Opioids other than buprenorphine	8	13	$p = .630$	1
Polysubstance	123	69	$p < .001$	2
Experiment 1b				
Buprenorphine only	32	115	$p < .001$	0
Opioids other than buprenorphine	8	13	$p = .630$	1
Poly-opioid and/or the addition of any amphetamine, barbiturate, or cocaine	111	41	$p < .001$	2
Any opioid plus benzodiazepine and/or marijuana	17	43	$p = .009$	0

Note: Methadone only category was not included in Experiment 1a because only two infant participants were categorized as methadone exposed.

Results and Discussion

Recall that sensitivity and specificity represent accuracy of the diagnostic screening tool. However, positive and negative predictive values present the probability of correctly identifying if a patient does or does not have the disease. It is important for a prediction tool to have a balance between all four metrics. Thus, sensitivity, specificity, positive predictive values, and negative predictive values were calculated for the TiTE and $TiTE^2$ scores using the cross tabs function in SPSS version 24.0 and are presented in Table 3. Following the structure of the Isemann and colleagues' (2017) analysis, two prediction models were examined: one predicting pharmacotherapy (treatment) and one predicting no pharmacotherapy (no treatment). Within the predicting treatment model, TiTE scores were dichotomized such that scores greater than or

www.manaraa.com

equal to 4 and TiTE2 scores greater than or equal to 5, were coded as "1" and scores less than 4/5 were coded as "0". Within the *predicting no treatment* model, TiTE and TiTE2 scores were dichotomized such that scores less than or equal to 1 were coded as "1" and scores greater than 1 were coded as "0".

Table 3.

Experiment 1A – Pure Replication Tool Validation (Sensitivity and Specificity Analysis).

TiTE Score Predicting No Pharmacotherapy			TiTE Score Predicting Pharmacotherapy		
	Not Treated	Treated		Treated	Not Treated
Score ≤ 1	61	18	Score ≥ 4	8	1
Score > 1	156	150	Score < 4	160	216
Sensitivity	28.1%		Sensitivity	4.8%	
Specificity	89.3%		Specificity	99.5%	
PPV	77.2%		PPV	88.9%	
NPV	49.0%		NPV	57.4%	
TiTE2 Score Predicting No Pharmacotherapy			TiTE2 Score Predicting Pharmacotherapy		
	Not Treated	Treated		Treated	Not Treated
Score ≤ 1	33	4	Score ≥ 5	54	12
Score > 1	179	164	Score < 5	114	200
Sensitivity	15.6%		Sensitivity	32.1%	
Specificity	97.6%		Specificity	94.3%	
PPV	89.2%		PPV	81.8%	
NPV	47.8%		NPV	63.7%	

PPV = positive predictive value; NPV = negative predictive value

The sensitivity, specificity, positive predictive values, and negative predictive values indicated that the TiTE² model was the best model when predicting pharmacotherapy. It was highly specific (94.3%) with a high positive predicative value (81.8%) and the highest sensitivity value (32.1%) compared to the other models in our replication. Overall, this experiment successfully replicated the pattern of results from Isemann and colleagues (2017). However, the prediction tools have poor sensitivity. Experiment 1B explored whether the low sensitivity could be improved by revising the categories of polysubstance exposure or changing the cut-off values.

www.manaraa.com

Chapter 3. Experiment 1B

First, Experiment 1B examined the contribution of additional types of polysubstance exposure to the sensitivity, specificity, positive predictive values, and negative predictive values of the TiTE² tool. The poor sensitivity reported in Experiment 1A may be due to the heterogeneity of the polysubstance category. It is well documented that many women do not consume a single drug during pregnancy (Davie-Gray, Moor, Spencer, & Woodward, 2013; D'Apolito & Hepworth, 2001; Johnson, Gerada, & Greenough, 2003). A review from Switzerland found that 62% of drug-using women took various combinations of heroin, methadone, cocaine, benzodiazepines, alcohol, and marijuana during pregnancy (Arlettaz et al., 2005). The effect of polydrug use on NOWS remains unclear and most likely depends on the particular combination and quantities of drugs used by the mother.

Recent research suggests that prenatal exposure to various psychotropic drugs, in combination with opioids, doubles the likelihood that newborns will be diagnosed with NOWS (Huybrechts et al., 2017). Benzodiazepines, for example, may distort the presentation of NOWS because benzodiazepine withdrawal may only start after the first week of life and continue in a subtle fashion for up to several months (Iqbal, Sobhan, & Ryals, 2002). Benzodiazepines in combination with opioids also appear to worsen the severity of NOWS (Sanlorenzo et al., 2019; Wachman et al., 2018). Infants exposed to combinations of benzodiazepines and opioids had the most rapid onset of withdrawal and the highest withdrawal scores during the first week of life compared to infants from single drug-using mothers (Abdel-Latif et al., 2006).

Additionally, the prevalence of marijuana use during pregnancy is increasing (Ryan, Ammerman, & O'Connor, 2018; Young-Wolff et al., 2017). Previous literature indicates that exposure to marijuana during pregnancy is associated with increased adverse outcomes in the

www.manaraa.com

neonatal period, such as low birth weight and increased incidence of neonatal intensive care admission (Conner et al., 2016; Gunn et al., 2016). However, few studies have examined concurrent opioid and marijuana use. One recent study reported that newborns with prenatal marijuana and opioid exposure had *decreased* odds of NOWS and prolonged hospital stay (Stein, Hwang, Liu, Diop, & Wymore, 2019). In contrast, O'Connor and colleagues found that prenatal marijuana use during the third trimester, in addition to buprenorphine use, may increase likelihood of treatment for NOWS (O'Connor, Kelly, & O'Brein, 2017).

Given the increased concurrent use of marijuana and opioids during pregnancy and the recent research indicating more severe withdrawal symptoms in benzodiazepine and opioid exposed newborns, the current experiment examined the impact of additional categories of polysubstance exposure on pharmacological treatment. If the incorporation of additional polysubstance exposure categories increases the sensitivity of the TiTE$_2$ without sacrificing the high positive predicative value, then the TiTE$_2$ 1B with additional consideration of benzodiazepine and marijuana exposure would be a better predictor of which infants require treatment for NOWS within 48 hours of life than the TiTE$_2$ 1A model that broadly defined polysubstance exposure.

A second explanation for the low sensitivity values obtained in Experiment 1A is that the cut-off values from Isemann et al. (2017) may not be the optimal cut-off values. Isemann and colleagues' (2017) cutoff values were selected with the goal of maximizing positive predictive values while maintaining at least 25% sensitivity.

Traditionally, the accuracy of a diagnostic test is described by examining sensitivity, specificity, positive predictive values, and negative predictive values. To describe tests in this manner requires the test results to be reported as dichotomous outcomes (positive/negative). A

www.manaraa.com

related way to illustrate the accuracy of a diagnostic test is to conduct a Receiver operating characteristic curve analysis (ROC). A ROC curve analysis has several advantages. First, in contrast to single measures of sensitivity and specificity, the diagnostic accuracy, such as area under the curve (AUC), is not affected by decision criterion. Second, a ROC curve analysis allows researchers to simultaneously compare several diagnostic tasks on the same subjects (Hanley & McNeil, 1983). Third, the optimal cut- off value can be determined (Greiner, Pfeiffer, & Smith, 2000). Previous research has used Youden's index to determine optimal cutoff values (Fluss, Faraggi, & Reiser, 2005; Roupp, Perkins, Whitcomb, & Schisterman, 2008). The selection of one cut-off value for predicting treatment may be more appropriate for an early screening test.

If the goal of the prediction model is to identify patients requiring treatment before the typical 5-7-day observation period, the proposed prediction tool is likely one of the first tests conducted on the patients. Thus, it is essential for the prediction tool to have higher sensitivity rates. The current experiment explored the three aforementioned potential modifications that could maximize sensitivity, specificity, positive predictive values, and negative predictive values for predicting treatment.

Methods

The methods for Experiment 1B were identical to those used in Experiment 1A with the exception of the calculation of the TiTE² score. Recall that Isemann and colleagues (2017) used only four exposure categories: buprenorphine only, methadone only, opioids other than buprenorphine or methadone, and polysubstance. An extra category was added to included marijuana and benzodiazepine exposure (see Table 4). A chi-square test of independence was performed to compare the proportion of infants who received pharmacotherapy or not for each

www.manaraa.com

category of exposure. A value of 0 (associated with no treatment), 1 (no statistical difference) or 2 (associated with treatment) are assigned based on the exposure categories association with treatment. The TiTE score plus the exposure "points" reflect the TiTE ² score. For example, using the values in Table 2, if an infant had a TiTE score of 4 and was exposed to buprenorphine they would receive zero TiTE2 points and a resultant TiTE2 score of 4. Sensitivity specificity, positive predictive value and negative predictive values were computed along with AUC-ROC curve analysis.

Table 4.

Exposure Categories for Experiments 1A, 1B, and Experiment 2.

Experiments 1A	Experiments 1B and 2
(i) Buprenorphine only	(i) Buprenorphine only
(ii) Opioids other than buprenorphine	(ii) Opioids other than buprenorphine
(iii) Polysubstance:	(iii) Polysubstance:
(iv) the addition of any amphetamine, barbiturate, benzodiazepine, or cocaine to any opioid	(iv) the addition of any amphetamine, barbiturate, or cocaine to any opioid
	(v) Any opioid plus benzodiazepine and marijuana

Results and Discussion

Sensitivity, specificity, positive predictive values, and negative predictive values were calculated for the TiTE² scores using the crosstabs function in SPSS version 24.0 and are presented in Table 5. Recall that the TiTE2 scores in the current experiment reflect the consideration of an additional category of polysubstance exposure and thus differ from the TiTE2 scores discussed in Experiment 1A. Frequencies for the *predicting treatment* and *predicting no treatment* models were calculated based on the same cut-off values described in Experiment 1A.

www.manaraa.com

The results revealed that the TiTE2 1B was highly specific (96.7%), with high positive predictive values (87.9%) and low sensitivity (30.4%). These frequencies indicate that modifying the polysubstance category did not improve sensitivity.

Table 5.

Experiment 1B- Expanded Polysubstance Categories: Tool Validation (Sensitivity and Specificity Analysis).

TiTE2 Score Predicting No Pharmacotherapy			TiTE2 Score Predicting Pharmacotherapy		
	Not Treated	Treated		Treated	Not Treated
Score ≤ 1	43	6	Score ≥ 5	51	7
Score > 1	169	162	Score < 5	117	205
Sensitivity	20.3%		Sensitivity	30.4%	
Specificity	96.4%		Specificity	96.7%	
PPV	87.8%		PPV	87.9%	
NPV	48.9%		NPV	63.4%	

PPV = positive predictive value; NPV = negative predictive value

Because the inclusion of an additional category of polysubstance exposure did not substantially improve sensitivity scores, we explored the impact of alternative cut-off values. The frequency data for the selection of alternative cut-off values for predicting treatment and predicting no treatment on sensitivity, specificity, positive predictive values, and negative prediction values are presented in the Appendices. The exploratory cutoff analyses showed that the TiTE2 was still highly specific, with high positive predictive values and low sensitivity when the 25th and 75th percentiles were used as alternate cut off values. However, using the median as a single cut off value produced a better balance between the sensitivity, specificity, positive predictive value and negative predictive value. This suggests that having one single cutoff value for predicting treatment may have led to a more balanced screening approach. While using the median score to differentiate between patients that require treatment and patients that not require treatment improved the model, it is possible that other cutoff values would be more meaningful than the median.

www.manaraa.com

An AUC-ROC curve analysis was conducted on the continuous TiTE and TiTE$_2$ scores to compare diagnostic accuracy among tests and determine optimal cutoff values. The AUC-ROC analysis and Youden's index are presented in Figure 1. A cutoff score of 3.85 represented the TiTE's and 3.96 represented the TiTE$_2$'s optimal ability to differentiate between treatment and no treatment while maximizing sensitivity and specificity. Sensitivity, specificity, positive predictive values, and negative predictive values for these cutoff values are listed in the Appendices.

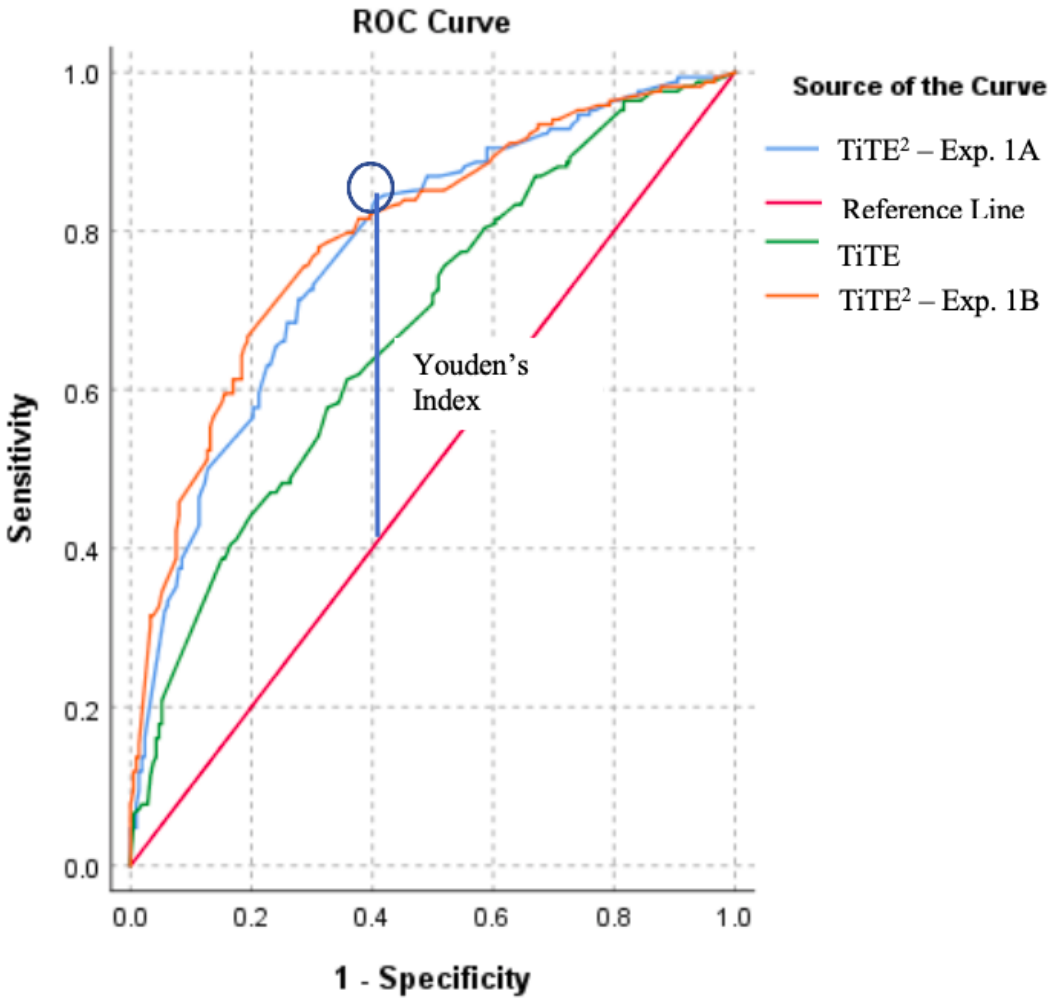

Figure 1. AUC-ROC Curve Analysis Examining TiTE, TiTE$_2$ (Exp 1A) and TiTE$_2$ (Exp 1B) Scores

www.manaraa.com

Furthermore, TiTE² scores from Experiment 1A and Experiment 1B were compared using an AUC-ROC curve to examine whether the inclusion of additional exposure categories improved the TiTE² prediction tool (see Figure 1). AUC analysis suggests that both TiTE² 1A (.776) and TiTE² 1B (.794) prediction models were significantly better than the TiTE (.678). There was not a significant difference between TiTE² 1A and the TiTE² 1B. Thus, the TiTE² from Experiment 1A was selected as the better model because it is more parsimonious. The inclusion of additional polysubstance categories did not increase sensitivity of this prediction model. It is possible that the low sensitivity of the prediction tools in Experiments 1A and 1B is due to the items included in the TITE. Perhaps the three items (i.e., muscle tone, tremors when disturbed, excoriation) were not a good fit for the data in the current study. In order to explore this possibility, a factor analysis was conducted.

www.manaraa.com

Chapter 4. Experiment 2

Given that the sensitivity values of Experiment 1A and 1B were not significantly improved by incorporating additional polysubstance categories or by using alternate cutoff values, Experiment 2 explored the possibility that the items included in the TiTE prediction model are not suitable for the current dataset. Thus, an exploratory factor analysis was conducted on the 21 individual items from the modified Finnegan. A factor analysis is a statistical test applied to the items in an instrument to summarize the patterns of correlations among the items. The goal of factor analysis is to decrease the number of items in a long instrument (Maguire et al., 2013).

Methods

An average score was calculated for each individual item on the Finnegan across the first 48 hours of life. The factor analysis was guided by Maguire and colleagues (2013). A principal axis factoring extraction with varimax rotation was selected. A scree plot was used to estimate the number of factors. The principal axis factor extraction confirmed that the data was appropriate to conduct a factor analysis and four factors were extracted. The 4-factor solution explained 36.4% of the total variance.

The ten items that loaded on to four factors formed the components of the new prediction tools, TEN and TEN$_2$. Individual scores on each of the ten items were summed to create the TEN. Then, an average TEN score was calculated for each infant, by summing each available TEN score and dividing by the number of observations. TEN scores could range from 0 to 26. A chi-square test of independence was performed to compare the proportion of infants who received pharmacotherapy or not for each category of exposure. A value of 0 (associated with no treatment), 1 (no statistical difference) or 2 (associated with treatment) are assigned based on the

www.manaraa.com

exposure categories association with treatment. The TEN score plus the exposure points reflect the TEN² score.

Results and Discussion

There were no observations of generalized convulsions in the sample. The zero variance on this item prevented the factor analysis from running in SPSS. Therefore, the MFNSS item, generalized convulsions, was not included in the present factor analysis. Ten items (crying, sleeping, excessive sucking, stools, poor feeding, projectile vomiting, moro reflex, tremors disturbed, tremors undisturbed and increased muscle tone) comprised the new prediction tool—TEN and TEN₂ (see Table 6 for factor loadings and communalities). Factor 3 included myoclonic jerks, but no other items loaded with it and it did not fit our communalities criteria of greater than .140; therefore, myoclonic jerks was not included in the TEN prediction mode

Table 6.

Factor Loadings, Communalities (h_2), and Percentages of Variances for Principle Factors Extraction with Varimax Rotation on MFNSS Items

Items	Factor 1	Factor 2	Factor 3	Factor 4	h_2
Crying	.133	**.491**	.214	.046	.248
Sleeping	-.011	**.395**	.261	.059	.148
Hyperactive moro reflex	**.640**	.207	-.129	1.06	.330
Tremors: disturbed	**.669**	-.056	.183	-.122	.338
Tremors: undisturbed	**.638**	-.115	.191	-.054	.317
Muscle tone	**.365**	.127	-.133	.088	.186
Excoriation	.018	.273	-.129	.020	.083
Myoclonic jerk	.033	.020	**.356**	-.098	.105
Generalized convulsions	-	-	-	-	-
Sweating	.041	.219	.088	-.152	.066
Fever	.138	.131	-.068	-.256	.090
Frequent yawning	.118	-.053	.181	-.195	.086
Mottling	.046	.005	-.096	-.097	.034
Nasal stuffiness	-.094	.138	.286	.091	.085
Sneezing	.042	.125	.347	.102	.128
Nasal flaring	.266	.141	-.220	.035	.122
Respiratory rate	.308	.259	-.037	-.019	.157
Excessive sucking	.009	**.565**	.133	.010	.225

www.manaraa.com

Poor feeding	.103	.111	-.012	**.537**	.150
Projectile vomiting	.214	-.030	.045	**.434**	.150
Bowel movement	.073	**.438**	-.021	-.024	.167
Percentage of Variance	12.74%	9.25%	7.38%	7.04%	

Note: Factor loadings > 0.35 are in boldface and retained for that factor. h_2 = communality coefficient. MFNSS represents the Modified Finnegan Neonatal Scoring System.

Sensitivity, specificity, positive predictive values, and negative predictive values were calculated for the TEN and TEN2 scores using the cross tabs function in SPSS version 24.0 (see Table 7). To examine which prediction model is better at predicating the eventual use of pharmacological treatment, TiTE² 1A, TEN, and TEN2 scores were compared using an AUC-ROC curve (see Figure 2). The results indicate that the TEN2 is a better predictor of treatment compared to the TEN and the TiTE2 1A. A cutoff score of 4.15 represents the TEN2's optimal ability to differentiate between treatment and no treatment while maximizing sensitivity and specificity.

Table 7.

Experiment 2- Prediction Tool Validation based on Factor Analysis (Sensitivity and Specificity Analysis).

TEN Score Predicting Pharmacotherapy			TEN2 Score Predicting Pharmacotherapy		
	Treated	Not Treated		Treated	Not Treated
Score ≥ 4.69	120	70	Score ≥ 4.15	148	93
Score < 4.69	48	147	Score < 4.15	20	122
Sensitivity	71.4%		Sensitivity	88.1%	
Specificity	67.7%		Specificity	56.7%	
PPV	63.2%		PPV	61.4%	
NPV	75.4%		NPV	85.9%	

PPV = positive predictive value; NPV = negative predictive value
Note: 4.69, 4.15 indicate cut off values based on AUC-ROC curve analysis and Youden's index.

www.manaraa.com

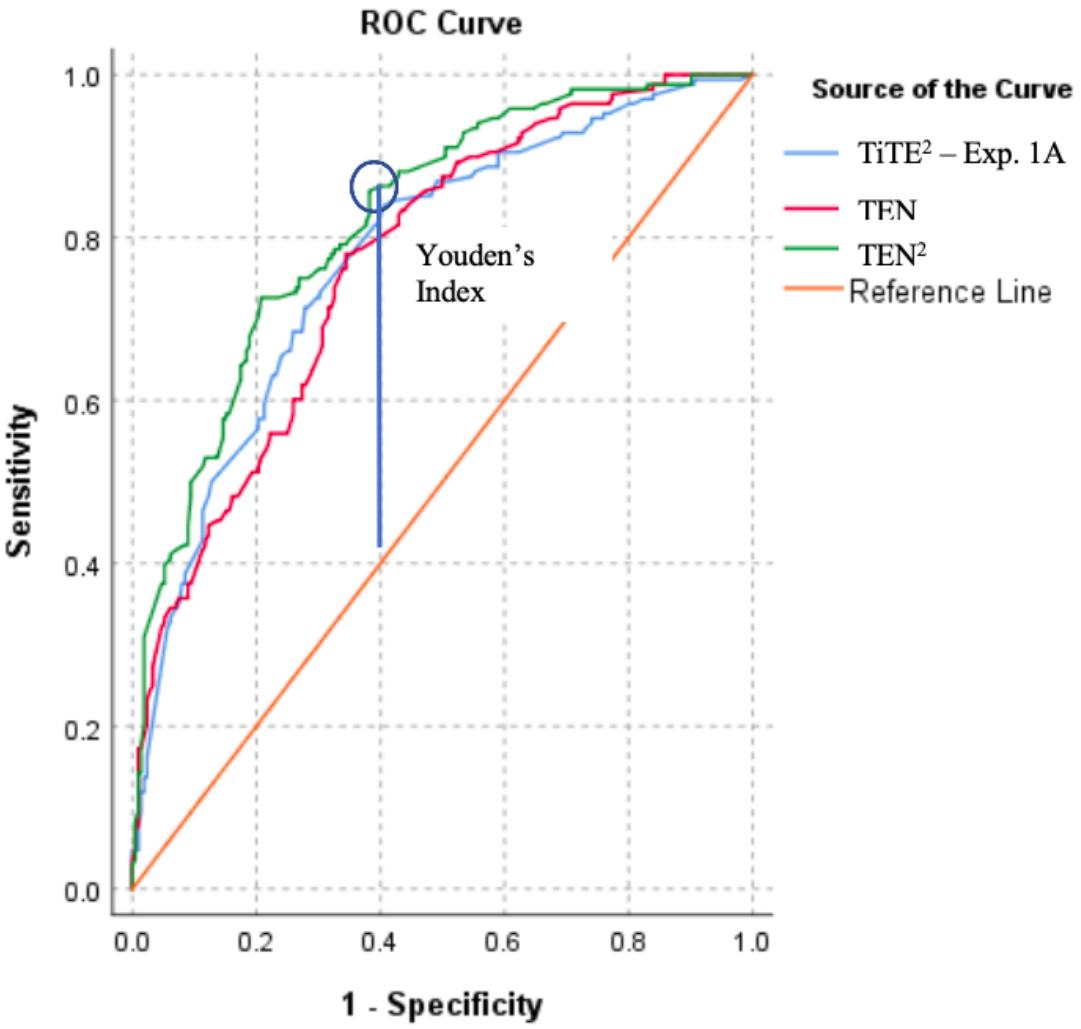

Figure 2. AUC-ROC Curve Analysis Examining TiTE$_2$ (Exp 1A), TEN, TEN$_2$ (Exp 2) Scores

The TEN$_2$ reduces the number of items clinicians would score from 21 to 10 and incorporates exposure type. The TEN$_2$ prediction model produced the highest AUC value (.821) and best balance between positive predictive value (61.4%) and sensitivity (88.1%).

www.manaraa.com

Chapter 5. General Discussion

This study replicates the findings of Isemann and colleagues' (2017) pair of prediction tools. The TiTE and TiTE² prediction models were applied to a retrospective dataset collected from the Appalachian Region. It was important to replicate the TiTE and TiTE2 using a sample from a rural region like Appalachia because this region has been disproportionally impacted by opioid use and NOWS (Villiapiano, Winkelman, Kozhimannil, Davis, & Patrick, 2017). If the goal of prediction models like the TiTE and TiTE2 is to reduce the burden of NOWS and subsequent developmental outcomes on families, hospital systems, and the country, then the prediction models need to generalize to regions hit especially hard by the opioid epidemic. Data from Experiments 1A and 1B successfully replicated the pattern of results presented in Isemann and colleagues' (2017) publication. The frequency metrics were highly specific and had high positive predictive values, but very low sensitivity. While the current study replicated the pattern of results obtained by Isemann and colleagues (2017), the sensitivity of the prediction tools was very low. While developing a highly specific prediction model is desirable because it minimizes the chance of over-treating neonates for their withdrawals symptoms. However, the risk of not treating patients and prematurely sending them home with caregivers that may not know how to respond to their withdrawals symptoms also needs to be considered. Therefore, it was important to explore whether a better balance among all four metrics could be obtained. The selection of alternative cutoff values for predicting treatment and predicting no treatment did not notably improve the sensitivity of the TiTE and TiTE2 prediction models.

It is important to note there were a few differences between Isemann et al.'s (2017) study and the current study. First, the original sample is from a more urban region while this study uses a sample from a rural region. Second, MFNSS scores with details on scores for individual items

www.manaraa.com

(rather than overall score) were not available for all infants in the dataset and some infants were did not have detailed scores recorded during the first 48 hours of life. Additionally, the dataset did not have consistent information on the time each score corresponded to just the day of life. This is why the current study used first 48 hours of life rather than 36 as in the Isemann publication. Lastly, the prediction models created in experiment 2 looked at one viewpoint of the model (predicting treatment), instead of assessing two viewpoints of the model (predicting treatment and predicting no treatment).

There are a couple of reasons why the TiTE and TiTE2 prediction models presented in the current study may have low sensitivity. It could be because there were not enough items within the prediction tool and the specific items (increased muscle tone, tremors when disturbed and excoriation) are not the same items that are important in this particular dataset. Additionally, when considering the impact of polysubstance exposure, it is possible patients did not always report or the toxicology reports did not include *all* of the substances mothers used during pregnancy. In addition, the polysubstance exposure categories were condensed because of the limited number of participants in certain categories. Also, this study was conducted with a retrospective dataset, therefore, it may be difficult to draw conclusions because retrospective data are prone to unintended consequences such as errors in medical chart reporting, missing data, conflicting information in different chart locations and changes in power and structure throughout the hospital (Campbell, Sittig, Ash, Guappone, & Dykstra, 2006). Finally, despite the widespread use of the modified-Finnegan as the "gold standard", it is assessed in a subjective manner and does not have established reliability and validity when it comes to making pharmacological treatment decisions. Zimmerman-Baer and colleagues (2010) empirically examined modified-Finnegan scores in a non-opioid exposed sample and concluded that a score

www.manaraa.com

of "8" can be used to differentiate those with narcotic exposure from those without narcotic exposure. Based on this study, the cutoff score of 8 was not examined as a cutoff score to differentiate among opioid-exposed neonates who may require treatment although it is often incorrectly cited as support for treatment decisions. Prediction models such as the TiTE and TITE2 could help to quantify the severity of withdrawal in drug exposed infants, but future treatment prediction models need to be developed with observations and data that is not dependent on modified Finnegan scores. For example, the current study uses information from the electronic medical records on whether the infant received pharmacological treatment for their opioid-withdrawal. Pharmacological treatment decisions are made based on the infants' modified Finnegan scores. Our prediction model is also built based on pieces of the modified-Finnegan. Until researchers and clinicians tease apart the dependency of pharmacological treatment decisions and modified Finnegan scores, the weaknesses of the modified Finnegan scoring system will also be weaknesses of prediction models constructed from modified Finnegan scores.

In Experiment 2 an exploratory factor analysis examined the possibility that the items included in the TiTE prediction model were not well-matched for the current dataset. Experiment 2 used Youden's index cutoff scores in an attempt to maximize the prediction tools' ability to differentiate between treatment and no treatment. The TEN and the TEN2 displayed high sensitivity without sacrificing the positive predictive value. After looking at the AUC-ROC curves across all experiments, the TEN2 was the best predictor of treatment because it had the highest AUC and maintained the best balance between all four metrics (i.e., sensitivity, specificity, positive prediction value and negative predictive value).

If hospitals administered neonatal withdrawal scoring based on the 10 items in the TEN and TEN2, instead of the full 21 items in the Finnegan, then there might be an increase of

www.manaraa.com

accuracy and consistency with scoring among nurses/clinicians that assess infants' severity of NOWS, because they would only have to focus on assessing the infants withdrawal on 10 items. Additionally, the ten items that constitute the TEN converged on three main factors. The organization of items within factors appears to align with previous research efforts. For instance, one factor contained mostly items related to central nervous system functioning. It is logical for these items to significantly contribute withdrawal because the central nervous system is heavily concentrated with opioid receptors. Additionally, the other two factors contain items that relate to the ESC approach. Recall that ESC is a function-based assessment tool that places focus on infant's overall progress and ability to eat, sleep, and be consoled to guide treatment decisions. One factor that emerged in the current study included items such as crying, sleeping, excessive sucking, and bowel movements. Future research should examine how the TEN prediction models align with the ESC literature. The ESC approach is the one of the first alternatives to the modified Finnegan that has been integrated into hospitals and data from the first empirical studies should be considered when developing or replicating pharmacological prediction models.

Moreover, future research should replicate the current factor analysis of the TEN prediction model to examine the generalizability of the prediction models. Critically, replication studies can increase generalizability, propose meaningful modifications, and improve effect size estimates (Bonett, 2012).The ultimate goal is to develop a prediction tool that clinicians can administer to differentiate between infants that require pharmacotherapy and those who do not within the first 48 hours. Making treatment decisions before the typical 5-7-day window could potentially reduce length of hospital stay, reduce hospital cost, enhance the mother-infant bond, and target specific interventions or referrals based on the particular withdrawal symptoms observed during the first two days of life. In order to maximize the potential of the prediction

www.manaraa.com

tools clinicians can use an objective scoring tool to differentiate withdrawal symptoms from typical newborn behaviors (Lucas & Knobel, 2012; Timpson, Killoran, Maranda, Picarillo, & Bloch-Salisbury, 2019). For instance, Timpson and colleagues (2019) created a reference guide that provides education about conditions that could interfere with withdrawal symptoms (e.g. wet diaper). This guide gives nurses instructions on how to score infants with the modified Finnegan, to ensure that environmental influences are not confounding withdrawal symptoms. This and other aids could reduce the inconsistencies in the scoring of the modified Finnegan. Until a measure with better psychometric properties is implemented to measure or quantify withdrawal in neonates, it will be hard to create a more effective prediction model than the one presented in the current study (Zimmerman-Baer et al., 2010).

In conclusion, the current study successfully replicated the pattern of results from Isemann and colleagues (2017). More importantly, the current study extended the original findings from an urban region to a unique sample from a rural region of Appalachia. Additionally, the type of prenatal drug exposure is important. All of the current prediction models were improved when type of drug exposure was included. Finally, the TEN_2 prediction model is the best predictor of pharmacological treatment across all of the models considered in the current study. The TEN_2 created the best balance between sensitivity and positive predictive value and had the highest AUC value indicating it was better at distinguishing between patients requiring treatment and patients not requiring treatment.

www.manaraa.com

References

Abdel-Latif, M. E., Pinner, J., Clews, S., Cooke, F., Lui, K., & Oei, J. (2006). Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among Infants of drug-dependent mothers. *Pediatrics, 117*. https://doi.org/10.1542/peds.2005-1561

Arlettaz, R., Kasgiwagi, M., Das-Kundu, S., Fauchére, J. C., Lang, A., & Bucher, H. U. (2005). Methadone maintenance program in pregnancy in a Swiss perinatal center (II): Neonatal outcome and social resources. *Acta Obstetricia et Gynecoloica Scandinavica*, *84*, 145–150. https://doi.org/10.1111/j.0001-6349.2005.00510.x

Azuine, R., Ji, Y., Chang, H. Y., Kim, Y., Ji, H., DiBari, J. B., … Wang, X. (2019). Prenatal risk factors and perinatal and postnatal outcomes associated with maternal opioid exposure in an urban, low-Income, multiethnic US population. *JAMA Network Open*, *2*(6). https://doi.org/10.1001/jamanetworkopen.2019.6405 (Reprinted)

Bateman, B., Hernandez-Diaz, S., Ratmell, J., Seegar, J., Doherty, M., Fischer, M., & Huybrechts, K. (2014). Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology*, *120*(5), 1216–1224. https://doi.org/10.1097/ALN.0000000000000172

Bakhireva, L. N., Holbrook, B. D., Shrestha, H., Leyva, Y., Ashley, M., Cano, S., … Leeman, L. (2019). Association between prenatal opioid exposure, neonatal opioid withdrawal syndrome, and neurodevelopmental and behavioral outcomes at 5-8 months of age. *Early Human Development*, *128*, 69–76. https://doi.org/10.1016/j.earlhumdev.2018.10.010.

Beckwith, A. M., & Burke, S. A. (2015). Identification of early developmental deficits in infants with prenatal heroin, methadone, and other opioid exposure. *Clinical Pediatrics*, *54*(4), 328–335. https://doi.org/10.1177/0009922814549545

www.manaraa.com

Bernstein, V. J., Jeremy, R. J., Hans, S. L., & Marcus, J. (1984). A longitudinal study of offspring born to methadone-maintained women. II. Dyadic Interaction and Infant Behavior at 4 months. *The American Journal of Drug and Alcohol Abuse*, *10*(2), 161–193. https://doi.org/10.3109/00952998409002779

Bonett, D. G. (2012). Replication and Extension Studies. *Association for Psychological Science*.

Campbell, E. M., Sittig, D. F., Ash, J. S., Guappone, K. P., & Dykstra, R. H. (2006). Types of unintended consequences related to computerized provider order entry. *JAMIA*, *13*(5), 547–556.

Caritis, S., & Panigrahy, A. (2019). Opioids affect the fetal brain: Reframing the detoxification debate. *American Journal of Obstetrics Gynecology*, *221*(6), 602–608.https://doi.org/10.1016/j.ajog.2019.07.022

Conner, S. N., Bedell, V., Lipsey, K., Macones, G. A., Cahill, A. G., & Tuuli, M. G. (2016). Maternal marijuana use and adverse neonatal outcomes: A systematic review and meta-analysis. *Obstetric Gynecology*, *128*(4), 713–723. https://doi.org/10.1097/AOG.0000000000001649

Conradt, E., Flannery, T., Aschner, J., Annett, R., Croen, L., Duarte, C., … Lester,B. (2019). Prenatal opioid exposure: Neurodevelopmental consequences and future research priorities. *Pediatrics*, *144*(3). https://doi.org/10.1542/peds.2019-0128

D'Apolito, K., & Hepworth, J. T. (2001). Prominence of withdrawal symptoms in polydrug-exposed infants. *Perinatal and Neonatal Nursing*, *14*(4), 46–60. https://doi.org/10.1097/00005237-200103000-00005

Davie-Gray, A., Moor, S., Spencer, C., & Woodward, L. J. (2013). Psychosocial characteristics and poly-drug use of pregnant women enrolled in methadone maintenance treatment. *Neurotoxicology and Teratology*, *38*, 46–52. https://doi.org/10.1016/j.ntt.2013.04.006

www.manaraa.com

Devlin, L., Lau, T., & Radmacher, P. (2017). Decreasing total medication exposure and length of stay while completing withdrawal for neonatal abstinence syndrome during the neonatal hospital stay. *Frontiers in Pediatrics*, *5*(216). https://doi.org/: 10.3389/fped.2017.00216

Finnegan, L. P., Connaughton, J. F., Kron, R. E., & Emich, J. P. (1975). Neonatal abstinence syndrome: Assessment and management. *Addictive Diseases*, *2*.

Fluss, R., Faraggi, D., & Reiser, B. (2005). Estimation of the Youden Index and its associated cutoff point. *Biometrical Journal*, *47*(4), 458–472. https://doi.org/10.1002/bimj.200410135

Greig, E., Ash, A., & Douiri, A. (2012). Maternal and neonatal outcomes following methadone. *Archives of Gynecology and Obstetrics*, *286*, 843–851. https://doi.org/10.1007/s00404-012-23729

Greiner, M., Pfeiffer, D., & Smith, R. D. (2000). Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Preventive Veterinary Medicine*, *45*(1–2), 23–41. https://doi.org/10.1016/s0167-5877(00)00115-x

Grossman, M., Minear, S., Whalen, B., & Wachman, E. (2017). Eating, sleeping, consoling (ESC) neonatal abstinence syndrome (NAS) care tool. *Boston Medical Center Corporation*.

Gomez-Pomar, E., & Finnegan, L. P. (2018). The epidemic of neonatal abstinence syndrome, historical references of its origins, assessment, and management. *Frontiers in Pediatrics*, *6*. https://doi.org/10.3389/fped.2018.00033

Gunn, J. K., Rosales, C. B., Center, K. E., Nunez, A., Gibson, S. J., Christ, C., & Ehiri, J. E. (2016). Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open*, *6*(4). https://doi.org/10.1136/bmjopen-2015-009986.

www.manaraa.com

Haight, S., Ko, J., Tong, V., Bohm, M., & Callaghan, W. (2018). Opioid use disorder documented at delivery hospitalization—United States, 1999–2014. *MMWR Morb Mortal Wkly Rep*, *67*(31), 845–849. http://dx.doi.org/10.15585/mmwr.mm6731a1

Handal, M., Engeland, A., Ronning, M., Skurtveit, S., & Furu, K. (2011). Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: A population-based cohort study. *European Journal of Clinical Pharmacology*, *67*(9), 953–960. https://doi.org/10.1007/s00228-011-1030-7

Hanley, J. A., & Mcneil, B. J. (1983). A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*, *148*(3), 839–843.

Hans, S. L., & Jeremy, R. J. (2001). Post neonatal mental and motor development of infants exposed in utero to opioid drugs. *Infant Mental Health Journal*, *22*(3), 300–315. https://doi.org/10.1002/imhj.1003

Hudak, M., & Tan, R. (2012). Neonatal drug withdrawal. *Pediatrics*, *129*(2), 540–560. https://doi.org/10.1542/peds.2011-3212

Hunt, R. W., Tziomi, D., Collins, E., & Jeffery, H. E. (2008). Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Human Development*, *84*(1), 29–35. https://doi.org/10.1016/j.earlhumdev.2007.01.013

Huybrechts, K. F., Bateman, B. T., Desai, Rishi. J., Hernandez-Diaz, S., Rough, K., Mogun, H., … Patorno, E. (2017). Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: Cohort study. *BMJ*, *358*. https://doi.org/10.1136/bmj.j3326

Iqbal, M. M., Sobhan, T., & Ryals, T. (2002). Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatric Services*, *53*(1), 39–49. https://doi.org/10.1176/appi.ps.53.1.39

www.manaraa.com

Isemann, B. T., Stoeckle, E. C., Taleghani, A. A., & Mueller, E. W. (2017). Early prediction tool to identify the need for pharmacotherapy in infants at risk for neonatal abstinence syndrome. *Pharmacotherapy*, *37*(7), 840–848. https://doi.org/10.1002/phar.1948

Jansson, L. M., Velez, M. L., & Harrow, C. (2009). The opioid exposed newborn: Assessment and pharmacologic management. *Journal of Opioid Management*, *5*(1), 47–55. https://doi.org/10.5055/jom.2009.0006

Johnson, K., Gerada, C., & Greenough, A. (2003). Substance misuse during pregnancy. *British Journal of Psychiatry*, *183*, 187–189. https://doi.org/10.1192/bjp.183.3.187

Jones, H. E., Seashore, C., Johnson, E., Horton, E., O'Grady, K. E., & Andringa, K. (2016). Measurement of neonatal abstinence syndrome: Evaluation of short forms. *Journal of Opioid Management*, *12*(1).

Kahila, H., Saisto, T., Kivitie-Kallio, S., Haukkamaa, M., & Halmesmäki, E. (2007). A prospective study on buprenorphine use during pregnancy: Effects on maternal and neonatal outcome. *Acta Obstetricia et Gynecoloica Scandinavica*, *86*(2), 185–190. https://doi.org/10.1080/00016340601110770

Kaltenbach, K., O'Grady, K. E., Heil, S. H., Salisbury, A. L., Coyle, M. G., Fischer, G., … Jones, H. E. (2018). Prenatal exposure to methadone or buprenorphine: Early childhood developmental outcomes. *Drug and Alcohol Dependence*, *185*, 40–49. https://doi.org/10.1016/j.drugalcdep.2017.11.030

Lind, J., Interrante, J., Ailes, E., Gilboa, S., Khan, S., Frey, M., … Broussard, C. (2017). Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review. *Pediatrics*, *139*(6). https://doi.org/10.1542/peds.2016-4131.

www.manaraa.com

Logan, B. A., Brown, M. S., & Hayes, M. J. (2013). Neonatal abstinence syndrome: Treatment and pediatric outcomes. *Clinical Obstetric Gynecology*, *56*(1), 186–192. https://doi.org/10.1097/GRF.0b013e31827feea4.

Lucas, K., & Knobel, R. B. (2012). Implementing practice guidelines and education to improve care of infants with neonatal abstinence syndrome. *Advanced Neonatal Care*, *12*(1), 40–45. https://doi.org/10.1097/ANC.0b013e31824bd73

Ludlow, J.P., Evans, S. F., & Hulse, G. (2004). Obstetric and perinatal outcomes in pregnancies associated with illicit substance abuse. *Australian and New Zealand Journal of Obstetrics and Gynecology*, *44*, 302–306. https://doi.org/10.1111/j.1479-828X.2004.00221.x

Maguire, D., Cline, G. J., Parnell, L., & Yi Tai, C. (2013). Validation of the Finnegan neonatal abstinence syndrome tool-short form. *National Association of Neonatal Nurses*, *13*(6), 430–437. https://doi.org/doi: 10.1097/ANC0000000000000033

McGlone, L., & Mactier, H. (2015). Infants of opioid-dependent mothers: Neurodevelopment at six months. *Early Human Development*, *91*(1), 19–21. https://doi.org/10.1016/j.earlhumdev.2014.10.006

Merhar, S. L., McAllister, J. M., Wedig-Stevie, K. E., Klein, A. C., Meinzen-Derr, J., & Poindexter, B. B. (2018). Retrospective review of neurodevelopmental outcomes in infants treated for neonatal abstinence syndrome. *Journal of Perinatology*, *38*(5), 587–592. https://doi.org/10.1038/s41372-018-0088-9

Messinger, D. S., Bauer, C. R., Das, A., Seifer, R., Lester, B. M., Lagasse, L. L., … Poole, K. W. (2004). The maternal lifestyle study: Cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. *Pediatrics*, *113*(6), 1677–1685.

www.manaraa.com

Miller, A. M., McDonald, M., & Warren, M. D. (2016). Neonatal Abstinence Syndrome Surveillance Annual Report 2016. *TN Department of Health*.

Naguib, M., Alton, K., Avula, V., Hagglund, K., & Anne, P. (2014). Heart rate variability evaluation in the assessment and management of in-utero drug-exposed infants. *SAGE Open Medicine*, *2*. https://doi.org/2050312114556525

Nygaard, E., Moe, V., Slinning, K., & Walhovd, K. B. (2015). Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. *Pediatric Research*, *78*, 330–335. https://doi.org/10.1038/pr.2015.95

Nygaard, E., Slinning, K., Moe, V., & Walhovd, K. B. (2016). Behavior and attention problems in eight-year-old children with prenatal opiate and poly-substance exposure: A longitudinal study. *PLos One*, *11*(6). https://doi.org/10.1371/journal.pone.0158054

O'Connor, A. B., Kelly, B. K., & O'Brien, L. M. (2017). Maternal and infant outcomes following third trimester exposure to marijuana in opioid dependent pregnant women maintained on buprenorphine. *Drug and Alcohol Dependence*, *180*. https://doi.org/10.1016/j.drugalcdep.2017.08.012

Oei, Ju. L., Melhuish, E., Uebel, H., Azzam, N., Breen, C., Burns, L., … Wright, I. M. (2017). Neonatal abstinence syndrome and high school performance. *Pediatrics*, *139*(2). https://doi.org/10.1542/peds.2016-2651

Oji-Mmuo, C. N., Schaefer, E. W., Liao, L., Kaiser, J. R., & Sekhar, D. L. (2019). The possibility of early discharge for newborns being monitored for neonatal abstinence syndrome based on modified Finnegan score distributions. *Clinical Pediatrics*, *58*(6), 641–646.

www.manaraa.com

Patrick, S., W., Schumacher, R., E., & Bennyworth, B., D. (2012). Neonatal abstinence syndrome and associated health care expenditures. *JAMA*, *307*(18), 1934–1940. https://doi.org/10.1001/jama.2012.3951

Patrick, S., Davis, M., Lehman, C., & Cooper, W. (2015). Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *Journal of Perinatology*, *35*(6).

Parikh, R., Mathai, A., Parikh, S., Sekhar, G. C., & Thomas, R. (2008). Understanding and using sensitivity, specificity and predictive values. *Indian J Ophthalmology*, *56*(1), 45–50.

Pomar, E. G., Finnegan, L. P., Devlin, L., Bada, H. S., Concina, V. A., Ibonia, K. T., & Westgate, P. M. (2017). Simplification of the Finnegan neonatal abstinence scoring system: Retrospective study of two institutions in USA. *BMJ Open*, *7*. https://doi.org/10.1136/bmjopen-2017-016176

Roupp, M. D., Perkins, N. J., Whitcomb, B. W., & Schisterman, E. F. (2008). Youden Index and optimal cut-point estimated from observations affected by a lower limit of detection. *Biometrical Journal*, *50*(3), 419–430. https://doi.org/doi: 10.1002/bimj.200710415

Ryan, S. A., Ammerman, S. D., & O'Connor, M. E. (2018). Marijuana use during pregnancy and breastfeeding: implications for neonatal and childhood outcomes. *Pediatrics*, *142*(3). https://doi.org/10.1542/peds.2018-1889

Salo, S., Politi, J., Tupola, S., Biringen, Z., Kalland, M., Halmesmaki, E., … Kivitie-Kallio, S. (2010). Early development of opioid-exposed infants born to mothers in buprenorphine-replacement therapy. *Journal of Reproductive Infant Psychology*, *28*(2). https://doi.org/10.1080/02646830903219109

Sanlorenzo, L. M., Cooper, W. O., Dudley, J. A., Stratton, S., Maalouf, F. I., & Patrick, S. W. (2019). Increased severity of neonatal abstinence syndrome associated with concomitant antenatal opioid

www.manaraa.com

and benzodiazepine exposure. *Hospital Pediatrics*, *9*(8), 569–575. https://doi.org/10.1542/hpeds.2018-0227

Stein, Y., Hwang, S., Liu, C. L., Diop, H., & Wymore, E. (2019). The association of concomitant maternal marijuana use on health outcomes for opioid exposed newborns in Massachusetts, 2003-2009. *Journal of Pediatrics*, *19*. https://doi.org/10.1016/j.jpeds.2019.10.071

Stover, M., & Davis, J. (2015). Opioids in pregnancy and neonatal abstinence syndrome. *Seminars in Perinatology*, *39*(7), 561–565. https://doi.org/10.1053/j.semperi.2015.08.013

Timpson, W., Killoran, C., Maranda, L., Picarillo, A., & Bloch-Salisbury, E. (2018). A quality improvement initiative to increase scoring consistency and accuracy of the Finnegan tool: Challenges in obtaining reliable assessments of drug withdrawal in neonatal abstinence syndrome. *Advanced Neonatal Care*, *18*(1), 70–78. https://doi.org/doi:10.1097/ANC.0000000000000441

Towers, C. V., Hyatt, B. W., Visconti, K. C., Chernicky, L., Chattin, K., & Fortner, K. B. (2019). Neonatal head circumference in newborns with neonatal abstinence syndrome. *Pediatrics*, *143*(1).

Trevethan, R. (2017). Sensitivity, Specificity, and Predictive values: Foundations, pliabilities, and pitfalls in research and practice. *Frontier Public Health*, *5*(307).

Velez, M. L., McConnell, K., Spencer, N., Montoya, L., Tuten, M., & Jansson, L. M. (2018). Prenatal buprenorphine exposure and neonatal neurobehavioral functioning. *Early Human Development*, *117*, 7–14.

Villapiano, N. L., Winkelman, T. N., Kozhimannil, K. B., Davis, M. M., & Patrick, S. W. (2017). Rural and Urban differences in neonatal abstinecne syndrome and maternal opioid use, 2004 to 2013. *JAMA Pediatrics*, *171*(2), 194–196.

www.manaraa.com

Wachman, E. M., Warden, A. H., Thomas-Lewis, J. A., Shrestha, H., Nikita, F., Shaw, D., Saia, K., & Schiff, D. M. (2018). Impact of psychiatric medication co-exposure on neonatal abstinence syndrome severity. *Drug and Alcohol Dependence*, *1*(192), 45–50. https://doi.org/10.1016/j.drugalcdep.2018.07.024

Walhovd, K., Watts, R., CandPsychol, A., & Woodward, L. (2012). Neural tract development of infants born to methadone-maintained mothers. *Pediatric Neurology*, *47*, 1–6. https://doi.org/10.1016/j.pediatrneurol.2012.04.008

Yeoh, S. L., Eastwood, J., & Wright, I. M. (2019). Cognitive and motor outcomes of children with prenatal opioid exposure. *Pediatrics*, *2*(7). https://doi.org/10.1001/jamanetworkopen.2019.7025

Young-Wolff, K. C., Tucker, L.Y., Alexeeff, S., Armstrong, A., Conway, A., Weisner, C., & Goler, N. (2017). Trends in self-reported and bio-chemically tested marijuana use among pregnant females in California From 2009-2016. *JAMA*, *318*(24), 2490–2491. https://doi.org/10.1001/jama.2017.17225

Yuan, Q., Rubic, M., Seah, J., Rae, C., Wright, M. R., Kaltenbach, K., … Oei, J. L. (2014). Do maternal opioids reduce neonatal regional brain volumes? A pilot study. *Journal of Perinatology*, *34*, 909–913. https://doi.org/10.1038/jp.2014.111

Zimmerman-Baer, U., Notzli, U., Rensch, K., & Bucher, H. (2010). Finnegan neonatal abstinence scoring system: Normal values for first 3 days and weeks 5-6 in non-addicted infants. *Addiction*, *105*, 524–528.

www.manaraa.com

APPENDICES

Appendix A: TiTE and TiTE$_2$ Experiment 1A with 25th and 75th Percentile Cutoff Values

TiTE Score Predicting No Pharmacotherapy			TiTE Score Predicting Pharmacotherapy		
	Not Treated	Treated		Treated	Not Treated
Score ≤ 1.33	78	28	Score ≥ 3	65	32
Score > 1.33	139	140	Score < 3	103	185
Sensitivity	35.9%		Sensitivity	38.7%	
Specificity	83.3%		Specificity	85.3%	
PPV	73.6%		PPV	67.0%	
NPV	50.2%		NPV	64.2%	
TiTE$_2$ Score Predicting No Pharmacotherapy			TiTE$_2$ Score Predicting Pharmacotherapy		
	Not Treated	Treated		Treated	Not Treated
Score ≤ 2	80	16	Score ≥ 4.5	72	24
Score > 2	132	152	Score < 4.5	96	188
Sensitivity	37.7%		Sensitivity	42.9%	
Specificity	90.5%		Specificity	88.7%	
PPV	83.3%		PPV	75.0%	
NPV	53.5%		NPV	66.2%	

PPV = positive predictive value; NPV = negative predictive value

www.manaraa.com

Appendix B: TiTE and TiTE2 Experiment 1A with Median Cutoff Values

TiTE Score Predicting Pharmacotherapy		
	Treated	Not Treated
Score ≥ 2	119	108
Score < 2	49	109
Sensitivity	70.8%	
Specificity	50.2%	
PPV	52.4%	
NPV	68.9%	
TiTE2 Score Predicting Pharmacotherapy		
	Treated	Not Treated
Score ≥ 3	137	83
Score < 3	31	129
Sensitivity	81.5%	
Specificity	60.8%	
PPV	62.3%	
NPV	80.6%	

PPV = positive predictive value; NPV = negative predictive value

www.manaraa.com

Appendix C: TiTE and TiTE2 Experiment 1B with 25th Percentile and 75th Percentile Cutoff Values

TiTE2 Score Predicting No Pharmacotherapy		
	Not Treated	Treated
Score ≤ 1.75	83	17
Score > 1.75	129	151
Sensitivity	39.2%	
Specificity	89.9%	
PPV	83%	
NPV	53.9%	
TiTE2 Score Predicting Pharmacotherapy		
	Treated	Not Treated
Score ≥ 4	86	27
Score < 4	82	185
Sensitivity	51.2%	
Specificity	87.3%	
PPV	76.1%	
NPV	69.3%	

PPV = positive predictive value; NPV = negative predictive value

www.manaraa.com

Appendix D: TiTE and TiTE2 Prediction Models Experiment 1B with Median Cutoff Values

TiTE2 Score Predicting Pharmacotherapy		
	Treated	Not Treated
Score ≥ 2.88	129	64
Score < 2.88	39	148
Sensitivity	76.8%	
Specificity	69.8%	
PPV	66.8%	
NPV	79.1%	

PPV = positive predictive value; NPV = negative predictive value

www.manaraa.com

Appendix E: TiTE and TiTE2 Experiment 1B with Youden's Index Cutoff Values

TiTE Score Predicting Pharmacotherapy		
	Treated	Not Treated
Score ≥ 3.85	9	159
Score < 3.85	1	216
Sensitivity	90.0%	
Specificity	57.6%	
PPV	5.36%	
NPV	99.5%	
TiTE2 Score Predicting Pharmacotherapy		
	Treated	Not Treated
Score ≥ 3.96	86	82
Score < 3.96	27	185
Sensitivity	76.1%	
Specificity	69.3%	
PPV	51.2%	
NPV	87.3%	

PPV = positive predictive value; NPV = negative predictive value

www.manaraa.com

VITA

LONI PARRISH

Education:	M.A. Psychology, concentration in Experimental Psychology, East Tennessee State University, Johnson City, Tennessee, 2018
	B.A. Psychology, Tennessee State University, Nashville, Tennessee, 2018
	Fort Zumwalt East Highschool, St. Peters, Missouri, 2014
Professional Experience:	Graduate Assistant, East Tennessee State University, College of Arts and Sciences, 2018-Current
Publications:	Parrish, L., Chroust, A. 2020. Who Needs Morphine? A Replication and Extension of a Prediction Tool Identifying Need for Treatment Among Opioid Exposed Infants. International Congress of Infant Studies. Glasgow, United Kingdom (poster presentation)
	Parrish, L., Chroust, A., Eveland-Sayers, B., Boynewicz, K., Dotterweich, A. 2019. Serial Spatial Memory Performance and Physical Activity 5-11 years old. Appalachian Student Research Forum. Johnson City, TN (poster presentation)
Honors and Awards:	Excellence in Teaching Award for Graduate Assistants, East Tennessee State University, 2020
	Psychology Department Inclusion Task Force Representative, 2020

www.manaraa.com

Graduate Student Board of Psychology Representative, 2019

Priester- Sloan Family Psychology Scholarship, 2019

www.manaraa.com