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Effects of Adjunct Therapy Medications on Length of Stay of NAS Infants Treated with Rescue Dosing

Morgan E. Graham
University of Tennessee, mgraha36@vols.utk.edu

EFFECTS OF ADJUNCT THERAPY MEDICATIONS ON LENGTH OF STAY OF NAS INFANTS TREATED WITH RESCUE DOSING

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Morgan E. Graham
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INTRODUCTION

Neonatal Abstinence Syndrome (NAS) is a diagnosis given to infants who exhibit multiple physiological symptoms of withdrawal upon the cessation of prenatal substance exposure at birth (Conradt et al., 2019; Hartgrove et al., 2019; Sanlorenzo et al., 2018). The incidence of mothers giving birth to infants with NAS skyrocketed to levels that were unheard of following the third wave of the United States' opioid epidemic in 2013 (Sanlorenzo et al., 2018). Particularly in the rural regions of the southern United States, the rates of NAS births in some areas have increased nearly 400 times what they were in 2000, during the early years of the epidemic (Harder & Murphy, 2019; Sanlorenzo et al., 2018). However, despite the increased prevalence of the syndrome, there is no standard protocol for treating these infants, and much of the research on drug treatment comparisons has produced conflicting results. Moreover, the effects of different drug treatments have yet to be examined within the context of newly introduced protocols. Therefore, there still clearly exists a need for further research and analyzation on NAS treatment protocols and their effects. This project serves to fill a gap in the literature on NAS by examining the effect of adjunct therapy medications on the length of hospital stay (LOS) in the context of East Tennessee Children's Hospital's (ETCH) rescue dosing treatment protocol.

LITERATURE REVIEW

Methadone versus Morphine

There is much debate regarding whether morphine or methadone is the better treatment for NAS infants going through withdrawal, but the body of this comparative research yields inconclusive results. Though both are acceptably used for treatment, they are two genetically different substances that operate through similar mechanisms of action. The main differences between the two being (1) the way in which they are created and (2) the type of neurotransmitter receptor they bind to.

First, morphine is a natural opioid. Natural opioids are the naturally-produced, organic

substances that can be taken directly from the opium poppy and require no alteration to produce effects (Narcotics, 2019; Fookes, 2019). One of these natural opioids, morphine, is commonly used as an analgesic as well as a treatment for drug withdrawal (Robinson, 2002). In the case of NAS, morphine is the most common treatment for infant withdrawal used in the United States (Brown, Hayes, & Thornton, 2015). Regarding its mechanism of action, morphine can bind to mu, kappa, and delta opioid receptors in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it inhibits the pain signals passing through the body (Murphy & Barrett, 2019).

In contrast to morphine's genetics, methadone is a synthetic opioid that was created primarily for the purpose of treating opioid addiction by "maintenance therapy or detoxification" and it is typically the most common treatment for addiction during pregnancy (Robinson, 2002, p. 377; Sanchez et al., 2008; Mcglone, Mactier, & Weaver, 2009; Whelan & Remski, 2012; Monnelly et al., 2018). Synthetic opioids are the antithesis of natural opioids in regard to their origin. While natural opioids are derived directly from the opium poppy, synthetic opioids lack any poppy-based components (Narcotics, 2019). These opioids are made exclusively in laboratories with chemical properties and structures that resemble that of natural opioids (Narcotics, 2019). Methadone's main mechanistic difference from morphine is that methadone only targets and binds to mu receptors to achieve its pain-inhibiting goal (Anderson & Kearney, 2000). This treatment drug was originally believed to fully prevent NAS in infants, but this was proved to be false among further investigation (Whelan and Remski, 2012; Stevens, Heffnera, Flaughera, & Mohan, 2017; Monnelly et al., 2018).

In the context of the current study, which will be discussed in further detail later, ETCH has developed a new protocol for NAS known as "rescue dosing" and uses morphine as both their primary withdrawal treatment and their rescue dose of medication. Infants who need additional help weaning under this new protocol are treated with clonidine and/or phenobarbital to aid in the control of their

withdrawal symptoms.

Clonidine and Phenobarbital

While ETCH's rescue dosing is not the most commonly practiced treatment protocol for NAS, the hospital's use of clonidine and phenobarbital as adjunct treatment medications is not uncommon. Each of the two drugs have been studied for nearly a decade as adjunct therapies to be used with morphine as well as possible replacements for morphine in the treatment of NAS (Agthe et al., 2009; Nayeri et al., 2015; Siu & Robinson, 2014; Streetz et al., 2016). However, similar to the research on morphine versus methadone, the findings on whether clonidine or phenobarbital is the better treatment for NAS withdrawal are somewhat contradicting, so they tend to be used in different situations.

Clonidine is an alpha-2 adrenergic receptor agonist that binds alpha-2a, alpha-2b, and alpha-2c receptors to affect the sympathetic nervous system and the CNS in ways that produce analgesic, sedative, and stabilizing effects that combat opioid withdrawal symptoms (Basker et al., 2009; Siu & Robinson, 2014; Streetz et al., 2016). Multiple studies have found the addition of clonidine as an adjunct therapy with morphine to significantly decrease infants' LOS when compared to withdrawal treatment by morphine alone, while also finding the drug to be safe for infants in regards to adverse side-effects (Agthe et al., 2009; Siu & Robinson, 2014; Streetz et al., 2016). Additionally, when tested against morphine as a primary withdrawal therapy, also referred to as a single-drug therapy, infants that received clonidine had a treatment duration that was nearly two-weeks shorter than that of the infants that received morphine (Streetz et al., 2016). Other related studies have also seen similar results, suggesting that clonidine could be a safe and more efficient alternative to morphine (Siu & Robinson, 2014).

Phenobarbital is a barbiturate that produces both sedative and anti-seizure effects in infants going through multi-drug withdrawal by binding to GABA-A receptors and thus inhibiting signals in the CNS

(Lewis & Adams, 2020; Siu & Robinson, 2014). Similar to clonidine, phenobarbital was also found to significantly decrease the duration of withdrawal treatment when paired with morphine as an adjunct treatment in comparison to morphine alone (Siu & Robinson, 2014). In contrast to the clonidine findings, researchers have come to different conclusions regarding phenobarbital as a primary treatment. Some research has shown that there are no significant difference in the effects of phenobarbital as a single-drug therapy on LOS or treatment duration when compared to morphine, while others have found that phenobarbital as a primary treatment causes a significantly longer treatment duration (Nayeri et al., 2015; Siu & Robinson, 2014).

ETCH most often introduces clonidine as an adjunct therapy to control severe symptoms before introducing phenobarbital. This decision reflects the position of the many researchers and healthcare providers that recommend clonidine for withdrawal in children, most likely due to clonidine's lower potentials for abuse and overdose as well as its shorter duration of treatment in relation to phenobarbital (Francois et al., 2015; Siu & Robinson, 2014). Although both drugs still require research regarding their long-term effects on infants, the current known effects of phenobarbital provide several disadvantages for its use as an NAS treatment. Phenobarbital has been found to cause CNS depression, increased tolerance, an impaired sucking reflex, and potentially harmful drug interactions, and much is still unknown about its long-term cognitive effects (Francois et al., 2015; Siu & Robinson, 2014; Surran et al., 2013). Moreover, while phenobarbital has been found to decrease both LOS and number of morphine treatment days as an adjunct therapy compared to clonidine, it has an overall treatment duration that is significantly longer than clonidine (Siu & Robinson, 2014; Streetz et al., 2016; Surran et al., 2013). It is important to acknowledge, though, that the most significant findings regarding clonidine's effects were obtained from infants exposed to opioids, like methadone or heroin, and that some research suggests phenobarbital is the safer treatment in respect to withdrawal caused by

benzodiazepines, sedatives—hypnotics, or any combination of those with opioids (Agthe et al., 2009; Surran et al., 2013). In general, current research supports ETCH's use of clonidine as the first approach at adjunct therapy for NAS withdrawal; not only is it the safest option for the infants, but it also decreases their overall treatment time and their likelihood of long-term effects (Streetz et al., 2016).

While many of these studies have found that the addition of clonidine and/or phenobarbital as an adjunct treatment with morphine does decrease an NAS infant's LOS, it must be noted that these studies were comparing treatment groups with NAS symptoms of similar severity. The current study does not classify infants' NAS by severity when examining adjunct therapy's effect on LOS, and it is important to remember this key difference when examining this study's results.

CURRENT PROJECT

Population

Tennessee NAS Rates and Appalachian Region

Tennessee is one of the southern states that has experienced the full extent of the NAS aftermath of the opioid epidemic (Sanlorenzo et al., 2018). By 2016, the east regions of the state were diagnosing infants with NAS in approximately 27 out of every 1,000 births (Sanlorenzo et al., 2018). Moreover, the Tennessee counties included within the Appalachian region have reported rates of 60 NAS infants per 1,000 births, exceeding over "10 times the national average" (Erwin et al., 2017; Warren et al., 2015). As of December 2019, though rates are decreasing, there had been nearly 800 new NAS diagnoses in Tennessee, with the largest number of cases occurring in those same Appalachian regions (Health, 2019). These rates are unsurprising given that nonmedical opioid use and abuse in the rural Appalachian regions are the highest rates in the United States
(Moody et al., 2017).

Appalachian History and Risk Factors

The drug use throughout the Appalachian counties is highly representative of the region's high rates of job related injuries, chronic pain, unemployment, and drug availability and low levels of academic education, health education, and access to medical care (Moody et al., 2017). While these variables are not all directly linked to opioid use during pregnancy, each variable plays or has played a role in creating the risk factors faced by mothers and potential mothers in this area.

Appalachia's relationship to coal mining could be regarded as one of the most influential factors in the region's struggles with opioid abuse. First, isolated communities developed around coal mining have long been correlated with poverty and poor economic outcomes, and past research has found this correlation to be stronger for the Appalachian region than any other coal mining community in the U.S. (Betz et al., 2015). The overall lack of resources in the community provides few individuals with the means to leave, offering them no choice but to stay and work in the coal industry. Then, the chronic pain induced by the physicality of mining created a large necessity for opioid treatment beginning around the 1990's, but the opiates' inadequate regulations within the community quickly produced an environment of readily available opioid
drugs (Moody et al., 2017).

Furthermore, the lack of health education and access to health care within the Appalachian communities poses an increased risk for addiction and blood-borne diseases like Hepatitis C (Erwin et al., 2017; Moody et al., 2017). The risk for opioid-using women developing Hepatitis C before or during pregnancy is specifically high due to the drastically increasing rate of people under 30 being diagnosed with the disease in the Appalachian regions, which is the same maternal age range that includes over 75% of NAS births in the state (Erwin et al., 2017; Moody et al., 2017). However, many women who want to receive treatment for their addiction, Hepatitis C, or prenatal care will be unable to for any of the following reasons: (1) lack of insurance, (2) inability to travel to a qualified health professional, and/or

(3) lack of knowledge of treatment, all of which reflect back on the region's poverty and scarce resources (Moody et al., 2017). Additionally, another possible factor that prevents women from seeking treatment is the "self-contained culture" that is commonly seen within Appalachian communities, which typically leads to individuals being weary of outsiders or approaches that may be unfamiliar or unknown to them, and this again reflects on the regions lack of available education (Moody et al., 2017).

Independent from drug use, the Appalachian region communities have also been found to report notably higher rates of psychological stress and depressive disorders than those reported throughout the rest of the country (Zhang et al., 2008). These findings reflect the insurmountable amount of research that shows an association between poverty and psychological stress and mental disorders (Belle, 1990). Further, women, particularly those who are unemployed, single mothers, or lacking a support system, are significantly more likely to show diagnosable depressive symptoms (Belle, 1990). Considering that many of the mothers of NAS infants are un-partnered, mental health should also be considered as a risk factor before and after pregnancy (Erwin et al., 2017).

NAS at East Tennessee Children's Hospital

Treatment Protocol – Rescue Dosing at ETCH

In many cases of NAS treatment comparisons, researchers typically focus on infants' length of stay (LOS) in the Neonatal Intensive Care Unit (NICU) as a determination of treatment protocol success (Hartgrove et al., 2019; Lanier, 2019). Studies performed at Knoxville, Tennessee's East Tennessee Children's Hospital (ETCH) have taken this same approach to assess the success of their change in NAS treatment protocol that was introduced in 2014 (Lanier, 2019). Before 2014, ETCH's protocol for treating NAS infants involved scoring the infant's withdrawal symptoms using the standardized Finnegan scale assessment to determine a proper maintenance dosage of morphine (Hartgrove et al., 2019; Lanier, 2019). Failure of this maintenance dosage to properly control symptoms would lead to an

increase in morphine dosage, and the treatment process would start at the beginning, thus resulting in a prolonged LOS (Lanier, 2019). This treatment protocol seems to be the most common practice for NAS in the United States, typically only varying by the choice of treatment drug, like morphine or methadone or drug combinations. Nevertheless, ETCH developed a new protocol termed "Rescue Dosing" with the goals of preventing the restart of treatment and decreasing LOS (Hartgrove et al., 2019; Lanier, 2019; *Neonatal Intensive Care In East Tennessee*). This new protocol involved administering an extra "rescue" dose of morphine for infants whose symptoms were not being properly managed at the previously determined level (*Neonatal Intensive Care In East Tennessee*). Two separate analyses have been performed to compare the effect of treatment type on LOS, with both resulting in the conclusion that the rescue dosing protocol has a significant effect on decreased LOS (Hartgrove et al., 2019; Lanier, 2019).

Additional Variables Affecting LOS

With the discovery of the benefits of a rescue dosage protocol in decreasing LOS, it is important to examine additional variables outside treatment protocol that could further affect an infant's LOS. There is not currently any existing research that examines the possible effects of the additional administration of drugs other than morphine during the weaning process in relation to LOS in NAS infants. As mentioned earlier, under their protocol, ETCH's treatment drug of choice is morphine. Multiple studies comparing morphine to methadone for NAS treatment conducted within the past five years have produced conflicting results in regard to which drug better decreases LOS (Davis et al., 2018; Young et al., 2015), with the most recently conducted meta-analysis finding no significant difference in LOS between the two drugs (Xiao et al., 2019). With the large majority of the focus having been placed on morphine versus methadone, there is a lack of information surrounding the possible effects of additional medications administered with morphine on LOS compared to the LOS of infants who receive morphine only. Again, ETCH's rescue dosage weaning protocol includes the administration of

phenobarbital and/or clonidine to infants experiencing increased symptom severity (Hartgrove et al., 2019). An important next step would be to investigate whether or not infants who receive these additional drug treatments have increased or decreased LOS when compared to morphine only infants, specifically in the context of rescue dosing.

Hypothesis

For my analysis, I want to explore the possible effects of additional drug dosages on NAS infants' LOS in the context of ETCH's rescue dosing methods. I will attempt to answer if LOS varies significantly for infants who receive morphine only compared to infants who receive a combination of (a) morphine and clonidine or (b) morphine, phenobarbital, and clonidine. I hypothesize that infants who require adjunct treatment in addition to their morphine dosages will have a longer LOS than morphine-only infants.

METHODS

Sample

All data used for this analysis was taken from the data collected as part of the East Tennessee Family Strengths Study and was selected to be indicative of the East Tennessee and Appalachian populations. This study, conducted by researchers within the Early Experiences Lab at the University of Tennessee in collaboration with East Tennessee Children's Hospital, is currently in the process of collecting data on the strengths and challenges faced by families in East Tennessee with a focus on those with children born with NAS. The researchers recruited infants from the ETCH NICU that were admitted with a diagnosis of NAS and had a gestational age of 32 weeks or greater. All infants were considered for the study, but 14 of the 67 total infants were excluded from the sample due to their lack of drug treatment data. The sample included 53 infants (31=males, 22=females), 5 of which received morphine and clonidine and 3 that received morphine, clonidine, and phenobarbital. These infants did

not have any diagnoses of HIV, fetal alcohol syndrome (FAS), or severe congenital abnormalities. The data regarding the infants' received drug dosages was extracted directly from their medical records obtained through ETCH's medical record database. Further information regarding the specific characteristics of the infants included in the sample, as well as their birth mothers, can be found in Table 1.

Table 1.
Sample description at time of data collection.

Descriptor	Observed							
	N		M		SD		%	
Infants								
Sex								
Male	31						58.5	
Female	22						41.5	
Birthweight (grams)	53		2970.3		627.5			
Gestational Age at Birth (weeks)	53	37.7		1.9				
LOS (days)	53		19.2		9.7			
Finnegan Score at Admission	35		9.5		3.2			
NAS Treatment								
Morphine Only	45						84.9	
Morphine & Adjunct Treatment	8						15.1	
Biological Mothers								
Age (years)	53		28.4		5.7			
Race								
African American	3						5.7	
Latina	1						1.9	
White	48						90.6	
Mixed Race	1						1.9	
Education Level								
Some High School	12						22.6	
High School Graduate or GED	25					47.2		
Trade/Technical/Vocational Training	4						7.5	
College	10						18.9	
Graduate	1						1.9	
Employment								
Employed	14					26.4		
Unemployed	37						69.8	
Student	2						3.8	
Smoked during Pregnancy								
Yes	35						72.9	
No	13						27.1	
Consumed Alcohol								
Yes	2						4.1	
No	47						95.9	
Feelings of Depression								
Rarely or None of the Time	20						37.7	
Sometimes	24						45.3	
Most or All of the Time	9					17		

Note: LOS = length of stay; NAS = Neonatal Abstinence Syndrome; GED = general education degree

Study Design

The 53 qualifying infants were first sorted into two groups for the "Treatment Received" variable: (1) Morphine Only, and (2) Morphine & Clonidine/Phenobarbital. From there, the data for those specific infants was transferred from the original medical records data file, obtained from the East Tennessee Family Strengths Study database, to an independent SPSS file. All data variables were included for each of the qualifying infants, but not all variables were considered for this study. The variables of interest for this study included those most closely related to the diagnosis of NAS and its treatment, such as the infants' LOS at ETCH, Finnegan scores at admission, received treatments, and the duration of treatment. To determine the possible relationship between the main variables LOS and type of treatment received, the two variables were analyzed together before additional analyses were performed to explore possible confounding variables.

Statistical Analysis

All analyses for the current study were performed using the Statistical Package for Social Sciences (SPSS) software version 26. A t-test was performed with the two variables "Treatment Received" and "LOS" to measure whether there was a significant difference in the average LOS of infants who received morphine only compared to those who received adjunct treatments. A boxplot diagram and a scatterplot were also created using the same variables to provide a visual representation of their relationship. Multiple scatterplots were produced with fit lines for possible mediator variables for the LOS and treatment type relationship, and these variables included "Finnegan Score at Admission," "Infant Highest Morphine Dose," and "Morphine Duration." Additionally, Pearson's correlation coefficients (r) were for the relationships between these variables as represented by the scatterplots. A 95% confidence interval was used to evaluate the significance of all relationships examined.

RESULTS

LOS versus Treatment Received

The results of the t-test concluded that there is a significant difference between the LOS of infants who received adjunct treatments ($M = 30.75$, $SD = 6.21$) and those that received morphine only ($M = 17.27$, $SD = 9.11$; $p < 0.001$). While a t-test cannot be visualized through a figure, the LOS versus Treatment Received boxplot serves to provide a visual representation of the significant difference between the mean LOS of the two infant treatment groups (Figure 1B). The scatterplot serves to provide a simple visualization of the independent data points in each treatment group (Figure 1A).

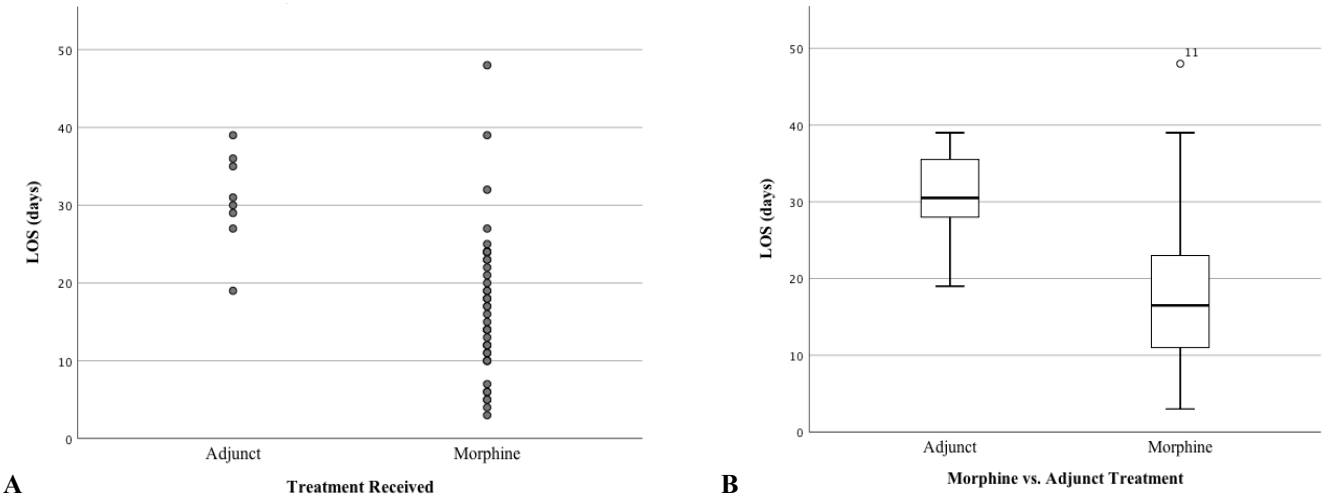

Figure 1. (A) Scatterplot of LOS by the type of treatment infants received. **(B)** Boxplot of LOS by the type of treatment infants received.

Additional Variables

The scatterplots for the Finnegan score, highest morphine dose, and morphine duration variables all established slight, positive relationships with LOS, and the Pearson's correlations values for these relationships exhibited multiple significant findings (Figure 2A,B,C; Table 2). First, the highest morphine dose that infants' received was found to have a significant relationship with LOS ($r = 0.69$; $p < 0.0001$), Finnegan score ($r = 0.36$; $p = 0.047$), and morphine duration ($r = 0.96$; $p < 0.0001$) (Table 2). In addition, infants' duration of morphine treatment was found to be significantly related to infants' LOS

($r = 0.71$; $p < 0.0001$), as would be expected due to the requirement that the infants must remain in the hospital to receive their treatment until it is completed (Table 2).

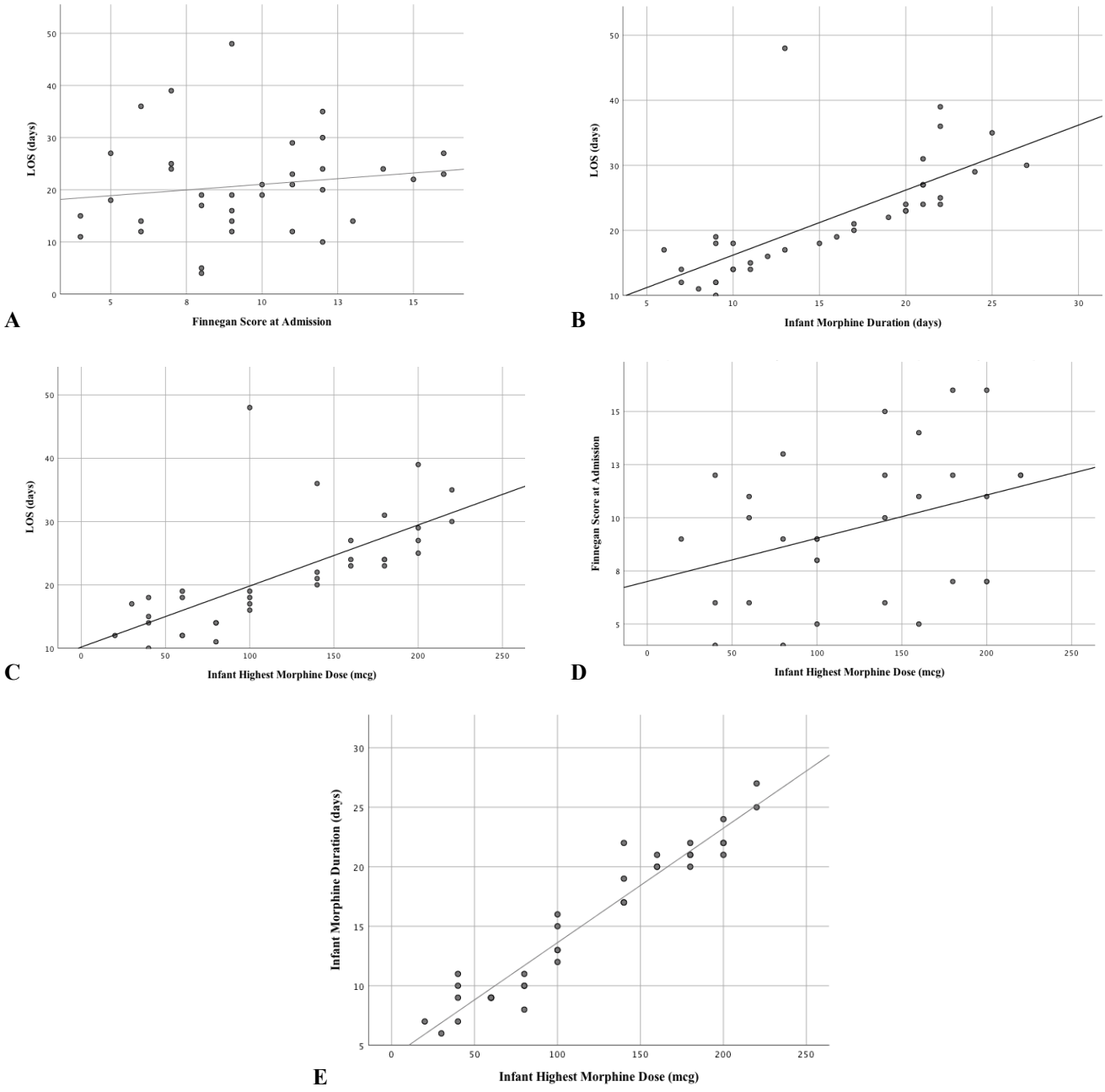

Figure 2. Scatterplots of various relationships between additional variables. **(A)**, **(B)**, and **(C)** represent the relationships between the three additional variables (Finnegan score at admission, morphine duration, and highest morphine dose) and LOS. **(D)** and **(E)** represent the relationship between the highest morphine dose infants received and the other two additional variables, Finnegan score and morphine duration, respectively.

Table 2.

Table of Pearson's Correlations for additional variables.

		Finnegan Score at Admission	Infant Highest Morphine Dose	Infant Morphine Duration	Length of NICU Stay
Finnegan Score at Admission	Pearson Correlation	1	.360*	.305	.149
	Sig. (2-tailed)		.047	.095	.392
	N	35	31	31	35
Infant Highest Morphine Dose	Pearson Correlation	.360*	1	.964**	.687**
	Sig. (2-tailed)	.047		.000	.000
	N	31	36	36	36
Infant Morphine Duration	Pearson Correlation	.305	.964**	1	.710**
	Sig. (2-tailed)	.095	.000		.000
	N	31	36	36	36
Length of NICU Stay	Pearson Correlation	.149	.687**	.710**	1
	Sig. (2-tailed)	.392	.000	.000	
	N	35	36	36	55

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

This study found that infants with NAS being treated with rescue dosing who receive adjunct therapies in addition to their morphine treatment have a significantly longer LOS than their counterparts that receive only morphine. While this conclusion may seem to oppose the findings of many researchers who have examined this relationship before, the current findings make sense in the specific context of this study. As mentioned previously in the literature review, the previous studies that have examined clonidine and phenobarbital's effects on LOS when used as adjunct therapies have done so in the context of NAS severity. These studies have comparison groups that contain infants that all have similar levels of NAS symptom severity, which is typically determined the infants' Finnegan scores (Agthe et al., 2009; Nayeri et al., 2015; Surran et al., 2013). However, in the case of the current study, I did not have access to the Finnegan scores for all of the infants included in the sample ($N = 35$ compared to $N = 53$),

so further sorting and classification of NAS severity would have significantly cut down on the study's sample size. The decision to examine the effects of adjunct treatment on LOS without controlling for NAS severity still allows for the addition of foundational data to the literature on ETCH's rescue dosing treatment protocol. The finding that adjunct treatments are related to prolonged LOS is consistent with what would be expected based on the literature. As alluded to previously, the infants that meet the criteria for receiving any of the adjunct treatments are those that experience more severe withdrawal (Agthe et al., 2009; Nayeri et al., 2015; Surran et al., 2013). These infants with severe withdrawal typically must undergo longer periods of treatment to be fully weaned from the drugs in their systems, and longer treatment duration thus leads to a longer LOS. These trends are clearly represented in the scatterplot of the LOS and treatment group data (Figure 1A).

In addition, the findings produced by the analyses of the additional variables Finnegan score at admission, highest morphine dose received, and duration of morphine treatment showed multiple significant relationships between the data. The most obvious finding was the significance between the duration of morphine treatment and LOS, which is unsurprising because the infants are required to stay in the hospital while receiving their treatment. The other findings from these analyses showed a significant relationship between infants' highest morphine dosages and the LOS, Finnegan scores, and duration of morphine treatment, with the Finnegan score relationship having the least significance (r = 0.36; p = 0.047) and morphine duration having the highest significance (r = 0.96; $p < 0.0001$). It is important to acknowledge the significance of these findings due to their possible interactions with the relationship between adjunct treatment and LOS. While I have not yet examined the data for such relationship, it could be assumed that infants receiving the highest dosages are those who have the most severe symptoms and are therefore most likely to receive an adjunct treatment. Moreover, it may be that the Finnegan score, with its positive relationship to highest morphine dose, could be used as a predictor

for infants' needing of an adjunct therapy. It could also be possible that, based on other adjunct treatment literature, these clonidine and phenobarbital can be used as adjunct treatments to decrease the strength of the relationship between highest morphine dose an infant receives and their duration of morphine treatment in the context of rescue dosing (Agthe et al., 2009; Nayeri et al., 2015; Surran et al., 2013).

Overall, this study and its findings add to small amount of literature that exists on the effects of adjunct therapy medications on the LOS of NAS infants being treated with rescue dosing. The finding that adjunct therapies prolong infants' LOS when not controlled for NAS severity is an important conclusion to acknowledge when considering both adjunct therapies and rescue dosing in the future. It is necessary that analyses of these variables that do control for symptom severity are conducted in the context of rescue dosing. Furthermore, other future investigations should continue to examine this relationship with regard to additional variables such as infants' Finnegan scores at NICU admission, the highest dose of morphine they receive during treatment, and the overall duration of their morphine treatment.

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