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Polysubstance Exposure and its Relationship to Pharmacological Treatment Characteristics

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Abstract

Neonatal Abstinence Syndrome (NAS) remains an ever-growing public health issue and a continued avenue for future research. The research question for this retrospective study was whether polysubstance exposure is related to the dose of medication the infant received or to the number of opioid-medications required to treat the infants' withdrawal symptoms? The hypothesis for the retrospective study was there will be a significant relationship between polysubstance exposure and the dose of medication the infant received as well as the number of opioid-medications required to treat the infants' withdrawal symptoms. A bivariate correlational indicated that there was not a significant association between the number of substances exposed to prenatally and the total number of drugs infants were treated with (n = 294, r = 0.093, p = .113). Additionally, within the largest group of pharmacologically treated infants (i.e., morphine), the highest dosage of morphine was not related to the number of drugs infants were exposed to prenatally, n = 195, r = -0.098, p = .172.

Polysubstance Exposure and its Relationship to Pharmacological Treatment Characteristics

With President Donald Trump's declaration that the opioid crisis is a public health emergency in October 2017, it comes as no surprise to find that Neonatal Abstinence Syndrome (NAS) remains a continuing public health issue. Almost 64,000 Americans died from a drug overdose in 2016 with opioid overdoses making up 42,000 of these deaths, more than any previous recorded year (White House, n.d.). Drug addiction is difficult to treat due to those who have become addicted suffering from chronic relapse. Even after extended periods of abstinence from drugs, a high percentage of addicted individuals in treatment programs eventually relapse. In a study of heroin users, relapse rates to reuse after cessation of the drug were 60% within 3 months and at least 75% within 12 months (Robinson, Robinson, & Berridge, 2013).

NAS is a condition affecting newborns that are exposed to opioids prenatally (Finnegan, Connaughton, Kron & Emich, 1975). Clinical outcomes of NAS deviate with a multitude of influencing variables such as the type of opioid used, the drug history of the mother, the most recent use of the drug by the mother before delivery of the newborn, how much of the drug crosses the placenta, as well as infant metabolism and excretion of the drug. Maternal use of other substances like cocaine and cigarettes may additionally influence the severity and duration of NAS. Since opioid receptors are concentrated in the central nervous system and the gastrointestinal tract, the symptoms of opioid withdrawal are related to neurologic excitability and gastrointestinal dysfunction. Symptoms of neurologic excitability include tremors, increased wakefulness and increased muscle tone. Symptoms of gastrointestinal dysfunction include poor feeding, vomiting, and poor weight gain. Additionally, increased environmental stimuli and hunger can worsen the severity of NAS (Hudak & Tan, 2012). Typical onset of symptoms of neonatal withdrawal from heroin begin within 24 hours of birth, while withdrawal from

methadone, a drug that blocks heroin-induced euphoria, usually happens around 24 to 72 hours of age (Zelson, Rubio, & Wasserman, 1971). For both opioids, evidence of withdrawal may be delayed until 5 to 7 days of age or later (Kandall & Gartner, 1974).

A major development in understanding and treating NAS was the development of the Neonatal Abstinence Scoring System (NASS), also known as the "Finnegan Scoring System" (Finnegan et al., 1975). The developers of the NASS designed the assessment by choosing what they considered 20 common signs of neonatal withdrawal. There are 32 items requiring scores on the assessment (Jones & Fielder, 2015). The NASS is the most widely used assessment tool in either its original 1975 format or a modified version as recommended by the American Academy of Pediatrics. However, there have been many adaptations of the modified tool with no single modified version that has been applied universally (McQueen & Murphy-Oikonen, 2016).

Infants with NAS are at increased risk for admission to the neonatal intensive care unit as well as a prolonged hospital stay. Both outcomes can separate the mother and her infant during a critical time for infant development and bonding. The average length of stay for infants with NAS is 17 days overall and 23 days for those requiring treatment (McQueen & Murphy-Oikonen, 2016; Patrick, Davis, Lehmann, & Cooper, 2015). The primary goals when managing NAS are to promote normal growth and development of the infant, and to minimize negative outcomes that could impair maternal bonding. The initial care of all infants who have been exposed to substances in utero should be supportive and nonpharmacologic. A soothing environment with minimal stimulation should be created in order to calm the infant. This involves limiting exposure to lights and noise as well as swaddling and holding the infant. Sixty to eighty percent of infants with NAS do not have a response to nonpharmacologic treatment and require medication (Kocherlakota, 2014; McQueen & Murphy-Oikonen, 2016).

Identification of infants at risk for NAS is crucial to ensure early intervention as well as manage signs of withdrawal in the newborn. However, many women are hesitant to discuss substance use due to social and legal consequences. It is recommended clinicians use a nonjudgmental approach when interviewing pregnant women about substance use during pregnancy to encourage and facilitate disclosure. In addition to maternal self-report, results of biologic testing of the pregnant mother or the newborn can help provide accurate assessment of substance exposure (McQueen & Murphy-Oikonen, 2016). Since there are no federal guidelines establishing criteria for the testing of newborns or pregnant women, it is up to health care institutions to determine guidelines for newborn and maternal drug testing to best identify and manage substance abuse in their unique population. Evidence has shown that the rate of positive results is higher for biological specimens than the rate of self-reported substance use (Cotten, 2012). The American College of Obstetrics and Gynecology and the American Academy of Pediatrics both recommend universal screening of substance use in pregnancy to avoid bias (American College of Obstetricians and Gynecologists, 2017; Patrick & Schiff 2017). The primary advantage of universal screening is increased sensitivity. However, for most health care institutions, universal screening of newborns for maternal non-medical drug use is impractical and not cost effective. The alternative to universal screening is targeted screening which identifies women that are at a higher risk. Each method of biologic testing is beneficial in identifying drug exposure in the newborn, but the tests have limitations including how far back in the pregnancy the tests detect for drug exposure.

Possible biological samples from the mother that can be used in testing include urine and hair while collection for the newborn include urine, hair, and meconium, the first stool of an infant passed in the first 72 hours after birth. Additionally, umbilical cord blood and tissue can be

analyzed. Maternal hair has the widest window of drug detection with months to years depending upon hair length. Meconium is the current gold standard and most common biological sample due to its wide detection window. It detects drug exposure primarily from the third trimester. Umbilical cord tissue is becoming an alternative to meconium since the two share similar windows of detection. Advantages of umbilical cord tissue include always being available at birth, its collection being noninvasive, and it being a waste product. However, meconium and umbilical cord tissue differ in composition, origin, and function. These differences affect what specific drugs and metabolites accumulate (Concheiro & Huestis, 2018). Colby, Adams, Morad, Presley, and Patrick (2018) found umbilical cord tissue and meconium may not be equivalent for confirming in utero substance exposure. Some disadvantages of meconium include sample loss if meconium is passed in utero as well as neonatal urine contaminating the meconium sample (Concheiro & Huestis, 2018).

An infant urine test detects drug exposure within the last few days of fetal life. Careful sample collection is necessary because the first urine specimen is the most highly concentrated. False negative results are possible because drugs can escape through the urine quickly (McQueen & Murphy-Oikonen, 2016). When analyzing maternal urine samples, different opioids have different urine detection windows. 6-acetylmorphine, a metabolite of heroin, has a detection window less than a day while methadone has a detection window of 1-14 days (ARUP Laboratories, 2019).

Two final methods of biologic testing in infants include infant hair and umbilical cord blood. Infant hair detects drug exposure from the beginning of the third trimester. An advantage of using infant hair is it can be collected for several months after birth. Detection of drug exposure is limited when there is an insufficient hair sample. Umbilical cord blood detects drug

exposure in the last few hours or days of fetal life. A sample of cord blood is collected at the time of birth. Since drug concentrations are lower in cord blood, testing is less sensitive than testing of other biological specimens (McQueen & Murphy-Oikonen, 2016).

After screening a mother with a newborn at risk for NAS, it is a possibility that polysubstance exposure to the infant could have occurred. Polysubstance abuse during pregnancy is associated with impaired fetal markers like heart rate and a greater need for pharmacologic therapy to treat the infants' withdraw symptoms (Jansson et al., 2012). A retrospective study by Seligman and colleagues (2012) demonstrated that the length of NAS treatment for infants exposed to opioids only was 31 days compared with 38 days for polysubstance exposed infants.

NAS remains an ever-growing public health issue and a continued avenue for future research. The US incidence of NAS has increased from 1.19 per 1000 hospital births in 2000 to 5.63 in 2012. During the same time period, the number of infants treated for NAS in US neonatal intensive care units increased by five times (Patrick, Davis, Lehmann, & Cooper, 2015). Additionally, the recent rise of opioid use in pregnancy and NAS has disproportionately occurred in rural areas (Cicero, Ellis, Surratt, & Kurtz, 2014). One avenue of research would be to investigate if there is a relationship between polysubstance exposure and to the dose of medication the infant received, or to the number of opioid-medications required to treat the infants' withdraw symptoms. Since NAS is growing in a more rural population, it seems fitting to focus on a population in East Tennessee as well as Appalachia. The research question for this retrospective study was focused on whether polysubstance exposure is related to the dose of medication the infant received or to the number of opioid-medications required to treat the infants' withdrawal symptoms? The hypothesis for this retrospective study was there will be a significant association between polysubstance exposure and the dose of medication the infant

received as well as the number of opioid-medications required to treat the infants' withdrawal symptoms.

Methods

The current study utilized an existing database of all deliveries within a regional health care system between July 1, 2011 and June 30, 2016 (n = 18,728). Infant characteristics included in this study are length of hospital stay, Finnegan score, whether the infant was treated pharmacologically for their withdrawal, the drug and highest dosage of the drug used for treatment, and drug screening results (i.e., urine, meconium, cord stat, cord blood). Maternal characteristics included reports of prenatal drug use (i.e., self-report, urine). In the larger database of 18,728 births, 2,638 were coded as having opioid-exposure based on drug screens, self-report, newborn withdrawal, or other conditions indicative of opioid-exposure. Five-hundred seven of those cases had an ICD code of 9/10 indicating an NAS diagnosis. Upon further examination of the cases, 294 cases met the clinical criteria for NAS diagnosis, and 158 cases did not meet the clinical criteria for NAS. For the purposes of this study authors defined clinical criteria as patient had 2 or more consecutive Finnegan scores greater than or equal to 10, or 3 consecutive scores of greater than or equal to 8, or they received pharmacological treatment for withdrawal symptoms.

The number of substances infants were exposed to prenatally was summed by examining all variables related to drug screening results from mother and infant (i.e., maternal self-report, maternal urine drug screen, infant urine drug screen, infant cord blood, infant meconium, infant cord stat). If multiple tests were positive for the same substance (e.g., marijuana), it was only counted once. However, if multiple substances of the same category were documented these were added together. For example, if the drug screening results indicate prenatal exposure to

buprenorphine and morphine the category total for opioids would be equal to two. Table 1 displays the frequency of infant/mother dyad exposure within each category of substances examined in the current study. The number of substances infants were exposed to prenatally ranged from 0 to seven (see Table 2 for more information). If an infant required pharmacological treatment, it is possible that they required more than one drug to control their withdrawal symptoms. The number of drugs required to treat an infant's withdrawal symptoms was summed and ranged from zero to four. The electronic medical records also included information on the highest dosage of drug used during pharmacological treatment of withdrawal symptoms, infant's Finnegan score and infant's length of stay in the hospital.

Results

A bivariate correlational indicated that there was not a significant association between the number of substances exposed to prenatally and the total number of drugs infants were treated with (n = 294, $r = 0.093$, $p = .113$). Additionally, within the largest group of pharmacologically treated infants (i.e., morphine), the highest dosage of morphine was not related to the number of drugs infants were exposed to prenatally, (n = 195, $r = -0.098$, $p = .172$, see Table 3).

However, polysubstance exposure was significantly related to infant's length of stay ($r = 0.226$, $p < .001$). Infants who were exposed to more substances prenatally stayed in the hospital longer. Additionally, the more drugs required to treat an infant's withdrawal, the higher the infant's highest Finnegan score ($r = 0.385$, $p < .001$) and the longer the infant stayed in the hospital ($r = 0.753$, $p < .001$).

Discussion

It was hypothesized that there would be a significant association between the number of drugs infants were exposed to prenatally and the dosage of medication and the number of

medications required to treat the infants' withdrawal symptoms. The data failed to support the hypothesis. There was not a significant correlation between the number of substances infants were exposed to prenatally and the total number of drugs infants were treated with. Additionally, within the largest group of pharmacologically treated infants (i.e., morphine), the highest dosage of morphine was not related to the number of drugs infants were exposed to prenatally.

The lack of an association between polysubstance exposure and the dose of medication the infant received as well as the number of opioid-medications required to treat the infants' withdrawal symptoms documented in the current study may be due to several factors. First, the current study does not account for the impact of nonpharmacological treatment. While 60 to 80% of infants with Neonatal Abstinence Syndrome (NAS) do not have a response to nonpharmacologic treatment and require medication (Kocherlakota, 2014; McQueen & Murphy-Oikonen, 2016), nonpharmacological treatments like breastfeeding, swaddling, and massage have been associated with a decrease in severity of NAS (Mangat, Schmölzer, & Kraft, 2019; Ryan, Dooley, Gerber Finn, & Kelly, 2019). Hospital protocols often involve the implementation of nonpharmacologic interventions before starting pharmacological interventions (Kocherlakota, 2014; McQueen & Murphy-Oikonen, 2016), the effects of polysubstance exposure in infants could have been lessened before pharmacological treatment commenced. The current database had limited information on the implementation of nonpharmacological interventions.

Additionally, studies examining prenatal drug exposure are difficult because there are a multitude of additional variables that may affect each infant's severity of NAS. For example, differences in the mechanisms of the drug used, how recent the drugs were used by the mother before delivery of the newborn, the amount of drug that crossed the placenta, and variability in the infants' metabolism and excretion of the drugs (Hudak & Tan, 2012). Moreover, observed

variability in metabolism of a given drug among mothers and infants has been related to their individual genetics (Wilkinson, 2005).

Although the current data failed to support the hypothesis, significant associations between polysubstance exposure and infant's length of stay were observed. The more drugs infants were documented to have been exposed to prenatally, the longer they stayed in the hospital. Furthermore, these results replicate patterns observed in previous research (Nellhaus, Murray, Hansen, Loudin, & Davies, 2019). Complex pharmacologic interactions between substances can lead to difficulty in treating NAS as the withdrawal symptoms often present different than NAS symptoms resulting from only opioid exposure. Additionally, there were significant associations between the number of drugs used to treat infant's withdrawal and the infant's length of stay and highest Finnegan scores. Again, these results were not surprising given that infants must be weaned off of the pharmacological treatments before they are discharged home. The more drugs they are treated with the longer that process takes.

One limitation of the current study is that it did not investigate specific combinations of polysubstance exposure. That is, by collapsing across all types of polysubstance exposure the current study may be concealing important patterns. For instance, it may not be the total number of substances that infants are exposed to that matter but rather the specific combination of substances. Recent research by Sanlorenzo and colleagues (2019) indicates that benzodiazepine and opioid exposure increases an infants' odd of requiring pharmacological treatment for NAS whereas there was not a significant increase risk of requiring pharmacological treatment if infants were exposed to opioids and other drugs (e.g., tobacco, marijuana, selective serotonin reuptake inhibitors, etc.).

The current study failed to find an association between the number of drugs infants were exposed to prenatally and the number of drugs required to treat their withdrawal. Future research with this data should consider more complex statistical analysis to account for additional variance. For instance, the complexity of polysubstance interactions may be more appropriately modeled using multilevel modeling. Nonetheless, the study is an important first step in examining the complex relationship between polysubstance exposure and pharmacological treatment.

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Table 1. Frequency of Substances.

Type of Substance	Number of Different Substances Within Category	Frequency
Alcohol	0	278
	1	16
Barbiturate	0	289
	1	5
Benzodiazepine	0	247
	1	34
	2	9
	3	3
	4	1
Hallucinogen (non-marijuana)	0	294
	1	0
Marijuana	0	239
	1	55
Opioids	0	90
	1	192
	2	8
	3	3
	4	1
Stimulants	0	265
	1	24
	2	5
Tobacco	0	35
	1	259

Table 2. Descriptive Statistics.

Variable	n	Min, Max Value	Mean (SD)
Number of Drugs Exposed to Prenatally	294	0, 7	2.23 (1.19)
Number of Drugs used to Treat	294	0, 4	0.77 (0.66)
Highest Morphine Dose (mg)	195	.13, 4.0	0.30 (0.28)
Highest Finnegan	294	6, 23	14.09 (2.73)
Length of Stay	294	1, 70	15.10 (11.50)

Table 3. Bivariate Correlations.

	1.	2.	3.	4.	5.
1. Number of Drugs Exposed to Prenatally	-				
2. Number of Drugs used to Treat	0.093	-			
3. Highest Morphine Dose	-0.098	0.041	-		
4. Highest Finnegan	0.099	0.385**	-0.016	-	
5. Length of Stay	0.226**	0.753**	0.044	0.394**	-

* indicates $p < .05$; ** indicates $p < .001$