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Symptomology Associated with in Utero Exposures to Polysubstance in an Appalachian Population.

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Symptomology associated with in utero exposures to polysubstance in an Appalachian population

Abstract

Neonatal abstinence syndrome (NAS) is seen at a very high rate at our institution in Huntington, West Virginia, and the majority of exposures are polysubstance in nature. Polysubstance can have different meanings for different regions. At our institution, polysubstance is any combination of opioids, gabapentin, methamphetamine, cocaine, marijuana, benzodiazepines, nicotine or other neuroactive substances with three to four substances being the norm. Rapidly changing combinations of drug use and the lack of literature creates a difficult situation for clinicians who are often reliant on treatment recommendations that lack references or conclusive data supporting the clinical approaches. Elucidating withdrawal symptoms consistent with *in utero* exposures to particular drug combinations is difficult. Many substances induce similar withdrawal symptoms in neonates and the vast majority of cases present as polysubstance exposure. Standard methodology often leads to a research approach which isolates populations and substance of exposure to determine the individual effects on the neonate. In some drug combinations, like opioid and gabapentin exposure, the substances in concert create symptoms and complications that are not observed with either drug alone. The history of responses to substance use epidemics has been to handle each drug as a separate disease process; this is no longer a viable option. The following is a review of the literature available discussing individual substance withdrawal characteristics in neonates combined with the clinical insight gained at our hospital from treating such high rates of complex polysubstance exposure.

Keywords

NAS, polysubstance, opioids

Introduction

Our institution in Huntington, West Virginia is at the center of the opioid epidemic, and because of this, we see many cases of neonatal abstinence syndrome (NAS). Despite our institution's experience treating NAS, it is important to note the limitations and complications of treatment and research. The lack of literature and studies involving substance abuse outcomes for neonates is crippling. Kraft and van den Anker describe a deficit of reliable data to assist practitioners in determining the best NAS treatment and gaps in knowledge become more prominent when discussing polysubstance abuse.[1] Furthermore, polysubstance abuse in the literature is described more as co-substance abuse. For example, opioid and gabapentin or opioid and nicotine are both described as polysubstance abuse. The polysubstance abuse our institution and many others face is a result of mixing opioids, gabapentin, methamphetamine, cocaine, marijuana, nicotine, as well as fads and designer cocktails that are seen from time to time. As a result, practitioners are reliant upon clinical findings, limited case studies, and off-label use in an attempt to manage withdrawal symptoms in complicated severe NAS cases.

According to Carrasco, Rao, Bearer and Sundararajan, readily established protocols are available for the treatment of NAS.[2] While the framework from treatment remains largely consistent as described by Kraft and van den Anker, the details of treatment can differ greatly, potentially

contributing to infant outcomes.[1] These protocols are based upon knowing the substance of exposure and largely are not adapted to include polysubstance exposure. Identifying and confirming the substance used during pregnancy is often times frustrating and a complication to treatment. According to Behnke and Smith there are two main methods of identifying substances used during pregnancy: self-report and biological specimens.[3] No single approach can accurately determine the presence, dosage, or duration of substances used during pregnancy and each method both for biological samples and self-report has strengths and weaknesses. Urine drug screens (UDS), umbilical cord toxicology, and self-report are the most common methods of substance abuse detection. Confirming the exact exposures, therefore, is often limited to what happens close to time of delivery and is also limited by what the biological test itself is designed to detect.

A third notable limitation is the ever-changing trends in common combinations of drug abuse. Pregnant women use a wide variety of substances with common patterns of polysubstance abuse with polysubstance use as high as 50% in some studies.[4] The common combinations have been known to follow trends in substance abuse including substances that are popular or readily available at the time. The problem in identifying trends in substance abuse is the high turn-over of popular trends. Due to the ever-changing substance abuse environment, it is impossible to predict the next trend, common combinations of substances, or which substance will be the next epidemic.

Although not all substances used during pregnancy will induce a withdrawal syndrome in the neonate, post-delivery symptomatic evidence of exposure for each of most commonly used substances during pregnancy exists. When used in differing combinations, unique symptoms are present in the neonate indicating which substances may have been combined during pregnancy. While confirming exposure would still be limited, symptoms can provide more information creating a more complete picture. By identifying how substances and differing combinations change the neonatal symptoms, it could be possible to eliminate some of the limiting factors of NAS treatment. The unique symptomology could provide a roadmap to treatment helping practitioners make more informed treatment decisions resulting in more appropriate, timely treatment and possibly improved neonatal outcomes.

The following aims to combine our clinical observations with information from the literature to create a document for recognizing NAS and inform treatment decisions. Included in this document are reviews of symptomology and outcomes according to substance exposure, pharmacological treatment of NAS, and descriptions of common combinations of drugs seen in polysubstance-induced NAS including some generalized treatment plans as reflected in Table 1.

Table 1: Proposed Treatment for Polysubstance Exposure

Substance Combination	**Percentage of Exposed Patients Observed with Combination Exposure**	**Proposed Treatment**
Opioid and Gabapentin	27.7%	Stepwise weaning with accepted opioid alternative. If the neonate does not respond, stepwise weaning with gabapentin may be required.
Opioid and THC	29.4%	Stepwise weaning with accepted opioid alternative. Clonidine as adjunctive agent in severe withdrawal cases.
Opioid and Benzodiazepine	13%	Stepwise weaning with accepted opioid alternative. Clonidine or a matched benzodiazepine as adjunctive agent in severe withdrawal cases.
Opioid and Stimulant	14.7%	Stepwise weaning with accepted opioid alternative. Clonidine as adjunctive agent in severe withdrawal cases.
Opioid and Nicotine/Caffeine	88%	Stepwise weaning with accepted opioid alternative. Clonidine as adjunctive agent in severe withdrawal cases.

Scope and Purpose

A literature search of published research related to neonatal abstinence syndrome and polysubstance exposure was combined with clinical experience from a hospital with a dedicated NAS unit that treats 200-300 neonates annually with proven prenatal exposure and severe withdrawal symptoms to produce this manuscript.[5]

The goal was to combine what was published in literature with what our hospital sees on a day-to-day basis in hopes of presenting a guide for each presentation of neonatal abstinence syndrome due to polysubstance exposure. The literature search was not limited based on date or study design. We did not look at alcohol exposure for this review due to low reliability in testing.

Common Combinations of Substance Abuse

In the discussion of the withdrawal symptoms consistent with particular in utero exposures it is important to consider the difficulty of these evaluations. Not only do many substances induce similar withdrawal symptoms in neonates, but in many populations, including that at our institution, the vast majority of neonates with NAS present with polysubstance exposure. This reality may change the withdrawal symptoms altogether. Therefore, we consider the symptoms that are indicative of certain drug exposures that are seen in cases of neonates exposed to the substance alone (Table 2) and those accompanied by other substances.

Table 2. In utero substance exposure and characteristic withdrawal symptoms

Substance	Characteristic Symptoms	Reported Complications	Reference No.
Opiates (Including heroin, Subutex, and Methadone)	Fever, sweating, tremors, irritability, excessive crying, hypertonic, hyperactive Moro reflex, myoclonic jerks, skin mottling, sleep disturbance, vomiting, sneezing, abdominal cramping/gas, excoriation, yawning, diarrhea (loose/liquid stools), tachypnea, poor feeding, excessive/disorganized suck	Low birth weight, IUGR, prematurity, preeclampsia, small head circumference, impaired learning and memory Reduced cognitive function and school performance Motor delays	(11, 24)
Marijuana	Irritability, hyperactive Moro reflex, excessive suck, increased startles and tremors	Low birth weight, shorter gestation, prolonged sleep disturbances Visual development issues, cognition and memory issues	(11) (12) (25)
Benzodiazepines	Delayed symptom onset, fever, tremors, irritability, sleep disturbance, vomiting, diarrhea, sneezing, muscle twitching, yawning, excessive crying, grimacing, jitteriness, seizures	Low birth weight Preterm delivery	(1) (26)
Barbiturates	Delayed symptom onset, Irritability, hypertonia, diarrhea, vomiting, feeding difficulty, vasomotor instability	Birth defects	(27)
Amphetamines/ Methamphetamines	Fever, tremors, excoriation, vomiting, loose stools, sneezing	Low birth weight, premature birth Long-term adverse effects on behavior, cognitive skills, and physical dexterity	(18)

Cocaine	Fever, tremors, irritability, sleep disturbance, vomiting, diarrhea, sneezing, feeding difficulty, failure to thrive, jitteriness, excessive suck, hyperactive Moro reflex	Poor fetal growth, prolonged growth restriction, developmental delay, learning disabilities, lower IQ	(11)
Gabapentin	Back arching, continuous extremity movement, tongue thrusting, wandering eye movements, increased muscle tone	Preterm birth, low birth weight	(8) (2) (8)
SSRI's	Irritability, seizure, agitation, tremors, hypertonia, increased respiratory rate, nasal congestion, emesis, diarrhea, feeding difficulty, fever, hypoglycemia	Effects on motor development and motor control	(28, 29)
Tobacco	Greater need for handling, poor self-regulation, irritability, hypertonia	Low birth weight, intrauterine growth restriction Inattention and externalizing behavior, poor language development	(3, 20)

1. Common Combinations of Substance Abuse

The following will outline the common combinations of substance abuse attributing to NAS as seen in a high volume specialized unit in Huntington, West Virginia. Literature descriptions of each combination will be included when available however, due to the volume of polysubstance related NAS cases seen in our hospital, the focus of this section is to give a brief outline of our own observations in hopes of providing a guide to distinguish the different types of polysubstance induced NAS.

1.1 Opioid/Gabapentin Withdrawal

Several studies have been published analyzing the abuse of opioids in combination with gabapentin, which is traditionally used to treat partial seizures, neuropathic pain, and restless leg syndrome. Baird, Fox and Colvin[6] found that 22% of their 129 surveyed respondents abused gabapentin in conjunction with methadone, with 38% of those respondents citing gabapentin's

ability to potentiate the effects of methadone as their reason for the concurrent drug use. An additional study from Bastiaens, Galus, and Mazur[7] found that 26% of their 250 surveyed respondents admitted to illegally obtaining or abusing gabapentin. Despite being currently deemed safe for prescription used during pregnancy, in utero gabapentin exposure has been associated with risk for preterm birth and low birth weight.[8] Although opioid/gabapentin NAS has not been widely explored, there have been reports of withdrawal syndromes in neonates exposed to gabapentin alone, in which symptoms of poor feeding, poor coordination, sneezing, irritability, jitteriness, and loose stools were observed.[2]

Neonates presenting with withdrawal secondary to in utero exposure to both opioids and gabapentin has grown over the last few years at our institution, although prevalence is difficult to describe due to our previous primary reliance on maternal admission of drugs abused. Symptom-based diagnoses have increased as the hallmark symptoms of opioid/gabapentin withdrawal have become better described. The symptoms associated with opioid/gabapentin neonatal withdrawal in a cohort at our institution were described by Loudin et al.[9] The symptoms included increased neurobehavioral issues such as tongue thrusting, nystagmus, excessive arching of the back, and exaggerated myoclonic jerks of the extremities. These symptoms prohibit typical weaning of the neonate from the opioids, and in the study on opioid/gabapentin withdrawal, 10 of the 19 neonates described by Loudin et al. required additional pharmacologic therapy in order to wean.[9] These 19 neonates included in this study comprised 10% of the neonates treated for NAS in our hospital for that year.

Our institution has developed a protocol for opioid/gabapentin withdrawal which involves a step-wise weaning of the neonate. This treatment protocol begins with the standard treatment of NAS using an accepted opioid alternative. If the neonate does not respond to this, gabapentin may be required as well, stepping down dosage of gabapentin every three days until symptoms subside.[9] The average length of treatment for neonates treated throughout the combined weaning therapy in that early study was 47 +/- 8.8 days.[9] The long-term effects of opioid/gabapentin withdrawal are not well known, and is an area for further study.

In response to the growing incidence of NAS associated with opioid/gabapentin exposure, we have recently adopted a new urine drug screen (UDS) that is capable of detecting gabapentin use. This new UDS provides physicians with the advantage of supplemental information regarding potential exposures in addition to maternal confession. However, this adaptation also highlights the importance of recognizing specific symptoms in neonates. Before the addition of a new UDS physicians had to rely on maternal admission and neonatal symptoms to determine the likely exposure and to decide on appropriate treatment for the neonate. As trends in substance abuse change it is likely that UDS readily available may not screen for popular substances of abuse and that physicians will rely more heavily on symptom base diagnosis.

1.2 Opioid/THC Withdrawal

The use of marijuana during pregnancy amongst women seeking substance abuse treatment at federally funded treatment centers is on the rise, at 43% nationally.[10] Even outside the population of individuals with substance abuse disorders, marijuana is the most commonly used illicit drug during pregnancy,[4] and is considered to be safe among users and a subset health care

professionals. Conversely, in utero marijuana exposure is thought to cause long-term complications, although it is difficult to flawlessly describe as it is often used in conjunction with other illicit substances. Furthermore, the existing studies focused on marijuana use in isolation during pregnancy are conflicting. Some studies report significant long-term effects, some report subtle effects while others report no lasting long-term effects making it difficult to discern the neonatal outcomes. Similarly, the studies that exist for short-term outcomes are also conflicting.

In our hospital, we see marijuana exposure in many of our complex polysubstance presentations of NAS. Statistics from our institution from 2013-2015 data show that amongst our positive umbilical cord blood toxicology tests from neonates presenting with NAS, roughly 36% (431/1212) test positive for cannabinoids. When analyzed for combination of substances, opioids and cannabinoids are used concurrently in 16% (198/1212) of cases. The symptoms that have been reported in the literature associated with in utero marijuana exposure include increased irritability, tremors, hyperactivity Moro reflex, excessive suck and increased startles.[11,12] These symptoms are often accompanied by decreased birth weight, shorter gestation, and sleep disturbances.[12] While these symptoms are similar to that of opioid withdrawal, and often difficult to differentiate, a true withdrawal syndrome secondary to marijuana exposure has not been described in the literature.[13] Furthermore, while symptoms exist in the neonate no reports of treatment used to manage the symptoms have been reported in the literature.

The use of marijuana with opioids seems to lead to a more severe withdrawal profile as noted within our patient population. This may indicate the need to resort to self-report or a different biological specimen to confirm exposure. Treatment for the cases with confirmed marijuana exposure at our institution is often dependent on the treatment of the opioid withdrawal, involving a step-wise weaning of the neonate using an acceptable opioid alternative with the addition of clonidine as an adjunctive agent in the more severe cases. Worsening severity is of concern for infants exposed to marijuana in utero as the concentration of THC (Δ-9-Tetrahydrocannabinol) has gradually increased since selective cultivation.[12] Due to the wide use of marijuana, increasing THC concentrations, and the conflicting literature further research in the neonatal outcomes is warranted.

1.3 Opioid/Benzodiazepine Withdrawal

Co-abuse of opioids and benzodiazepines occurs frequently in our hospital. Corroborating statistics from 2013-2015 show that amongst our positive umbilical toxicology tests from neonates presenting with NAS, roughly 29% (346/1212) test positive for benzodiazepines and roughly 16% (199/1212) test positive for benzodiazepines in combination with opioids.

In a study analyzing the withdrawal effects of selective serotonin reuptake inhibitors (SSRI) both with and without concomitant benzodiazepines, Salisbury et al[14] found that benzodiazepines tend to worsen the withdrawal symptoms in the neonate. The symptoms mentioned in that study include low mobility of the neonate, high levels of CNS stress, and decreased arousal. Swortfiguer et al reported that in maternal benzodiazepine use in the last month of pregnancy resulted in symptoms of hypotonia and hypoventilation in 42% of the reviewed cases.[15]

At our institution, we have observed that neonates with NAS associated with in utero exposure to benzodiazepines exhibit a delayed onset, in which symptoms present two to three weeks after birth. This may present as a "set-back" for a neonate who had previously been weaning steadily. Characteristic withdrawal symptoms include fever, tremors, irritability, sleep disturbance, vomiting, diarrhea, sneezing, muscle twitching, yawning, excessive crying, grimacing, jitteriness, and seizures. In addition, these neonates often display a unique oral aversion. While the symptoms have been displayed frequently at our institution in infants exposed to both opioids and benzodiazepines, support by the literature is limited as polysubstance studies are infrequent or limited to exposures. Treatment for this particular combination of drugs involves the step-wise weaning of the neonate with an acceptable opioid alternative, with the addition of clonidine and/or a matched benzodiazepine if needed to control the withdrawal symptoms.

1.4 Opioid/Stimulant Withdrawal

Cocaine withdrawal in the neonate is well described, owing to the prevalence of cocaine abuse in the 1980s and the subsequent response by researchers to understand the implications of abuse. In utero stimulant exposure may lead to low birth weight and premature birth.[11] On its own, cocaine acts as a vasoconstrictor to decrease blood flow in utero while blocking the reuptake of dopamine and other neurotransmitters during development, producing defects in CNS formation.[16] Intrauterine cocaine exposure has been shown to epigenetically decrease the expression of 11B-HSD-2, which normally changes cortisol to cortisone in an effort to decrease glucocorticoid exposures in the fetus.[16]

In our experience, neonatal withdrawal from the combination of opioid and cocaine in utero exposure can produce more irritable neonates with tremors and a high-pitched cry. In addition, symptoms characteristic of this exposure combination includes failure to thrive further complicated by fever, sleep disturbance, diarrhea, sneezing, difficulty feeding, jitteriness, excessive suck and hyperactive Moro reflex. Treatment for these neonates involves stepwise weaning of the neonate from the opioids with an acceptable opioid alternative with the addition of clonidine to help control withdrawal symptoms in the more severe cases.

In addition to concerns regarding cocaine use, methamphetamine use has grown world-wide, with Terplan et al[17] reporting that 24% of pregnant women in federally funded treatment centers in the United States admitted to using methamphetamines during pregnancy. We have observed at our institution that opioid/methamphetamine withdrawal is increasingly common among neonates with NAS, and its treatment mirrors the treatment for opioid/cocaine withdrawal. The neonates with in utero methamphetamine withdrawal typically exhibit fever, tremors, excoriation, vomiting, loose stools, and sneezing.

While the use of methamphetamine increasing, including the use in pregnant women or in women of child bearing age, little is known about the neonatal outcomes both short and long-term. Some studies report neonatal neurobehavioral patterns of decreased arousal, increased stress, poor movement quality, and increased incidence of small for gestational age and prematurity associated with in utero exposure to methamphetamine.[18] The exposure has also been associated with a high incidence of being admitted to the newborn intensive care unit and more likely to exhibit poor suck and have small head circumference at birth.[18] Other studies

regarding methamphetamine exposure have focused on issues of the social, economic, and psychological disadvantages that accompany the illicit drug use. One such study reports that pregnant substance users face elevated risks that subsequently affect child development.[17] While vastly important details confound many of the research studies, these findings and the lack of literature warrant further research.

1.5 Withdrawal Combined with Nicotine/Caffeine

While not an illegal substance, tobacco use during pregnancy occurs at a high frequency, especially amongst pregnant women using opiates. Forray et al[19] reported that 77% of women in their study with concurrent substance abuse smoked cigarettes and throughout their pregnancy only 29% of those women achieved abstinence. Therefore, it is important to report on nicotine withdrawal as this often compounds the withdrawal of other substances.

Tobacco use during pregnancy is a well-known risk factor for low birth weight and intrauterine growth restriction.[3] Cornelius and Day reported that in utero tobacco exposure is associated with a greater need for handling, poor self-regulation, irritability, and hypertonia.[20] Tobacco use during pregnancy has been correlated to altered maternal-fetal attachment which can lead to many negative short and long-term outcomes.[4]

In our experience with opioid/nicotine withdrawal in neonates, we observe low birth weight and many neonates that are small for gestational age. While a unique symptomology is not created with opioid/nicotine use, nicotine exacerbates the symptoms of opioid withdrawal necessitating the use of clonidine in addition to the traditional weaning process with an acceptable opioid alternative. Nicotine is so widely used in our population and in many others with substance abuse that it has almost become a normality. A neonate with NAS that has no in utero exposure to nicotine is a novelty. However, it is important to emphasize the exacerbating effect of nicotine leading to a more severe withdrawal profile and note that additional pharmacological intervention may be needed to control the withdrawal symptoms. Many women substitute smoking for other substances during pregnancy and therefore smoking cessation may not be possible or maintainable for many. It is therefore important to know the implications and prepare for neonatal treatment.

In addition to nicotine, caffeine use, sometimes in excess, is common during pregnancy. In a case documented by Montes Bentura et al[21] it is described that excessive caffeine consumption during pregnancy can induce neonatal abstinence syndrome in the absence of opioids or other drugs. Symptoms of irritability, jitteriness, and vomiting have been reported and while these may be extreme cases, they endorse that caffeine consumption can induce withdrawal symptoms in neonates much like in adults. This should be considered during treatment of NAS, as caffeine is often taken by the mother and not reported as a drug of interest.

Discussion

In utero opioid exposure has become a significant problem in neonatal units as the prevalence is alarming and still growing. Although treatment of the opioid-induced withdrawal symptoms in the neonates is now well established in most hospitals throughout the United States, treating

these patients is becoming continually more complex with a disturbing upswing in co-occurring abuse. Opioids are just the beginning as exposure to a single substance is a novelty in many hospitals. Polysubstance exposure is the reality and it is difficult to understand this population by studying one substance at a time. While it is important to note that not all substances will induce withdrawal symptoms alone, co-exposure with opioids can cause differing short and long-term outcomes and alter severity of withdrawal. This phenomenon causes considerable complications for the health care team providing treatment for these neonates. Due to the fast-evolving combinations of drug use and the lack of literature, physicians are reliant on treatment recommendations that lack references to data supporting the clinical approaches of the institution. Physicians are reliant on clinical presentation, the limited power of biological samples, the limited literature available, and self-report to base the treatment decisions.

Concerning the pharmacologic therapy, uncertainty exists about the best drug and posology to be used to treat NAS.[22] When polysubstance abuse is evident, the pharmacologic therapy becomes much more difficult due to a combination of the uncertainty that already exists alongside the complicated symptom presentation and severity that is accompanied by polysubstance abuse. The rationale to use pharmacologic treatment is to ensure proper feeding and development, and to foster the maternal infant bond.[1] The ideal specific drug used for treatment would safely achieve these therapeutic goals while minimizing the total duration of therapy and length of hospitalization.[1] At our institution, the physicians are faced with complicated exposures leading to a severe and oftentimes unique withdrawal profile that renders neonates inconsolable, unable to feed, unable to gain weight, and in an overall deteriorating condition. With the lack of polysubstance research, our institution has incorporated a stepwise weaning protocol that often times includes the use of adjunctive medications such as clonidine, phenobarbital, (Table 3) and sometimes includes substances of exposure such as gabapentin to manage severe withdrawal symptoms. These treatment decisions are not made lightly due to the lack of supporting data and are decided as a last resort when all other treatment options have failed.

Table 3. Pharmacological treatment of NAS

Drug	Clinical Use	Mechanism of Action
Buprenorphine	Amelioration of withdrawal to opioids	Partial mu agonist, ORL-1 agonist, kappa antagonist, delta antagonist
Clonidine	Amelioration of autonomic hyperactivity	Alpha-2 adrenergic receptor agonist
Methadone	Amelioration of withdrawal to opioids	Synthetic complete mu agonist, N-methyl-D aspartate antagonist
Morphine	Amelioration of withdrawal to opioids	Mu opioid receptor agonist
Phenobarbital	Amelioration of hyperactivity, promotes disposition and excretion of opioids	GABAA receptor agonist
Lorazepam	Amelioration of central nervous system disturbances	GABA receptor agonist

Conclusion

As our communities put more emphasis on improving behavioral health and developing more community oriented overall approaches to substance use disorder, the consequences to the youngest patients in this epidemic continue to grow. Research models continue to be targeted at a single specific substance while the representative in utero exposed neonate is feeling the effect of multiple substances. Comprehensive analyses that includes dosage, gestational timing of exposure, frequency of exposure and pattern of exposure is extremely difficult to obtain in a substance using population when more than one substance is involved.[23] Despite these difficulties, research and treatment of NAS must consider multiple substances. When it comes to in utero exposure to neuroactive substances, polysubstance is now the norm.

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