Neonatal Abstinence Syndrome and Corresponding Pharmacotherapy Approaches from 2 University-affiliated Neonatal Intensive Care Units in Puerto Rico (2018–2020)

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Objective: Neonatal abstinence syndrome (NAS) is a set of drug withdrawal symptoms suffered by neonates exposed to drugs in utero. Several studies have widely described NAS incidence and treatment approach; however, little is known regarding the incidence and manifestations of this disease in Puerto Rico (PR). The principal aim of this study was to describe NAS incidence in the neonatal units of hospitals affiliated with the University of PR in terms of occurrence, clinical manifestations, and treatment approaches.

Methods: Our study evaluated the medical records of NAS babies diagnosed from 2018 through 2020 at 2 hospitals affiliated with the University of PR Medical Sciences Campus. Descriptive and inferential statistics were employed to analyze trends.

Results: We identified 12 neonates diagnosed with NAS, 5 with low birthweights (<2500 g); for a NAS incidence of 2 cases per 1000 admitted for the 3 years of recollected data. The urine toxicology results revealed that 9 had experienced intrauterine polydrug exposure. Phenobarbital loading dose were determined on the day of diagnosis (indicated by Finnegan score). The first manifestation of NAS symptoms varied: 8 neonates showed symptoms within 48 hours after birth, whereas 4 had withdrawal symptoms within 72-120 hours of their births. Differences between dosing practices and guidelines were observed, ranging from a 0.69% to a 25% difference during treatment initiation.

Conclusion: Further research on the incidence of NAS in PR (national level) is needed for a deeper understanding that we hope will lead to the development of enhanced treatment protocols in PR.

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Key words: Neonatal abstinence syndrome, Neonatal opioid withdrawal symptom, Pharmacotherapy, Puerto Rico

The group of drug withdrawal symptoms suffered by a neonates antenatally exposed to prescription or illicit drugs is called neonatal abstinence syndrome (NAS). An alternate name for NAS is neonatal opioid withdrawal syndrome (NOWS). The latter term is not commonly used since it restricts the definition of the syndrome to including only intrauterine exposure to opioids and excludes polydrug exposure (1,2). During the first 24 to 48 hours after delivery, health care personnel may observe tremors, high-pitched crying, inconsolability, increased muscle tone, insomnia, watery stools, reduced brain volume, and/or, in the worst case, seizures, jaundice, sepsis, tachypnea, and even unexpected death in drug-exposed newborns (1,3). Exposure to different prescribed drugs (antidepressants, stimulants, hallucinogens, etc.), including opioids (whether short or long acting), will result in varied symptom onset (4,5).

Neonatal abstinence syndrome's symptom severity may be individually assessed using the 21-item Finnegan Neonatal Abstinence Scoring Tool (FNAST) (6). Some have described its deficiencies and variability in terms of its accuracy and interpretation; however, it is one of the most utilized scales for NAS symptom assessment (7). Pharmacotherapy is administered for FNAST scores exceeding 8 (6–8). Methadone, morphine, and buprenorphine are considered first-line pharmacological treatments; these can be combined with clonidine or phenobarbital as adjunctive therapy (1). Recent studies show outcome differences in treatment and stay lengths for neonates exposed to opioids (methadone, buprenorphine, or morphine). Although methadone has shown better outcomes in relation to morphine (9), recent evidence suggests that buprenorphine is the primary pharmacotherapy for NAS; randomized controlled trials show significantly better outcomes for infants with this therapy (10). Breastfeeding, swaddling, rooming-in, acupuncture, positioning, and skin-to-skin contact are common non-pharmacological therapies for newborns with NAS (8). These early non-pharmacological interventions can improve neonatal outcomes, reducing hospitalizations and lessening pharmacological needs (11).

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The incidence of NAS in the US has shown a fivefold increase over the last 10 to 15 years (8,10–12). Despite the efforts of numerous clinical researchers and professional associations to provide guidelines for the treatment of NAS, said treatment still remains difficult, as it relies on a combination of factors, such as the type of drug(s) to which the affected neonate was exposed (ascertained via toxicological tests) and an appropriate assessment of it/them, the clinical presentations of abstinence, and the drug formulations available at the hospital, among others (13,14). Physicians throughout the US have an advantage (in terms of treating NAS) because of the extensive range of clinical studies considering differences in the determinants, prevalence, incidence, and clinical manifestations of NAS; the available knowledge allows the development of evidence-based approaches to care. There are some smaller territories, urban areas, and counties within the US where there is little or no information on NAS, its differential prevalence or incidence, or its diagnosis rates, much less treatment outcomes. This limits the decision-making process of the providers to their experiences and preferences rather than evidence-based care.

This retrospective study, which took place from 2018 through 2020, determined NAS incidence, as well as making clinical observations in terms of the clinical presentations of NAS and associated intrauterine drug exposure, and provided therapies and outcomes from the neonatal units of 2 hospitals affiliated with the University of Puerto Rico Medical Sciences Campus (UPRMSC). In PR, a US territory, substance use disorder is a health emergency, which was exacerbated after the passing of hurricanes Irma and Maria; it is even worse now because of the COVID-19 pandemic (15–20). Therefore, efforts to increase the understanding of these unintended consequences of substance use are important and very much timely. The principal aim of this study was to describe NAS incidence in the neonatal units of hospitals affiliated with UPR in terms of occurrence, clinical manifestations, and treatment approaches.

Materials and Methods

The recruitment of study participants and data collection were conducted via the examination of inclusion and exclusion criteria using electronic and paper medical records. The inclusion criteria for neonates were having a diagnosis of NAS or NOWS and receiving care for either syndrome at any of the neonatal intensive care units (NICUs) of the 2 UPRMSC-affiliated hospitals from 2018 through 2020. It is hospital protocol to transfer neonates with NAS/NOWS to intensive care units. The study included both NAS- and NOWS-diagnosed neonates for a broader description of the clinical manifestations exhibited by these patients. Subjects older than 4 weeks and diagnosed with NAS/NOWS were excluded from the study. The study collected the pharmacotherapy information of the recruited subjects with NAS/NOWS and, when pertinent, any comorbidities. Information regarding birthweight, assigned sex at birth, and gestational age was also collected. Daily Finnegan scores, associated NAS dosing practices, hospital length of stay, and the duration of NAS/NOWS treatment were also documented. Each neonate's antenatal opioid and other drug exposures were obtained from the toxicology results of the neonate and of the child's birth mother. Joint approval from the institutional review boards (IRBs) of the UPRMSC and the recruitment hospitals were granted in January of 2021 (IRB #B1080121 & #E010121), with data collection being initiated in February 2021. All the data were collected using IRB-approved forms.

Descriptive and inferential statistics were employed to analyze trends in the described cases. A Mann–Whitney U test and Fisher's exact test were used to assess associations between exposure to licit and/or illicit substances and outcomes (birthweight, gestational age, degree of prematurity), as well as the type of treatment and outcomes (length of stay and length of treatment).

Descriptive and inferential statistics, using absolute and relative values, were employed to describe cases Absolute and relative frequencies were used to describe the characteristics of the neonates. Medians and interquartile ranges (Q1 and Q3) were employed to describe continuous variables such as birth weight and gestational age, among others. Prior to statistical analysis, the distribution of data was assessed using the Shapiro–Wilk test. Associations between developmental characteristics (e.g., birth weight, gestational age, prematurity) and the type of substance exposure were performed using Fisher's exact test or the Mann–Whitney *U* test, as appropriate. Associations between the type of substance exposure and other outcomes, such as clinical manifestation, severity, length of treatment and length of stay, were evaluated using the Mann–Whitney *U* test. *P* values of .05 or lower were considered statistically significant in our study, and all the statistical analyses were performed using Stata/SE 16 (22).

The 2 hospitals' loading dose practices (weight normalized) were revised and compared with those reported in the current literature and those recommended by the guidelines for each drug (8,13,14,23,24). A comparison chart was created using XLSTAT to show the differences (if any) between the initial loading dose that was recorded (observed) and the recommended (expected) loading dose. A percent error calculation was used to describe potential dosing discrepancies between the observed and the expected doses for each neonate. Because all the neonates were first started on phenobarbital, the phenobarbital loading dose was compared with those of the guidelines or in the literature.

Results

The incidence of NAS per 1000 admissions to the 2 UPRMSC-affiliated NICU from 2018 through 2020 was 2; 12 neonates within the 2 UPRMSC-affiliated hospitals were diagnosed with NAS or NOWS from 2018 through 2020 (3 years). The total NICU admissions from 2018 through 2020 were 2365 neonates. Five infants (41%) were born with low birthweights (<2500 g), and 3 of these 5 infants were identified as premature neonates (with a gestational age < 37 weeks). The other 7 infants were born in the normal weight range (mean = 2566.08 g ± 605.44 g), with 4 being premature. Of the 12 neonates (5 males and 7 females) with NAS, 7 were born premature (60%); of them, urine toxicology results revealed that 71% (n = 5) had experienced intrauterine polydrug exposure, and 57% (n = 4) had experienced opioid exposure (illicit or non-illicit). Urine toxicology results were not found in the medical records of the remaining 3 infants.

The medical records showed that the Finnegan score and phenobarbital loading dose of each infant were determined on the same day; all the neonates started treatment with phenobarbital. The first manifestation of the clinical symptoms of abstinence varied; 66.7% (n = 8) showed symptoms within 48 hours after birth, whereas 4 neonates (33.3%) were recorded as having withdrawal symptoms after 72 to 120 hours of birth. Figure 1 shows the frequencies of the symptoms experienced by all the infants. Tremors, irritability, and high-pitched crying were the most commonly observed symptoms during treatment initiation. All the infants were first administered phenobarbital loading doses, 5 were later co-administered morphine, and 1 was treated only with morphine. Each child's Finnegan score was determined at least once daily (until discharge) and recorded in his/her medical record. One infant was breastfed, with parental presence and while rooming-in; there was no evidence of any kind of non-pharmacological treatment in the medical records of the other 11 neonates.

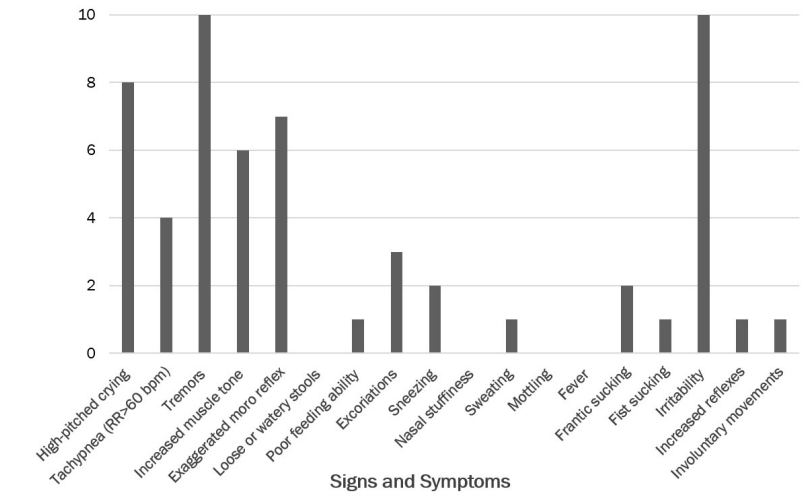
The average overall hospital stay of all the neonates was 38.8 (±14.43) days; however, those who were treated with combined therapy (phenobarbital/morphine; n = 5) stayed longer (53.2 ± 8.76 days) compared to those treated with a single therapy, i.e., phenobarbital (n = 6; 28.6 ± 5.97 days) or morphine (n = 1; 16 days).

Table 1. Characteristics of neonates with NAS > 8 (N = 12)

Measure	Frequency or Mean ± SD	Minimum	Maximum	Median
Sex				
Males (n = 5)	41.6%			
Females (n = 7)	58.3%			
Birth weight (g)	2566.08 ± 605.44	1225	3274	2612
Gestational age (weeks)	36.42 ± 3.06	31	40	36
Polydrug exposure				
Yes (n = 9)	75%			
No (n = 3)	25%			
Opioid exposure				
Yes (n = 8)	67%			
No (n = 4)	33%			
Initiation Finnegan score	14.42 ± 5.30	8	22	15
1st–line therapy				
Phenobarbital (n = 11)	91%			
Morphine (n = 1)	9%			
Adjunct therapy				
Morphine (n = 5)	41%			
None (n = 7)	58%			
Length of treatment for NAS (N = 12)	29.25 ± 12.88	15	58	25.5
Phenobarbital (n = 6)	21.14 ± 4.22	15	29	26
Phenobarbital/morphine (n = 5)	40.60 ± 12.38	58	22	35
Morphine (n = 1)	16 days	-	-	-

The initial weight-normalized loading doses (once daily, in mg) of all the neonates are shown in Figure 3; 11 neonates received an initial loading dose of phenobarbital, and 1 neonate was excluded due to the child's having received only morphine as pharmacological treatment. Following the initial loading dose of phenobarbital, the treatment for 5 neonates included morphine as an adjunct therapy. The bars represent the recorded (observed) phenobarbital loading doses, and the lines represent the recommended (expected) phenobarbital loading doses (per treatment guidelines). The striped stacked columns indicate the loading-dose percent error calculation.

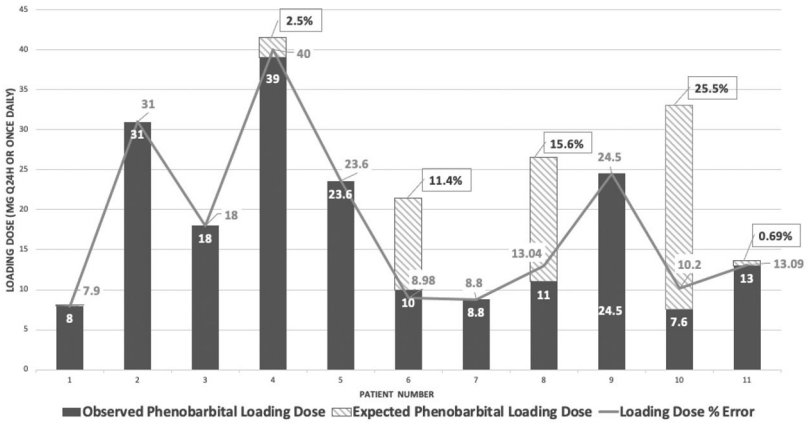
Figure 1. Signs and symptoms using the Finnegan scoring system; these were extracted from the medical records during initiation of treatment.



The observed phenobarbital loading-dose practices differ slightly from those of the suggested/expected doses (Figure 3). Although both doses shown (observed and expected) are weight-based, some observed phenobarbital loading doses were lower than expected (compared to the recommendations of the guidelines); higher doses than those suggested/expected were not found. Differences between observed and suggested/expected loading doses (per the medical records) ranged from 0.6% to 25.5%. When co-administered with phenobarbital (as a second-line agent), the average morphine dose for 6 infants was 1.103 (± 0.493) mg (range: 0.6 to 1.8 mg).

Table 2 shows examination outcomes of the neonates' exposures to drugs before birth on their birthweight, gestational age, and degree

Figure 2. Pharmacological treatment (with phenobarbital): initial loading dose across neonates comparing the recommended (expected) dose based on established protocols and the recorded (observed) doses.



of prematurity. No statistical significance was observed between exposure to polysubstances, methadone, or illicit opioids (or other illicit drugs) and neonate birthweight, gestational age, low birthweight, and degree of prematurity. An examination of the clinical manifestations of the withdrawal symptoms of the neonates in terms of the time for symptoms to occur (assuming that the first appearance of such symptoms was at the same time that said symptoms were detailed in each child's record), number of symptoms, and Finnegan score are presented in Table 3. No significant differences were noted. Table 4 shows observed differences in terms of the treatment lengths of the neonates who received the combined pharmacotherapy of phenobarbital and morphine and those of the infants who received morphine, only (*P* value=.006).

Discussion

Neonatal abstinence syndrome, a known consequence of substance use disorder, is a public health issue that is often overlooked. The syndrome has been well described in some rural and urban areas of the US mainland. The associations of treatment with health outcomes and the overall resulting development of the affected neonates are largely understood. However, in smaller countries—and even in US territories such as PR—little is known about the rate at which neonates are diagnosed with NAS, much less the pharmacotherapy treatment preferences or patterns used by providers when treating NAS symptoms. The scarcity, even complete absence, of information justifies the need to describe current treatment protocols and evaluate areas of opportunity for the optimization of therapy to include evidence-based practices. In this study, the incidence of NAS from 2018 through 2020 was determined by reviewing the medical records of 12 neonates diagnosed with and treated for NAS at 2 UPRMSC-affiliated hospitals from 2018 through 2020. Pharmacotherapy approaches used with these patients were described, as were important clinical NAS manifestations and outcomes. The described pharmacotherapy approaches were compared with treatment outcomes and reported NAS dosing guidelines.

Table 2. Impact of exposure to substances (illicit and non-illicit) on fetal development (*n* = 12)

Risk Factor Exposure	Birth Weight		Gestational Age		Low Birth Weight			Premature Birth		
	Median (Q1, Q3)	*P* value[a]	Median (Q1, Q3)	*P* value[a]	Yes *n* (%)	No *n* (%)	*P* value[b]	Yes *n* (%)	No *n* (%)	*P* value[b]
Polydrug		.079		.511			.523			>.999
Yes (*n* = 9)	2360 (2185, 2915)		36 (33, 39)		6 (66.7)	3 (33.3)		5 (55.6)	4 (44.4)	
No (*n* = 3)	3260 (2560, 3274)		36 (36, 40)		1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)	
Methadone		.465		.579			>.999			>.999
Yes (*n* = 6)	2512 (1985, 3020)		35.5 (33, 40)		3 (50.0)	3 (50.0)		3 (50.0)	3 (50.0)	
No (*n* = 5)	2560 (2245, 3260)		36 (36, 39)		3 (60.0)	2 (40.0)		3 (60.0)	2 (40.0)	
Illicit opioid		.257		.125			.545			.545
Yes (*n* = 4)	2303 (2115, 2512)		34 (33, 37)		3 (75.0)	1 (25.0)		3 (75.0)	1 (25.0)	
No (*n* = 7)	3020 (2185, 3260)		39 (36, 40)		3 (42.9)	4 (80.0)		3 (42.9)	4 (57.1)	
Illicit drug		.066		.535			.545			>.999
Yes (*n* = 8)	2306 (2085, 2842)		37 (33, 40)		5 (62.5)	3 (37.5)		4 (50.0)	4 (50.0)	
No (*n* = 3)	3260 (2560, 3274)		36 (36, 40)		1 (33.3)	2 (66.7)		2 (66.7)	1 (33.3)	

[a] *P* values were obtained using the Mann–Whitney *U* test.; [b] *P* values were obtained using Fisher's exact test.

The withdrawal symptoms most commonly observed in this study (tremors, high-pitched crying, and irritability) were the same as those identified in other studies (1,25). The fact that more than 50% of the neonates were prematurely born is also compatible with what has been described in the previous literature (23,25,26). In our study, polydrug exposure and prematurity were common in examined medical records. Average non-premature birthweights (2566 g), although considered adequate for gestational age, were lower than those seen in other NAS studies (>2700 g) (10,27,28). It is likely that, based on their toxicology results, most of the neonates in our study had suffered from polydrug exposure, antenatally. Our findings are consistent with recent ones investigating the relapse of mothers into polysubstance dependence prior to the births of their NAS-affected babies (3,27,28). Our study was not able to determine whether there were any significant associations between substance exposure and the development of the fetus or NAS severity, which we suspect might be due to the small sample size at our recruitment sites; this should be further confirmed with a larger sample size.

Physicians attempting to determine the best approach for treating an infant with NAS require an accurate assessment of that child's antenatal drug exposure (29). Meconium tests, urine toxicology, and umbilical cord analysis have proven to be accurate in determining in utero substance exposure for a more evidence-based approach to treating NAS-affected newborns (13,30). In our study, the only way to determine prenatal drug exposure was through urinary toxicology reports that were obtained from the neonates' medical records; this information provided an insight only into the most recent drug exposure of a given neonate. Moreover, early prenatal care can reveal illicit substance exposure, enabling providers to anticipate NAS, thus decreasing the need for meconium or urine toxicology tests (31).

Recorded pharmacotherapies in the sample group's medical records offered insights into treatment practices followed by neonatologists at the participating neonatal units. Amongst the types of pharmacotherapies documented was the administering of phenobarbital and morphine, alone or in combination. Adverse or fatal outcomes associated with the administered pharmacotherapy were not found. Morphine was administered as either primary treatment alone (n = 1) or as adjunct therapy alongside phenobarbital (n = 5). Furthermore, dosing practices for neonates given morphine (co-administered with phenobarbital or alone) slightly exceeded prior reported morphine dosing recommendations (32).

Only 1 neonate was treated with morphine in our study (as the only line of treatment); therefore, we were not able to establish a pattern or outcome trends for this treatment. However, this neonate had a length of stay of 29 days and a length of treatment for NAS of 16 days, this results are aligned with literature (12). Further studies are warranted to better assess both the use of morphine for babies with NAS in PR and the associated outcomes. Those treated with only phenobarbital experienced significantly shorter durations of treatment than did those receiving phenobarbital and morphine in combination. While our study found significant differences in stay and treatment length between these groups, larger samples are crucial for result confirmation. Neonates receiving phenobarbital as a first-line treatment all had mothers with reported polydrug use. The current literature supports the use of phenobarbital as the treatment of choice for neonates whose mothers report a history of polydrug use or non-opioid-related prenatal exposure to either illicit or prescribed substances (33). Although the American Association of Pediatrics favors opiates over phenobarbital in the treatment of opiate-induced NAS, the use of phenobarbital is supported when in utero polysubstance

Table 3. Impact of exposure to substances on the clinical manifestations and severity of NAS (n = 12)

Risk Factor Exposure	Time of Symptoms (days)		Number of Symptoms		Finnegan Score	
	Median (Q1, Q3)	*P* value[a]	Median (Q1, Q3)	*P* value[a]	Median (Q1, Q3)	*P* value[a]
Polydrug		.296		.635		.515
Yes (n = 9)	1 (0, 3)		4 (4, 6)		13 (9, 18)	
No (n = 3)	2 (1, 4)		5 (4, 6)		17 (11, 21)	
Methadone		.090		>.999		.233
Yes (n = 6)	0 (0, 1)		5 (3, 6)		18 (13, 19)	
No (n = 5)	2 (1, 3)		5 (4, 5)		11 (9, 17)	
Illicit opioid		.380		.247		>.999
Yes (n = 4)	2 (0.5, 4)		4 (3, 5)		15.5 (11, 18.5)	
No (n = 7)	1 (0, 2)		5 (4, 6)		17 (9, 21)	
Illicit drug		.206		.755		.682
Yes (n = 8)	.5 (0, 2)		5 (4, 6)		15.5 (9, 18.5)	
No (n = 3)	2 (1, 4)		5 (4, 6)		17 (11, 21)	

[a] *P* values were obtained using the Mann–Whitney *U* test.

Table 4. Impact of type of treatment (phenobarbital/morphine or phenobarbital) on the length of stay and length of treatment of the neonate.

Risk Factor Exposure	Length of Treatment		Length of Stay	
	Median (Q1, Q3)	*P* value[a]	Median (Q1, Q3)	*P* value[a]
Treatment type		.006		.006
Morphine/Phenobarbital (n = 5)	52 (47, 60)		51 (44, 59)	
Phenobarbital (n = 6)	30 (26, 32)		23 (21, 25)	

[a] *P* values were obtained using the Mann–Whitney *U* test.

exposure occurs (8). Constant assessment of drug blood levels is also essential so that adequate and non-threatening dose adjustments can be made (34,35).

The analysis of the neonates' medical records revealed differences—across patients—between dosing practices and dosing guidelines, ranging from a 0.69% to a 25% difference during treatment initiation. The initial identification of these differences raised questions related to possible toxicity implications for, prolonged treatment of, and future hospitalization for neonates; however, no report or study was found that detailed these risks. The current literature shows that the impact of protocol optimization on NAS infants is similar in hospitals across the US and that the dosing scenarios described in this case series are in wide use. In the face of the substance use crisis in PR and the potential growing incidence of NAS, effective pharmacotherapies that result in substantially reducing the average length of stay and improving the treatment outcomes of neonates are needed (27). The successful implementation of evidence-based standardized protocols can help prevent improper dosing throughout treatment, from loading to weaning off, and even the possible reversal of therapeutic progress due to a prolonged hospital stay (late-onset sepsis or nosocomial infections) (36).

The reported incidence of NAS within our study period was a limitation that may have prevented a higher power analysis and interpretation of our results. A larger study encompassing the entire island of PR is necessary to further confirm these results. The extent of prenatal drug exposure (evaluated through urinalysis) for each neonate was solely accessible in their medical records. This approach, although effective for rapid treatment assessment, offers room for optimization, integrating alternative drug-exposure evaluation methods, such as meconium testing or umbilical cord analysis. Accurate knowledge regarding antenatal exposure to illicit/licit substances is vital for tailoring patient-care plans for NAS babies. In addition, the lack of availability of other NAS-related studies that used the FNAST limited proper comparisons of our results (33,37,38). The wide variability of current NAS symptom–scoring tools also prevented the comparative analysis of our results (29,33). Lastly, the pharmacotherapy approach to treating NAS that was observed at these hospitals was limited to the administering of morphine and/or phenobarbital. As novel clinical evidence emerges, buprenorphine is increasingly exhibited to enhance outcomes, such as shorter treatment and hospital stays and improved safety, when prescribed as the primary NAS medication (1,2,8). Hospitals should consider adding buprenorphine to their formularies as an optimized pharmacological option for treating NAS.

Resumen

Objetivos: El síndrome de abstinencia neonatal (SAN) es un conjunto de síntomas de retirada que sufren los neonatos expuestos a drogas de manera intrauterina. Varios estudios han descrito a cabalidad la prevalencia y terapia de SAN, sin embargo, se sabe poco sobre esto en Puerto Rico (PR). El objetivo principal de este estudio fue describir la prevalencia de SAN en las unidades neonatales de dos hospitales afiliados a la Universidad de PR (UPR) en términos de ocurrencia, manifestaciones clínicas, y estrategias de tratamiento. Métodos: Se evaluaron los expedientes médicos de neonatos diagnosticados con SAN entre 2018-2020 en dos hospitales afiliados a la UPR, Recinto de Ciencias Médicas. Se analizaron los datos con estadística descriptiva e inferencial. Resultados: Se identificó 12 neonatos diagnosticados con SAN, 5 nacieron con bajo peso (<2,500 g); con un incidencia de 2 casos de SAN por cada 1000 admitidos durante los 3 años de datos recopilados. Según los resultados toxicológicos, 9 fueron expuestos a más de una sustancia. La dosis inicial de fenobarbital fue determinada el mismo día del diagnóstico (indicado por el puntaje de la escala Finnegan). Las manifestaciones clínicas del síndrome variaron: 8 neonatos mostraron síntomas 48 horas luego de nacer, mientras que 4 mostraron síntomas luego de 72-120 horas. Se observaron diferencias en términos de guías de dosificación y dosis administradas; 0.69%-25%. Conclusiones: Para un profundo entendimiento de SAN en PR, es sustancial que se realicen estudios con mayor número de casos, permitiendo el desarrollo de protocolos optimizados en la población de PR.

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