



Effects of polysubstance exposure on neonatal outcomes for infants with intrauterine opioid exposure

Corrie E. McDaniel^{1,2} · Matthew Test^{1,2} · Parimal Deodhar^{1,2} · Rebecca Jennings¹ · Joanna Bove³ · Kristen Carlin⁴

Received: 10 February 2020 / Revised: 21 May 2020 / Accepted: 25 June 2020 / Published online: 8 July 2020
© The Author(s), under exclusive licence to Springer Nature America, Inc. 2020

Abstract

Objective Quantify the effect of prenatal polysubstance exposure on neonatal outcomes compared to methadone exposure alone.

Study design This retrospective cohort study compared infants with methadone-only exposure to methadone with additional psychoactive substances. Outcomes included time to maximum Finnegan scores, proportion requiring scheduled morphine, and length of stay (LOS).

Results We identified 323 subjects. The median time to maximum Finnegan score was 38.0 h with 94% peaking within 96 h. Forty-five percent of methadone-only infants were started on scheduled morphine compared to 54% of polysubstance infants ($p = 0.10$). LOS for polysubstance-exposed infants was 1.30 times longer than infants with methadone-only exposure (95% confidence interval: 1.05, 1.60).

Conclusions Exposure to methadone with additional psychoactive substances is associated with longer LOS, but not postnatal morphine use or peak withdrawal symptoms. Most infants experience peak withdrawal symptoms within 4 days and may not benefit from longer observation.

Background

In the setting of the opioid epidemic, the incidence of neonatal abstinence syndrome (NAS) continues to rise exponentially [1]. Long-term neurodevelopmental issues for infants with NAS include behavioral and emotional problems, aggression, attention deficits, and lower general cognitive abilities [2].

While NAS is most commonly associated with prescribed and illicit use of opioids, infants with prenatal opioid exposure often have prenatal exposure to multiple psychoactive drugs, including multiple forms of opioids (e.g., methadone, hydromorphone, and oxycodone), tobacco, marijuana, methamphetamines, and other illicit substances [3]. Up to a quarter of all opioid users admit to using marijuana and almost 10% admit to using methamphetamines [4].

The care of infants with NAS is often a complex amalgam of medical and social dynamics. Medically, an infant with NAS typically experiences a constellation of symptoms including neurologic, gastrointestinal, and musculoskeletal disturbances due to opioid withdrawal [3]. Requiring close monitoring after birth, these infants experience prolonged hospitalizations and often require pharmacologic therapy with morphine for the management of their withdrawal symptoms [3, 5]. Historically, the initiation and titration of morphine have been based upon a standardized scoring system for opioid withdrawal, known as the modified Finnegan score, which assigns a numerical score to clinical signs of NAS up to a maximum score of 21 [6]. Although this scoring modality is designed to capture opioid withdrawal, many infants with polysubstance exposures may have overlapping symptoms

Supplementary information The online version of this article (<https://doi.org/10.1038/s41372-020-0717-y>) contains supplementary material, which is available to authorized users.

✉ Corrie E. McDaniel
corrie.mcdaniel@seattlechildrens.org

¹ Department of Pediatrics, University of Washington, Seattle, WA, USA

² Division of Women and Children's, Providence St. Joseph's Health System, Renton, WA, USA

³ Department of Internal Medicine, Providence St. Vincent Hospital, Portland, OR, USA

⁴ Seattle Children's Research Institute, Seattle, WA, USA

that can make it difficult to evaluate the relative contribution of opioids [7–11].

While methadone is the most common medication used in pregnancy for the maternal treatment of opioid addiction [12], there are limited studies examining the experience of infants with polysubstance exposure in addition to prescribed opioids.

The aim of this study was to characterize the difference between infants exposed to methadone only prenatally and infants prenatally exposed to methadone and additional psychoactive substances in regards to the severity of NAS symptoms. We hypothesized that infants with polysubstance exposure would have more severe NAS symptoms, and therefore potentially longer hospital stays, increased use of opioid-directed pharmacologic therapy, and higher costs.

Methods

Using a retrospective cohort study design, we compared two groups of infants with prenatal opioid exposure: infants with only methadone exposure, and infants with methadone and one or more additional psychoactive substances (tobacco, marijuana, serotonin reuptake inhibitors, benzodiazepines, and/or illicit drug), termed, “polysubstance exposure.” Patients were admitted July 2012–June 2018 at one of two general hospitals in Washington state, one with a Level 2 Neonatal Intensive Care Unit (NICU) and one with a Level 3 NICU. Both hospitals are primarily adult-focused institutions with designated pediatric beds. Infants at both sites were managed using the Finnegan scoring system with protocols for the initiation, titration, and discontinuation of pharmacologic interventions during the majority of the study period.

During the study period, there were two major NAS protocol changes. In 2015, the units began “rooming-in” the infants with their mothers as often as possible and in 2018 both sites converted to an “Eat–Sleep–Console” protocol for management of non-pharmacologic interventions. During this second transition, patients were still scored using Finnegan scores, although medication choices relied primarily on a patient’s ability to eat, sleep, and console.

The study was approved by Providence St. Joseph’s Institutional Review Board.

Study subjects

In order to identify infants with fetal methadone exposure, we undertook a four-step process. First, we identified maternal charts at birth hospitalization with “International Classification of Disease, 9th and 10th Revisions” diagnosis codes for delivery with drug dependence (648.3* and

099.32*, respectively) and opioid dependence and abuse (304.0*, 305.8*, and F11*, respectively). Second, charts were filtered for the presence of methadone on the medication list within the electronic medical record (EMR). Third, the infant’s chart that was linked to the maternal birth hospitalization record was then identified and extracted. Fourth, study subjects were then included if they were full term (defined as 37 0/7 weeks of gestation to 41 6/7 weeks of gestation) and born at a participating institution between July 2012 and June 2018. Infants were excluded if the mothers were not on methadone (prescribed or illicit), the infant had severe comorbidities (e.g., need for intubation and ventilation management), and/or the infant required transfer out of the birth hospitalization to a higher level of care.

Chart extraction

Administrative data from the EMR identified maternal and infant demographics along with maternal methadone use. We then used manual chart review to identify additional clinical and pharmacologic data for study subjects. Length of stay (LOS) was calculated in two ways: (1) total LOS, defined as the date of birth through date of discharge, and (2) NAS-related LOS, defined as date of birth until either the infant was no longer being observed for NAS symptoms or had weaned off any pharmacologic interventions that had been started during the hospitalization. This allowed for the exclusion of additional hospital days required for non-NAS reasons, such as placement with child protective services, or feeding immaturity. Prior to data extraction, a random sample of infants with NAS admitted to both hospitals after July 2018 was used to establish interrater reliability of the manual chart abstraction process. The abstraction process was reviewed and revised until kappa ratios were >0.8 across all raters.

Analysis

Patients were classified as prenatally exposed to a substance if: (1) the maternal urine toxicology screen was positive, (2) the infant urine or umbilical cord toxicology screen was positive, and/or (3) maternal self-report. A two-level exposure category was used for analyses: methadone only and methadone with one or more additional substance exposure, since exposure data relied on a combination of self-report and toxicology screens at a single point in time. Illicit drug exposure included heroin, methamphetamine, cocaine, or LSD. In addition, given that marijuana is legal in the state of Washington, it was not classified as an illicit exposure, but was grouped within the polysubstance exposures when taken with methadone. Practice changes were made in 2015 and 2018, so cohorts

were defined as 2014 and before, 2015, 2016–2017, and 2018.

Descriptive statistics were used to summarize socio-demographic and clinical features of the cohort. Continuous variables were evaluated for normality using histograms and Q–Q plots and compared across the two exposure groups using independent samples *t*-tests if normally distributed, or Wilcoxon rank sums tests if not normally distributed. Time-to-event data were compared using log-rank tests, and categorical variables were compared using chi-square or Fisher's Exact tests. A generalized linear model was used to assess differences in LOS between the two exposure categories, adjusted for gestational age and cohort. Residual plots were used to assess model assumptions and the assumption of heteroscedasticity was violated. Thus, a log transformation was applied to the dependent variable (LOS). Estimates from the model were then exponentiated for interpretability and can be interpreted as the ratio of the geometric mean LOS when comparing the two exposure groups. A significance level of 0.05 was chosen.

Cost data were obtained as charges, and converted to costs using the Health Care Authority's Medicaid cost-to-charge ratio [13, 14]. Each cohort was adjusted en bloc according to the June ratio for the last year of the cohort, i.e., the cohort of 2012–2014 was adjusted for the index for June 2014, and the 2015 cohort was adjusted for the index as of June 2015. SAS 9.4 (Cary, NC) was used for all analyses.

Power analysis

A previous paper by Jansson et al. found that the mean peak modified Finnegan scores for infants exposed to methadone during pregnancy was 11.6 with a standard deviation (SD) of 5 [15]. Sample sizes of 75 in each group achieves over 90% power to detect differences among the means versus the alternative of equal means using an *F*-test with 0.05 significance level. The size of the variation in the means is represented by their SD of 1.12 with the common SD within each group is assumed to be 5.

Results

We identified 600 subjects with fetal opioid exposure from 451 maternal charts. Of these, 226 subjects were exposed to buprenorphine alone without methadone exposure and were excluded, 48 were <37 weeks gestation, and 3 were duplicate entries, leaving 323 subjects (Table 1). From these 323, 167 (52%) were female, 285 (89%) were on public insurance, 112 (35%) identified as non-white, and 246 (76%) were born to mothers in a verified methadone treatment program. One hundred and

ten infants were exposed to methadone alone, while 213 had polysubstance exposure. Within the polysubstance cohort, 56 infants had cannabis exposure in addition to methadone and of those, 46 had exposure to methadone, cannabis, and additional illicit substances. Forty-nine infants were exposed to methadone and methamphetamine (15% of the total population; 23% of the polysubstance-exposed group) and <10 were exposed to methadone and benzodiazepines (<3% of the total population; <5% of the polysubstance-exposed group). Only five mothers self-reported alcohol use during pregnancy, two within the methadone-only cohort and three within the polysubstance cohort. Demographics were similar between infants with methadone-only exposure and polysubstance exposure, except that infants with polysubstance exposure had lower birth weights than those with methadone alone (3058 and 3192 g, respectively) and 70% of infants with polysubstance exposure had mothers enrolled in opiate treatment programs compared to 88% with methadone exposure only ($p < 0.001$).

Finnegan scores, morphine treatment, and infant characteristics

Fifty-eight and 61% of the methadone-only and polysubstance-exposed infants, respectively, were cared for in a nursery or pediatric unit (outside of the NICU) (Table 2). The maximum Finnegan score was 11.2 with an SD of 4.0 in methadone-only infants and 12.3 with an SD of 3.6 in infants with polysubstance exposure ($p = 0.01$). The median time to maximum Finnegan score was 37.6 and 38.1 h, respectively, with a mean across both cohorts of 44 h (Fig. 1). For methadone-only infants, 45% were started on scheduled morphine, while 55% of polysubstance infants were started on morphine ($p = 0.10$). Among those receiving morphine therapy, the median time to first morphine dose was 38.5 h for methadone-only infants and 35.8 h for polysubstance-exposed infants. The median maximum oral morphine dose was 250 mcg every 3 h for both groups. There was no difference in rates of transfer from a nursery or pediatric unit to a NICU or in 7- or 30-day readmissions. In total, ten infants were readmitted, with one thought to be related to NAS. Readmission diagnoses included: five due to hyperbilirubinemia, one for bronchiolitis, two for *Escherichia coli* urinary tract infections, and one with poor feeding not attributed to NAS as the infant exhibited no other symptoms of withdrawal. Finally one polysubstance-exposed infant with neonatal fever was found to have other symptoms of opioid withdrawal, and received supportive care but did not require additional pharmacologic management.

When cohorting infants by year of birth, maximum Finnegan scores demonstrate no temporal trends from 2012

Table 1 Demographics for infants with intrauterine opioid exposure.

	<i>N</i> with data	All, <i>N</i> (%)	Methadone exposed only, <i>N</i> (%) (<i>N</i> = 110)	Polysubstance exposure, <i>N</i> (%) (<i>N</i> = 213)	<i>p</i> value
Maternal age, years, mean (SD) ^a	323	28.7 (4.5)	28.1 (4.6)	29.0 (4.5)	0.118
No. of pregnancies, median (IQR) ^b	323	3.0 (3.0)	3.0 (3.0)	3.0 (3.0)	0.456
No. of living children, median (IQR) ^b	323	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)	0.780
Mother in opioid treatment	323				<0.001
Yes		246 (76.2)	97 (88.2)	149 (70.0)	
No		43 (13.3)	6 (5.5)	37 (17.4)	
Unknown		34 (10.5)	7 (6.4)	27 (12.7)	
Sex	323				0.617
Female		167 (51.7)	59 (53.6)	108 (50.7)	
Male		156 (48.3)	51 (46.4)	105 (49.3)	
Insurance ^c	323				0.505
Medicaid		285 (88.2)	94 (85.5)	191 (89.7)	
Private		34 (10.5)	14 (12.7)	20 (9.4)	
Government		4 (1.2)	2 (1.8)	2 (0.9)	
Race/ethnicity ^c	320				0.534
American Indian or Alaskan Native		31 (9.7)	7 (6.4)	24 (11.4)	
Asian		5 (1.6)	1 (0.9)	4 (1.9)	
Black or African American		9 (2.8)	2 (1.8)	7 (3.3)	
Hispanic		12 (3.8)	4 (3.7)	8 (3.8)	
Native Hawaiian or Pacific Islander		21 (6.6)	10 (9.2)	11 (5.2)	
White		208 (65.0)	75 (68.8)	133 (63.0)	
Unknown or Other		34 (10.6)	10 (9.2)	24 (11.4)	
Birth weight, grams, mean (SD) ^a	323	3103.4 (479.2)	3191.9 (452.1)	3057.7 (478.4)	0.017
Gestational age, days, mean (SD) ^a	323	273.1 (9.6)	274.3 (8.8)	272.5 (10.0)	0.120

All analyses are chi square unless otherwise indicated.

^aIndependent samples *t*-test.

^bWilcoxon rank sums test.

^cFisher's exact test with Monte Carlo estimates.

through 2018 (Supplementary Fig. 1). However, scheduled morphine use peaked in 2013 at 60% for methadone-only infants and 65% in 2014 for infants with polysubstance exposure and decreased to 16% and 14%, respectively, in 2018 (Supplementary Fig. 2). This drop corresponds with our protocol change in 2018.

Length of stay and cost

The median total LOS for methadone-exposed infants was 5.5 days and for polysubstance-exposed infants was 9.0 days ($p = 0.08$). After adjusting for gestational age and

cohort, LOS for polysubstance-exposed infants was 1.30 times (95% confidence interval (CI): 1.05, 1.60) that of methadone only exposed infants (Table 3). LOS decreased in years after practice changes by 21% (95% CI: 2, 38%) in 2016–2017 cohort and 44% (95% CI: 18, 61%) in 2018 when compared to the reference period of infants admitted in 2014 and before. Similarly, NAS-specific LOS was 5.5 and 8.0 days ($p = 0.22$) for methadone and polysubstance-exposed infants, respectively, with linear regression models showing an adjusted LOS of 1.23 (95% CI: 1.0, 1.52) when comparing polysubstance-exposed infants with methadone-only exposed infants. In addition, the NAS-specific LOS in

Table 2 Comparison of hospital course characteristics for infants with intrauterine opioid exposure.

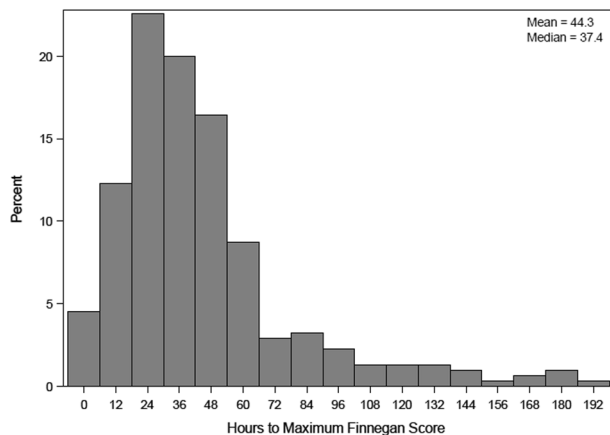
	<i>N</i> with data	All, <i>N</i> (%)	Methadone exposed only, <i>N</i> (%) (<i>N</i> = 110)	Polysubstance exposure, <i>N</i> (%) (<i>N</i> = 211)	<i>p</i> value
Unit for NAS Care	323				0.679
NICU Only		130 (40.3)	46 (41.8)	84 (39.4)	
Nursery/Pediatric Unit		193 (59.8)	64 (58.2)	129 (60.6)	
Average Finnegan score, mean (SD) ^a	122	5.4 (1.2)	5.0 (1.2)	5.5 (1.2)	0.068
Maximum Finnegan score, mean (SD) ^a	321	11.9 (3.7)	11.2 (4.0)	12.3 (3.6)	0.010
Time to maximum Finnegan score, hours, median (IQR) ^b	319	38.0 (32.0)	37.6 (32.0)	38.1 (31.1)	0.557
Started on scheduled morphine	321	165 (51.4)	49 (45.0)	116 (54.7)	0.098
Hours to 1st med, median (IQR) ^b	168	35.8 (27.7)	38.5 (30.8)	35.8 (22.3)	0.504
Hours to max dose, median (IQR) ^b	168	68.2 (71.6)	73.0 (70.4)	62.2 (71.3)	0.447
Maximum morphine (mcg), median (IQR)	168	250 (175)	250 (200)	250 (175)	0.462
Infant feeding	319				0.089
Exclusive breastfeeding/EBM/DBM		35 (11.0)	15 (13.8)	20 (9.5)	
Partial supplementation		187 (58.6)	69 (63.3)	118 (56.2)	
Exclusive formula		97 (30.4)	25 (22.9)	72 (34.4)	
Septic work-up obtained	322	67 (20.8)	19 (17.4)	48 (22.5)	0.286
Transfer to NICU from Pediatrics Unit ^c	316	6 (1.9)	1 (0.9)	5 (2.4)	0.450
Readmission					
7 day	323	6 (1.9)	4 (3.6)	2 (0.9)	0.189
30 day	322	5 (1.6)	1 (0.9)	4 (1.9)	0.659
NAS related	10	1 (10.0)	0 (0.0)	1 (20.0)	1.00
Length of stay, median (IQR)	323				
Total length of stay		8.0 (13.0)	5.5 (13.0)	9.0 (12.0)	0.078
NAS-related length of stay		7.0 (13.0)	5.5 (13.0)	8.0 (13.0)	0.223
IP RCC-adjusted charges, median (IQR)	312	7059.47 (13,124.46)	5276.71 (12,676.43)	7903.06 (13,783.81)	0.030

All analyses are chi square unless otherwise indicated.

^aIndependent samples *t*-test.

^bLog-rank test.

^cFisher's exact test with Monte Carlo estimates.

**Fig. 1 Time to Maximum Finnegan Score.** The histogram demonstrates what percent of patients within the study cohort by hour reached their maximum Finnegan score.

2018 was 54% shorter (95% CI: 33, 68%) than in 2014 and before (Supplementary Table 1).

LOS by year demonstrated decreasing means from a peak of 12.8 days (SD: 10.9) in 2013 for methadone only exposed infants and 20.5 days (SD: 20.1) in 2012 for

Table 3 Relative ratio for unadjusted and adjusted length of stay for infants with prenatal methadone exposure.

	Unadjusted		Adjusted	
	Estimate (95% CI)	<i>p</i> value	Estimate (95% CI)	<i>p</i> value
Exposure				
Methadone only	Ref	Ref	Ref	Ref
Polysubstance	1.20 (0.98, 1.47)	0.082	1.30 (1.05, 1.60)	0.015
Gestational age (days)	—	—	1.01 (1.00, 1.02)	0.180
Cohort	—	—		
≤2014			Ref	Ref
2015			0.83 (0.62, 1.11)	0.214
2016–2017			0.79 (0.62, 0.98)	0.032
2018			0.56 (0.39, 0.82)	0.002

polysubstance-exposed infants to 5.6 days (SD: 4.7) and 6.8 days (SD: 4.4), respectively, in 2018 (Supplementary Fig. 3).

Unadjusted calculations showed a near significant difference in the cost of care for infants with polysubstance exposure in comparison to infants exposed to only

methadone. Cost for polysubstance-exposed infants was \$2336 more than methadone-exposed infants ($p = 0.07$). However, after adjusting for gestational age, LOS, and year, there was no difference in cost between methadone-exposed infants and polysubstance-exposed infants (Supplementary Table 2).

Discussion

In this retrospective cohort study, we demonstrate that, when compared to infants with only methadone exposure, infants with polysubstance exposure have similar onset and peak of withdrawal symptoms, and similar exposure to postnatal morphine for treatment of NAS, yet have a longer LOS. In addition, for infants in both groups, the median and the mean time to maximum Finnegan score was <48 h.

Sanlorenzo recently demonstrated significantly increased rates of pharmacologically treated NAS among infants exposed to methadone and benzodiazepines, but not methadone and any other illicit or psychoactive substances [16]. These results are similar to our own, although our relative exposures to illicit substances is different, with a much higher rate of methamphetamine exposure (15% of included subjects versus 4%) and lower rates of benzodiazepine exposure (3% of included subjects versus 53%). The low rate of benzodiazepine exposure may explain why we see no difference in morphine use.

Within our cohort, we saw a very low self-report use of alcohol use during pregnancy. Only five (1.6%) women reported alcohol use, which is significantly lower than national surveys reporting usage nearing 10% during pregnancy [17]. In contrast, our proportion of cannabis exposed infants (17%) exceeded the national average of 7% [18]. There are several potential reasons for these differences. First, our data on alcohol use rely on maternal self-report; routine alcohol testing is not part of the hospital admissions process, prenatal lab work-up, or a requirement for methadone program enrollment. Most alcohol testing methods also only reflect alcohol consumed in the 12–80 h prior to the test [19], and so would not reflect usage throughout a pregnancy. In addition, among 18–26 years old, national trends show increasing marijuana use with a relative decrease in binge drinking [20]. The combination of underreporting alcohol use and higher than national averages for marijuana exposure likely reflects the combination of societal trends with social desirability bias. While the deleterious effects of alcohol on the fetus are known, marijuana is often perceived as safer during pregnancy and with minimal risk of harm [21]. Particularly in states such as ours where the recreational use of marijuana is legal, admitting to marijuana use during pregnancy carries less social stigma than alcohol use [22].

There are multiple reasons that patients exposed to additional substances may have longer LOS than those exposed to methadone alone. First, some illicit substances used by mothers can potentially cause additional symptoms necessitating a longer LOS. For example, 15% of our mothers were tested positive for methamphetamine, which has been shown to cause significant feeding difficulties among infants [23]. Although infants in the polysubstance-exposed group did have a statistically lower birth weight, the mean remained >3 kg and is unlikely to have independently contributed to a prolonged LOS. Finally, the difference in LOS may reflect bias in how patients with multiple drug exposures are treated. We designed our treatment protocols partially to decrease unnecessary variations in care, but important variations can persist despite protocols. It is conceivable that infants with polysubstance exposure are treated for longer periods of time because they are assumed to have more severe withdrawal symptoms. As management decisions around medications are subjective, and the Finnegan scoring system is subject to potential bias, these biases may influence a provider to approach care more conservatively in these infants.

Our data demonstrate a significant drop in morphine utilization and LOS in both cohorts in 2018 with the initiation of an Eat–Sleep–Console protocol. This is consistent with other data published showing that a non-pharmacologically driven protocol reduces LOS and postnatal opioid exposure in both university systems [24, 25] and community hospitals [26, 27]. Our data further expands this trend to not only opioid exposed infants, but to infants exposed to multiple psychoactive substances.

Currently, the American Academy of Pediatrics recommends a standard observation period for infants with NAS of 4–7 days [28], but our results demonstrate that most methadone-exposed infants have a peak Finnegan scores within the first 40 h after birth, regardless of other illicit or psychoactive medication exposures. In our cohort, 94% of infants reached peak scores within 96 h, with those infants peaking later primarily already undergoing pharmacologic treatment requiring titrating of pharmacologic interventions. Prolonged and potentially unnecessary hospitalization days can impact not only the patient but also their families with risks including missed time from work for parents [29], risk of nosocomial infections [30], out of pocket expenses for families [31], and increased family burden with child care for other children and travel needs [29]. These results suggest that physicians may consider a discharge within 4 days for infants hospitalized with NAS with appropriate anticipatory guidance if the infant is not demonstrating significant withdrawal symptoms.

Our study has several important limitations. It is an observational study, and so it is difficult to determine causation of our results. Because of the relatively small

numbers of infants exposed to each individual psychoactive substance, we condensed our cohort into two groups: methadone alone compared to methadone with another illicit or psychoactive substance. Potentially, each illicit or psychoactive substance might have a different effect on NAS symptoms, either protective or additive, and so the effect of a specific substance might be mitigated by the grouping. In addition, many substances have additional impact on the integrity of the central nervous system and the neurobehavioral maturity of an infant beyond what is captured by the Finnegan assessment of withdrawal. The use of an additional scale, such as the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNS), that examines neurobehavioral organization, neurologic reflexes, motor development, and the stress of withdrawal could have more clearly elucidated the neurobehavioral impact of exposure differences [32]. As our data were collected retrospectively, we were limited to the assessments performed during the time of hospitalization. Other studies that have used broader assessment scales such as the NNS for infants exposed to illicit substances have varying results as to the neurobehavioral impact of exposure, ranging from no difference in methamphetamine exposure [33] to lower arousal states with cocaine exposures [34]. We also defined exposures based on testing at the time of birth, but this may result in inaccurate grouping if the mom used a substance earlier during the pregnancy and did not test positive at the time of delivery. Lastly, the Finnegan scale has low levels of interrater reliability and a potential for observer bias. In the first part of our study period, many of our outcomes, such as LOS, were reliant on Finnegan scoring and therefore subject to the same biases. However, even when we moved to an ESC model, which may be less influenced by biases, the outcome differences persisted.

Conclusion

The additional exposures of tobacco, marijuana, or illicit substances in addition to methadone have little impact on postnatal morphine use, the onset of withdrawal symptoms, and the intensity of withdrawal symptoms, but are associated with a longer LOS. Most infants hospitalized with NAS, regardless of exposure, have a peak in withdrawal symptoms within 4 days, and may not benefit from a longer observation period beyond 4 days.

Funding This study is supported by the Center for Clinical and Translational Research, Seattle Children's Hospital. The funder played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the paper.

Author contributions CEM contributed to the conception of the study, the acquisition, analysis, and interpretation of data, and the writing and revising of the paper. She has approved the final version. MT and PD contributed to the acquisition and interpretation of data and the writing and revising of the paper. They have approved the final version. JB contributed to the conception of the study and the acquisition of the data, and the writing and revising of the paper. She has approved the final version. RJ and KC contributed to the conception of the study, the analysis and interpretation of data, and the writing and revising of the paper. They have approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of neonatal abstinence syndrome—28 states, 1999–2013. *MMWR Morb Mortal Wkly Rep*. 2016;65:799–802.
- Nygaard E, Slinning K, Moe V, Walhovd KB. Behavior and attention problems in eight-year-old children with prenatal opiate and poly-substance exposure: a longitudinal study. *PLoS ONE*. 2016;11:e0158054.
- Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134:e547–61.
- Center for Behavioral Health Statistics and Quality SAaMHSA. Treatment Episode Data Set (TEDS): 2001–2003. https://www.samhsa.gov/data/sites/default/files/2003_2013_TEDS_National/2003_2013_Treatment_Episode_Data_Set_National.pdf. Accessed 20 May 2018.
- Greig E, Ash A, Douiri A. Maternal and neonatal outcomes following methadone substitution during pregnancy. *Arch Gynecol Obstet*. 2012;286:843–51.
- Finnegan LP, Connaughton JF Jr., Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2:141–58.
- Eyler FD, Behnke M, Conlon M, Woods NS, Wobie K. Birth outcome from a prospective, matched study of prenatal crack/cocaine use: II. Interactive and dose effects on neurobehavioral assessment. *Pediatrics*. 1998;101:237–41.
- Garcia-Algar O, Puig C, Mendez C, Vall O, Pacifici R, Pichini S. Neonatal nicotine withdrawal syndrome. *J Epidemiol Community Health*. 2001;55:687–8.
- Law KL, Stroud LR, LaGasse LL, Niaura R, Liu J, Lester BM. Smoking during pregnancy and newborn neurobehavior. *Pediatrics*. 2003;111:1318–23.
- Martin CE, Longinaker N, Mark K, Chisolm MS, Terplan M. Recent trends in treatment admissions for marijuana use during pregnancy. *J Addict Med*. 2015;9:99–104.
- Smith L, Yonekura ML, Wallace T, Berman N, Kuo J, Berkowitz C. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. *J Dev Behav Pediatr*. 2003;24:17–23.
- National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. National Consensus Development Panel on effective medical treatment of opiate addiction. *JAMA*. 1998;280:1936–43.

13. Washington State Healthcare Authority. Inpatient prospective payment system. 2019. <https://www.hca.wa.gov/billers-providers-partners/prior-authorization-claims-and-billing/hospital-reimbursement>. Accessed 2 Dec 2019.
14. Basu A. Estimating costs and valuations of non-health benefits in cost-effectiveness analysis. In: Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. *Cost-Effectiveness in Health and Medicine*. 2nd ed. New York: Oxford University Press; 2017. Chapter 8.
15. Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. *J Opioid Manag*. 2009;5:47–55.
16. Sanlorenzo LA, Cooper WO, Dudley JA, Stratton S, Maalouf FI, Patrick SW. Increased severity of neonatal abstinence syndrome associated with concomitant antenatal opioid and benzodiazepine exposure. *Hosp Pediatr*. 2019;9:569–75.
17. Denny CH, Acero CS, Naimi TS, Kim SY. Consumption of Alcohol Beverages and Binge Drinking Among Pregnant Women Aged 18–44 Years — United States, 2015–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68:365–8.
18. Volkow ND, Han B, Compton WM, McCance-Katz EF. Self-reported medical and nonmedical cannabis use among pregnant women in the United States. *JAMA*. 2019;322:167–9.
19. Drugsdetails.com. How long does alcohol stay in your system, blood, urine, hair and tests. https://drugsdetails.com/how-long-does-alcohol-stay-in-your-system-blood-urine-hair-and-tests/#Blood_Alcohol_Test. Accessed 20 April 2020.
20. Alley ZM, Kerr DCR, Bae H. Trends in college students' alcohol, nicotine, prescription opioid and other drug use after recreational marijuana legalization: 2008–2018. *Addict Behav*. 2020;102:106212.
21. Ko JY, Farr SL, Tong VT, Creanga AA, Callaghan WM. Prevalence and patterns of marijuana use among pregnant and non-pregnant women of reproductive age. *Am J Obstet Gynecol*. 2015;213:201.e1–201.e10.
22. Barbosa-Leiker C, Burduli E, Smith CL, Brooks O, Orr M, Gartstein M. Daily cannabis use during pregnancy and postpartum in a state with legalized recreational Cannabis. *J Addict Med*. 2020. [Epub ahead of print].
23. Shah R, Diaz SD, Arria A, LaGasse LL, Derauf C, Newman E, et al. Prenatal methamphetamine exposure and short-term maternal and infant medical outcomes. *Am J Perinatol*. 2012;29:391–400.
24. Grossman MR, Berkowitz AK, Osborn RR, Xu Y, Esserman DA, Shapiro ED, et al. An initiative to improve the quality of care of infants with neonatal abstinence syndrome. *Pediatrics*. 2017;139:e20163360.
25. Grossman MR, Lipshaw MJ, Osborn RR, Berkowitz AK. A novel approach to assessing infants with neonatal abstinence syndrome. *Hosp Pediatr*. 2018;8:1–6.
26. Dodds D, Koch K, Buitrago-Mogollon T, Horstmann S. Successful implementation of the eat sleep console model of care for infants with NAS in a community hospital. *Hosp Pediatr*. 2019;9:632–8.
27. Parlaman J, Deodhar P, Sanders V, Jerome J, McDaniel C. Improving care for infants with neonatal abstinence syndrome: a multicenter, community hospital-based study. *Hosp Pediatr*. 2019;9:608–14.
28. Hudak ML, Tan RC, Committee on Drugs, Committee on Fetus and Newborn, American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics*. 2012;129:e540–60.
29. Mumford V, Baysari MT, Kalinin D, Raban MZ, McCullagh C, Karmon J, et al. Measuring the financial and productivity burden of paediatric hospitalisation on the wider family network. *J Paediatr Child Health*. 2018;54:987–96.
30. Raymond J, Aujard Y. Nosocomial infections in pediatric patients: a European, multicenter prospective study. *European Study Group. Infect Control Hosp Epidemiol*. 2000;21:260–3.
31. DiFazio RL, Vessey JA. Non-medical out-of-pocket expenses incurred by families during their child's hospitalization. *J Child Health Care*. 2013;17:230–41.
32. Lester BM, Tronick EZ, Brazelton TB. The Neonatal Intensive Care Unit Network Neurobehavioral Scale procedures. *Pediatrics*. 2004;113:641–67.
33. Kiblawi ZN, Smith LM, Diaz SD, LaGasse LL, Derauf C, Newman E, et al. Prenatal methamphetamine exposure and neonatal and infant neurobehavioral outcome: results from the IDEAL study. *Subst Abus*. 2014;35:68–73.
34. Napiorkowski B, Lester BM, Freier MC, Brunner S, Dietz L, Nadra A, et al. Effects of in utero substance exposure on infant neurobehavior. *Pediatrics*. 1996;98:71–5.