

A Multicenter Cohort Study of Treatments and Hospital Outcomes in Neonatal Abstinence Syndrome

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KEY WORDS

drug withdrawal, opioid, methadone, morphine, neonatal abstinence syndrome, treatment protocol

ABBREVIATIONS

CI—confidence interval

NAS—neonatal abstinence syndrome

Drs Hall and Wexelblatt had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, and they drafted the initial manuscript; Dr Wexelblatt coordinated and supervised data collection at 1 of the 6 centers; Drs Crowley, Grow, Klebanoff, McClead, Mohan, Stein, and Ms Jasin each coordinated and supervised or co-supervised data collection for 1 of the 6 regional groups and reviewed and revised the manuscript; Dr Meinzen-Derr led statistical analysis and interpretation of data; Dr Walsh devised the study concept and design, supervised the multicenter study, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Neonatal narcotic abstinence syndrome (NAS) has become more prevalent in the United States. There is no strong evidence base for NAS treatment and thus no consensus regarding NAS management, including the best treatment drug or best taper strategy.



WHAT THIS STUDY ADDS: This study demonstrates that regardless of the initial treatment opioid chosen, use of a standard treatment protocol with stringent weaning guidelines reduces duration of opioid exposure and length of hospital stay for infants with NAS.

abstract

OBJECTIVES: To compare pharmacologic treatment strategies for neonatal abstinence syndrome (NAS) with respect to total duration of opioid treatment and length of inpatient hospital stay.

METHODS: We conducted a cohort analysis of late preterm and term neonates who received inpatient pharmacologic treatment of NAS at one of 20 hospitals throughout 6 Ohio regions from January 2012 through July 2013. Physicians managed NAS using 1 of 6 regionally based strategies.

RESULTS: Among 547 pharmacologically treated infants, we documented 417 infants managed using an established NAS weaning protocol and 130 patients managed without protocol-driven weaning. Regardless of the treatment opioid chosen, when we accounted for hospital variation, infants receiving protocol-based weans experienced a significantly shorter duration of opioid treatment (17.7 vs 32.1 days, $P < .0001$) and shorter hospital stay (22.7 vs 32.1 days, $P = .004$). Among infants receiving protocol-based weaning, there was no difference in the duration of opioid treatment or length of stay when we compared those treated with morphine with those treated with methadone. Additionally, infants treated with phenobarbital were treated with the drug for a longer duration among those following a morphine-based compared with methadone-based weaning protocol. ($P \leq .002$).

CONCLUSIONS: Use of a stringent protocol to treat NAS, regardless of the initial opioid chosen, reduces the duration of opioid exposure and length of hospital stay. Because the major driver of cost is length of hospitalization, the implications for a reduction in cost of care for NAS management could be substantial. *Pediatrics* 2014;134:e527–e534

Neonatal abstinence syndrome (NAS) is characterized by central nervous system hyperexcitability and autonomic instability among newborns withdrawing from in utero opioid exposure. Previous reports indicate that withdrawal signs develop in 55% to 94% of exposed infants.¹⁻⁴ Neonatal drug withdrawal symptoms typically begin within 24 hours of birth after heroin exposures and within 72 to 96 hours for methadone-exposed newborns,⁵ although manifestations may be delayed for more than a week.⁴ In addition to the type and extent of drug exposure,^{6,7} withdrawal severity and duration are affected by many factors, including tobacco use during pregnancy⁸ and breastfeeding after delivery.^{9,10} Among the 3.39 per 1000 infants treated for NAS in the United States annually, average length of hospitalization is ~16 days, but prolonged stays are common.^{2,11,12}

NAS is becoming more prevalent in the United States. Nationally, opioid prescription rates, distribution quantities, and average prescription size all increased from 2000 to 2010, with an accompanying escalation in the rate of unintentional drug overdose deaths.¹³ Concurrently, maternal antepartum opioid use increased from 1.19 to 5.63 per 1000 hospital births annually.² In 2011, up to 12.9% of women were dispensed an opioid at some point during pregnancy.¹⁴ Over the last decade, newborns have experienced a threefold increase in NAS hospitalizations. Recently, a collaborative of neonatology groups representing Ohio's 6 regional perinatal centers recognized the emergence of an NAS epidemic. Baseline data confirmed that the groups managed >600 infants diagnosed with NAS in 2011, representing an increase of ~50% in NAS cases compared with 2009 (The Ohio Children's Hospital Neonatal Research Consortium, unpublished data, July 2012).

Significant knowledge gaps remain regarding optimal treatment of NAS, for which there is no nationally accepted,

evidence-based treatment protocol. Common treatments include nonpharmacologic measures (eg, swaddling, comforting, reduction of sensory stimuli), but more severe symptoms often warrant pharmacologic therapy. Most pharmacologic treatment strategies include gradual weaning of a single opioid (predominantly methadone or morphine), but sedatives, primarily phenobarbital or clonidine, may be added as a second agent when opioid treatment is perceived to be ineffective.¹⁵ However, there remains a lack of consensus about which taper strategy or initial treatment opioid provides optimal NAS management.^{16,17} Furthermore, there have been few evaluations of treatment variations among in-hospital NAS protocols or the impact of various protocols on duration of postnatal opioid exposure and length of stay.

The purpose of this statewide study was to identify pharmacological treatment strategies associated with optimal short-term outcomes including total duration of opioid treatment and length of inpatient hospital stay. Secondary analyses compared the outcomes of infants treated initially with methadone with the outcomes of those treated initially with morphine among infants receiving protocol-driven weaning.

METHODS

From January 2012 through July 2013 we conducted a cohort study of neonates of ≥ 34 weeks' gestational age who were diagnosed with NAS necessitating opioid treatment. Participants were identified by using the administrative code for neonatal abstinence syndrome (ICD-9 779.5) and through review of logbooks by study personnel at each nursery. Records were reviewed to verify that opioid treatment was administered. Primary outcomes measured were the number of days of opioid treatment and length of hospital stay. For infants discharged from the hospital with

prescribed opioid therapy, actual treatment days were recorded when known. When actual treatment days were unavailable for home therapy patients, treatment days were estimated using the duration of the complete course of opioid prescribed at discharge. Maternal opioid exposures during pregnancy (either by self-report or by positive maternal or infant toxicology testing), including exposures to buprenorphine, fentanyl, heroin, hydrocodone, hydromorphone, methadone, morphine, oxycodone, or other opioids, were captured. Exposures to nonopioids including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and phencyclidine were captured through self-report or by positive toxicology test. Maternal clinical and demographic predictors, infant measures, and potential confounders including pregnancy exposures to selective serotonin reuptake inhibitors, tobacco, and alcohol were also captured.

Neonatology groups representing each of the 6 Ohio children's hospitals (Akron Children's Hospital, Cincinnati Children's Hospital, Dayton Children's Hospital, Nationwide Children's Hospital [Columbus], ProMedica Toledo Children's Hospital, and Rainbow Babies and Children's Hospital [Cleveland]) had developed independent NAS protocols based on local evaluations of existing evidence. Collectively the 6 regional groups provided coverage for newborn nurseries in 20 hospitals. All 6 groups followed guidelines specifying parameters for NAS identification, scoring, and initiation of pharmacologic treatment. Additionally, 3 of the 6 strategies specified stringent pharmacologic weaning guidelines, whereas the other 3 had not formalized a weaning approach. Although treatment protocols were established by each of the 6 neonatology groups, some physicians deviated from their established regional strategy. Thus, weaning protocol adherence and management

opioid type were assigned as infant-specific variables. As a first step at standardizing treatment, the collaborative provided training with D'Apolito Reliability Training for the Finnegan Neonatal Abstinence Scoring Tool¹⁸ (including an interactive DVD and supervised scoring) throughout the 6 regions. More than 90% of nurses performing Finnegan assessments completed the training.

We conducted statistical analyses by using SAS version 9.3 (SAS Institute, Inc, Cary, NC) software. Data distributions were assessed for normality. Differences in infant and maternal characteristics between infants receiving protocol-driven weaning management and infants not receiving such management were tested with χ^2 tests (for categorical variables) or *t* tests (for continuous variables). Because infants could be considered as clustered or grouped by treatment site, mixed effects models were used to test mean differences in the main outcomes between groups (ie, protocol-driven weaning versus no protocol-driven weaning). The protocol group was treated as a fixed effect; random effects were used to account for patients clustered within each of the 6 regions. Results from models were reported as least squares means with 95% confidence intervals (CIs) for continuous variables and estimated probabilities with 95% CIs for categorical variables. Potential confounders were selected to be tested in the model if those factors had clinical or biological plausibility, or if those factors appeared to act as statistically relevant confounders in an unadjusted analysis. Potential confounders assessed in the models included infant-specific factors (ie, gestational age, highest level of care) and maternal-specific factors (ie, insurance status, race and ethnicity, receipt of prenatal care, methadone use). Factors statistically significant at $P < .05$ would remain in the models. Based on initial model results, post hoc interaction

effects were tested between level of nursery care (level 1–3 nurseries) and the use of a strict weaning protocol. Models were assessed for influential outliers or observations (through model diagnostic statistics), and a sensitivity analysis was performed to determine the effect of removing potentially influential observations from the overall model. Among infants receiving protocol-driven opioid weaning, we compared differences in outcomes among those who were treated with only morphine and those treated with only methadone. Infants who began a weaning protocol but who deviated from the protocol remained assigned to the original treatment regimen in an intention-to-treat analysis. Multiple imputation was used to address missing data for maternal or infant characteristics.

Each participating hospital either accepted a reliant institutional review board review based on a primary review at University Case Medical Center or completed an independent institutional review board review. Waivers of informed consent for the collection of deidentified data were obtained for each of the 20 hospitals from which data were collected. To protect the participants and their mothers, a Certificate of Confidentiality was obtained from the National Institutes of Health. All data were obtained through manual data abstraction and chart review by clinical staff at each participating nursery by using standardized data definitions and study forms. Study data were collected and managed with Research Electronic Data Capture tools hosted at Cincinnati Children's Hospital.¹⁹ Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies, providing an interface for validated data entry, audit trails, and automated export procedures. The 6 regions have been deidentified and designated with the letters A through F.

RESULTS

Table 1 describes maternal and neonatal characteristics, exposures, and clinical measures of 547 infants pharmacologically treated for NAS. There were no significant differences between the maternal characteristics of race, ethnicity, marital status, or insurance status across regional settings managed by each of 6 NAS strategies. Mothers were predominantly non-Hispanic white, and unmarried and received public insurance. Most (89.0%) received ≥ 1 prenatal care visit. Although no mothers in the cohort were diagnosed with HIV or hepatitis B, 131 (26.1%) were hepatitis C positive, a rate 37 times higher than a recent statewide figure (Office of Vital Statistics, Ohio Department of Health, unpublished data, September 2013). Overall, these infants had weight, length, and head circumference appropriate for gestational age, were delivered vaginally, and had normal Apgar scores.

Among the 547 infants, mean time until onset of NAS symptoms was 46.1 hours (median of 38.0 hours), and 60.1% were treated in a level 3 NICU. Exposures to >1 opioid were identified in 20.5% of infants. In addition to opioids, 81.5% of infants were exposed to tobacco, 7.8% to selective serotonin reuptake inhibitors, and 43.7% to ≥ 1 nonopioid substance (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, or phencyclidine).

The diagram in Fig 1 presents the number of patients treated with a strict weaning protocol, the number who received each opioid treatment, and the number discharged with a prescribed opioid taper. Approximately half (50.8%) of the study infants received exclusively morphine and 41.0% received exclusively methadone. An additional 30 (5.5%) were treated sequentially with >1 opioid for failure on the primary assigned opioid: 27 with methadone and morphine and 3 with buprenorphine and methadone. Sixty-seven infants (12.2%) were discharged

TABLE 1 Characteristics of the Study Population With Univariate Comparison of Infants Who Received Protocol-Driven Weans Compared With Those Who Did Not

	Total, N = 547	No Stringent Weaning Protocol, N = 130	Stringent Weaning Protocol, N = 417	P	Missing or Unknown Values
Maternal characteristics					
Maternal age; y, mean ± SD	26.7 ± 4.6	26.5 ± 4.5	26.8 ± 4.7	.63	6
Race and ethnicity				.002	58
White, non-Hispanic	91.6%	83.8%	94.1%		—
Black, non-Hispanic	5.3%	8.5%	4.3%		—
Hispanic	1.4%	3.4%	0.8%		—
Other, non-Hispanic	1.6%	4.3%	0.8%		—
Married	15.9%	20.0%	14.7%	.16	38
Insurance				.002	45
Public	79.9%	71.0%	82.8%		—
Private	10.4%	18.5%	7.7%		—
Self-pay	9.8%	10.5%	9.5%		—
Gravidity, mean ± SD	3.4 ± 1.9	3.3 ± 1.8	3.4 ± 1.8	.55	1
Parity, living; mean ± SD	2.4 ± 1.4	2.4 ± 1.3	2.4 ± 1.5	.67	25
Prenatal care, ≥1 visit	89.0%	83.3%	90.8%	.026	64
Hepatitis C positive	26.1%	23.2%	27.1%	.39	46
Cesarean delivery	33.4%	32.3%	33.8%	.76	23
Other maternal drug exposures					
SSRIs	7.8%	8.3%	7.6%	.80	21
Tobacco	81.5%	81.0%	81.6%	.88	45
Alcohol	9.5%	9.1%	9.7%	.86	116
Any nonopioid	43.7%	39.2%	45.1%	.24	—
Infant characteristics					
Gestational age; completed wk, mean ± SD	38.3 ± 1.6	38.5 ± 1.6	38.3 ± 1.6	.25	—
Birth wt; kg, mean ± SD	3.0 ± 0.5	3.0 ± 0.50	3.0 ± 0.48	.90	—
Length; cm, mean ± SD	48.9 ± 3.0	49.0 ± 3.3	48.8 ± 2.8	.54	9
Head circumference; cm, mean ± SD	33.4 ± 1.6	33.2 ± 1.7	33.5 ± 1.6	.18	11
Infant gender, male	52.8%	56.2%	51.2%	.39	—
1-minute Apgar; mean ± SD	8.1 ± 1.4	8.1 ± 1.3	8.1 ± 1.4	.94	21
5-minute Apgar; mean ± SD	8.8 ± 0.8	8.8 ± 0.6	8.8 ± 0.8	.63	19
Hour of life onset symptoms; mean ± SD, median	46.1 ± 34.3, 38.0	48.9 ± 48.4, 35.0	45.3 ± 29.0, 40.0	.46	54
Highest level of care setting				.022	—
1 (normal nursery) or	39.9%	48.5%	37.2%		—
2 (step-down, transitional nursery, special care)					—
3 (NICU)	60.1%	51.5%	62.8%		—
Discharge disposition				.71	2
Home with mother	63.7%	61.5%	64.3%		—
Home with other family member	16.7%	20.0%	15.7%		—
Foster care or adoption	18.2%	16.9%	18.6%		—
Transfer to another facility	1.5%	1.5%	1.4%		—

Percentage calculations all based on ratios of known values. SSRI, selective serotonin reuptake inhibitors.

from the hospital with a prescribed opioid; actual treatment days were captured for 44 and estimated for 23 infants based on prescription at discharge. In 1 Region B nursery, 15 patients received buprenorphine only (following an NAS research protocol); these infants experienced an average of 10.1 opioid treatment days and a hospital stay of 16.3 days.

Impact of Protocol-Driven Weaning

Variation in treatments and the primary outcomes of opioid treatment duration

and length of stay among 6 regional NAS treatment strategies are presented in Table 2. Three regional strategies weaned predominantly with morphine and 3 with methadone. Phenobarbital was the most common adjuvant sedative. One outlier level 2 nursery in Region C discharged patients after 5 days of inpatient treatment to complete a methadone taper at home. Region D included a level 3 nursery from which babies were also routinely discharged with a prescribed opioid taper to be completed at home. Both nurseries had shorter lengths of

stay but had a longer duration of opioid treatment.

We identified a robust relationship between the use of a strict weaning protocol and reduced duration of opioid exposure. The 417 infants receiving protocol-driven weans experienced a significantly shorter duration of opioid treatment (17.7 vs 32.1 days, $P < .0001$) (Table 3) compared with the 130 patients managed without a weaning protocol. Results based on a multiple imputation model were nearly identical; for simplicity, only the unimputed results are

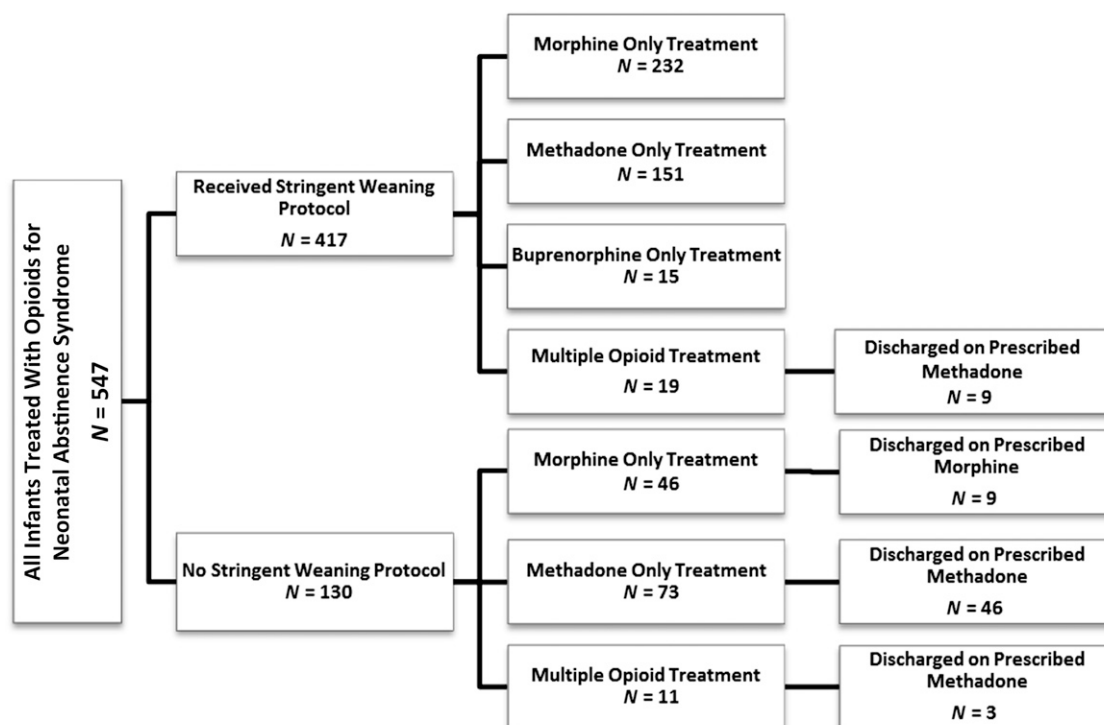


FIGURE 1

Flow diagram of the study population representing the numbers of subjects receiving a stringent weaning protocol, receiving each type of opioid treatment, and discharged with prescribed opioid, January 2012–July 2013.

presented. Sensitivity analysis revealed an interaction between highest level of care setting and use of a weaning protocol, but after we excluded data from the outlier nursery, the interaction between level of care and weaning protocol use was no longer significant. Results from the mixed effects regression models revealed a significantly

shorter length of stay among patients managed with protocol-driven weaning (22.7 vs 32.1 days, $P = .004$). Although race and ethnicity, insurance status, prenatal care, and highest level of care setting were associated with receipt of protocol-driven weaning (Table 1), these factors were not associated with opioid treatment days or length of hospital

stay; therefore, they were not retained in the final model. No significant differences in treatment characteristics, including the highest dose of opioid administered, use of phenobarbital, or treatment with multiple opioids, were identified between those treated with a strict weaning protocol and those treated without.

TABLE 2 Differences in Opioid Treatments and Outcomes Comparing 6 Regional NAS Management Strategies

	Region A, N = 102	Region B, N = 183	Region C, N = 187	Region D, N = 29	Region E, N = 32	Region F, N = 14	Total, N = 547
Protocol-driven weaning	Yes	Yes	Yes	No	No	No	—
Compliant with weaning protocol ^a (N, %)	102 (100%)	172 (94.0%)	143 (76.5%)	—	—	—	417 (76.2%)
Opioid treatment days, mean ± SD	14.3 ± 11.2	16.4 ± 10.2	22.6 ± 17.6	32.9 ± 16.0	31.1 ± 19.9	41.8 ± 18.0	20.5 ± 15.7
Day of life of discharge, mean ± SD	20.5 ± 13.4	22.1 ± 10.4	20.7 ± 14.1	13.3 ± 6.6	37.1 ± 19.7	48.6 ± 18.8	22.4 ± 14.4
Number of drugs used to treat, mean ± SD	1.3 ± 0.5	1.4 ± 0.7	1.7 ± 0.8	1.2 ± 0.4	1.5 ± 0.6	1.2 ± 0.4	1.5 ± 0.7
Treated with phenobarbital (N, %)	29 (28.4%)	49 (26.8%)	85 (44.5%)	2 (6.9%)	14 (43.8%)	0 (0.0%)	179 (32.7%)
Treated with morphine only (N, %)	102 (100%)	5 (2.7%)	130 (69.5%)	9 (31.0%)	32 (100%)	0 (0.0%)	278 (50.8%)
Treated with methadone only (N, %)	0 (0.0%)	151 (82.5%)	43 (23%)	17 (58.6%)	0 (0.0%)	13 (92.9%)	224 (41.0%)
Treated with multiple opioids (N, %)	0 (0.0%)	12 (6.6%)	14 (7.5%)	3 (10.3%)	0 (0.0%)	1 (7.1%)	30 (5.5%)
Home on oral morphine (N, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (31.0%)	0 (0.0%)	0 (0.0%)	9 (1.6%)
Home on methadone (N, %)	0 (0.0%)	0 (0.0%)	39 (20.9%)	19 (65.5%)	0 (0.0%)	0 (0.0%)	58 (10.6%)

^a Based on intention to treat according to weaning protocol.

TABLE 3 Outcomes and Treatment Characteristics Comparing Infants Receiving Protocol-Driven Weans and Those Not Receiving Protocol-Driven Weans, Accounting for Regional Variation

	No Stringent Weaning Protocol, N = 130	Stringent Weaning Protocol, N = 417	P
Outcomes			
Opioid treatment days ^a (mean, CI)	32.1 (28.7–35.5)	17.7 (14.5–20.8)	<.0001
Day of life of discharge ^b (mean, CI)	23.6 (11.5–35.8)	30.8 (18.6–43.0)	.0002
Adjusted day of life of discharge ^c (mean, CI)	32.1 (22.5–41.6)	22.7 (13.1–32.2)	.004
Treatment characteristics			
Highest morphine dose given ^d (mg/kg; mean, CI)	0.15 (0.04–0.27)	0.09 (0.03–0.14)	.33
Highest methadone dose given ^e (mg/kg; mean, CI)	0.15 (0.07–0.24)	0.14 (0.05–0.23)	.60
Treated with phenobarbital (%; CI)	20.7% (9.8–38.3)	27.5% (13.8–47.1)	.22
Phenobarbital treatment days (mean, CI)	15.2 (8.6–21.9)	19.4 (14.1–24.7)	.19
Received multiple opioids (%; CI)	6.3% (2.3–16.2)	2.9% (1.0–8.0)	.08

Mean and 95% CI for each outcome are reported as least squares means derived from mixed models for each outcome. Estimated probabilities and 95% CIs reported as percentages. All statistical comparisons reported from mixed models with treatment site as the random effect. No confounders were statistically significant ($P < .05$) in the models. Confounders tested included birth wt, race, any prenatal care, insurance status, marital status, and maternal methadone use.

^a Model includes gestational age as statistically significant covariate ($P = .025$). Level of care not statistically significant in model ($P = .5$).

^b Significant interaction with level 2 versus level 3 care.

^c Excluding 1 community outlier hospital driving interaction between protocol and level of care.

^d Among 305 infants receiving morphine treatment, 57 had no stringent weaning protocol and 248 had a stringent weaning protocol.

^e Among 254 infants receiving methadone treatment, 84 had no stringent weaning protocol and 170 had a stringent weaning protocol.

Impact of Initial Treatment Opioid

Among infants receiving protocol-driven weans, there was no significant difference between the duration of opioid treatment or length of stay with either morphine or methadone. In addition, although neither group was more likely to receive phenobarbital, those treated with phenobarbital and receiving a morphine-based protocol were treated with phenobarbital for a longer duration ($P < .002$) (Table 4).

DISCUSSION

Our study identified key differences in NAS management strategies that translated into shorter opioid exposures and reduced length of hospital stay. Results indicate that the use of a stringent weaning protocol, rather than the particular opioid chosen for treatment, was the most important predictor of length of hospital stay and duration of opioid treatment. Consistent with previous literature describing improvements in pediatric outcomes through standardization of care,^{20,21} study results suggest that the greatest

impact on outcomes is achieved through implementation and adherence to a formalized NAS treatment protocol with agreed-upon starting doses, explicit instruction about dose escalation, and strict weaning parameters. There was no statistically significant difference in length of treatment or length of stay

comparing formalized morphine- and methadone-based weaning. Outcomes associated with buprenorphine-based weaning were encouraging but inconclusive because of the very small sample size, warranting additional investigation. Secondary analysis identified longer duration of phenobarbital treatment among patients receiving a morphine-based treatment protocol. This is notable because oral phenobarbital preparations contain up to 13.5% alcohol,²² a central nervous system depressant with significant detrimental effects on neurodevelopment.³ This finding reemphasizes the importance of protocols that minimize ambiguity and limit dependence on subjective measures. Among infants receiving protocol-based weans, regardless of initial treatment drug, significantly more infants in Region C (49.0%) received phenobarbital compared with Region A (28.4%) or B (25.6%) ($P < .0001$). Both Region A and C used a morphine-based treatment protocol but specified the use of phenobarbital at different levels of severity. Region A described objective measures for determining initiation of phenobarbital compared with the Region C protocol,

TABLE 4 Outcomes and Treatment Characteristics Comparing Those Receiving a Single Opioid (Morphine Versus Methadone) According to a Formal Weaning Protocol, Accounting for Regional Variation

	Morphine Only, N = 232 (60.6%)	Methadone Only, N = 151 (39.4%)	P
Outcomes			
Opioid treatment days (mean, CI) ^a	15.6 (13.0–18.1)	16.2 (12.7–19.6)	.79
Day of life of discharge (mean, CI)	21.6 (19.9–23.4)	21.5 (19.2–23.8)	.9
Treatment characteristics			
Treated with phenobarbital (%; CI)	37.1% (21.7–55.7)	22.5% (9.1–45.8)	.29
Phenobarbital treatment days (mean, CI)	19.6 (17.2–22.1)	12.0 (8.0–15.95)	.002
Received multiple NAS treatment drugs (%; CI)	39.5% (21.6–60.6)	23.2% (8.2–50.4)	.31
Number of NAS treatment drugs (N, %) ^b			
1	137 (59.1%)	116 (76.8%)	
2	78 (33.6%)	34 (22.5%)	
3	16 (6.9%)	1 (0.7%)	
4	1 (0.4%)	0 (0.0%)	

Mean and 95% CI for each continuous variable are reported as least squares means derived from mixed models. Estimated probabilities and 95% CIs reported as percentages for categorical variables. All statistical comparisons reported from mixed models with treatment site as the random effect and treatment type (methadone or morphine) as the fixed effect. No confounders were statistically significant ($P < .05$) in the models. Confounders tested included birth wt, race, any prenatal care, insurance status, marital status, maternal methadone use.

^a Model includes gestational age as statistically significant covariate ($P = .025$). No other factors significant.

^b Actual number of NAS treatment drugs provided by treatment group, not accounting for infants clustering within treatment site.

which was open to individual interpretation. Thus, increased phenobarbital use among patients on a morphine-based protocol is probably a consequence of the protocol itself rather than the use of morphine.

The design and execution of a prospective trial comparing different treatment strategies to determine whether there truly is a “best practice” and “best drug” in a context of standardized care remain a priority. Furthermore, additional research is needed to determine whether treatments should be tailored in response to particular maternal exposures; this research is under way in the consortium.

The study population represents an NAS treatment cohort larger than that of any previously published single study or meta-analysis.^{23,24} Review of the statewide cohort's characteristics revealed opportunities to improve the efficiency of NAS care. As reported by Patrick et al,² the average daily charge for NAS patients was ~\$3337.50. The 9-day length of stay reduction for infants receiving protocol-based weaning represents an opportunity for cost savings. Because >80% of infants were discharged from the hospital with their mother or another family member, there is also opportunity to provide additional support for families through wise investments in public health interventions and community-based programs for high-risk mothers. Furthermore, the length of stay was similar for infants treated in level 2 and level 3 nurseries. Although referral to a level 3 nursery may be a marker for severity of illness, it may also reflect institutional policies for transfer regardless of illness severity. Managing infants with NAS in lower-acuity settings may support the mother–infant dyad in a less hectic setting, optimizing nonpharmacologic care and also achieving lower costs.

This multicenter study may be limited by unmeasured practices within and across study sites beyond opioid treatment. The

study was dependent on the accuracy and detail of already charted patient data. The Finnegan scoring system, developed to standardize NAS assessment,²⁵ was a central driver in weaning from pharmacologic treatment. Even with the inter-user reliability training, inconsistency in scoring may have affected final scores and hence weaning decisions, particularly during the early phase of the study.¹⁸ Among this deidentified study cohort, we were unable to accurately track readmissions that may have occurred in facilities other than those at which the initial NAS treatment was administered. Therefore, we were unable to compare readmission rates associated with various treatments.

Although the study captured the majority of infants who experienced pharmacologic treatment of NAS in Ohio during the study time period, we cannot account for newborns who received opioid treatment at a birth hospital outside the coverage of the 6 neonatology groups participating in the statewide collaborative, and we did not collect data from infants admitted to participating hospitals who did not need opioid therapy. In Ohio, the average length of stay of 15.9 days among the >1500 infants diagnosed with all severities of NAS annually is nearly identical to the national average of 16 days.²⁶ In contrast, the current study included only infants with the most severe NAS symptoms who needed pharmacologic treatment. The measured average length of stay of 22.4 days is consistent with the higher severity of illness.

CONCLUSIONS

Study results suggest that standardizing NAS treatment through adherence to an explicit weaning protocol may be effective in reducing the total duration of opioid treatment and length of stay, regardless of the primary opioid used. The reduction in duration of opioid and other drug treatments after protocol-driven weans offers numerous safety

benefits. In addition, because length of hospitalization is the major driver of health care costs, more efficient weaning has a significant potential to reduce health care expenditures. Because NAS has become a national epidemic, these findings have relevance to state Medicaid programs, which assume the largest financial burden of treatment, and to newborns across the United States affected by NAS.

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