Implementation of a Neonatal Abstinence Syndrome Weaning Protocol: A Multicenter Cohort Study

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abstract

OBJECTIVES: To evaluate the generalizability of stringent protocol-driven weaning in improving total duration of opioid treatment and length of inpatient hospital stay after treatment of neonatal abstinence syndrome (NAS).

METHODS: We conducted a retrospective cohort analysis of 981 infants who completed pharmacologic treatment of NAS with methadone or morphine from January 2012 through August 2014. Before July 2013, 3 of 6 neonatology provider groups (representing Ohio's 6 children's hospitals) directed NAS nursery care by using group-specific treatment protocols containing explicit weaning guidelines. In July 2013, a standardized weaning protocol was adopted by all 6 groups. Statistical analysis was performed to identify effects of adoption of the multicenter weaning protocol on total duration of opioid treatment and length of hospital stay at the protocol-adopting sites and at the sites with preexisting protocol-driven weaning.

RESULTS: After adoption of the multicenter protocol, infants treated by the 3 groups previously without stringent weaning guidelines experienced shorter duration of opioid treatment (23.0 vs 34.0 days, $P < .001$) and length of inpatient hospital stay (23.7 vs 31.6 days, $P < .001$). Protocol-adopting sites also experienced a lower rate of adjunctive drug therapy (5% vs 21%, $P = .004$). Outcomes were sustained by the 3 groups who initially had specific weaning guidelines after multicenter adoption (duration of treatment = 17.0 days and length of hospital stay = 23.3 days).

CONCLUSIONS: Adoption of a stringent weaning protocol resulted in improved NAS outcomes, demonstrating generalizability of the protocol-driven weaning approach. Opportunity remains for additional protocol refinement.

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Dr Hall had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis, and he drafted the initial manuscript; Drs Wexelblatt, Crowley, Grow, Klebanoff, McClead, Mohan, and 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 the 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.

www.pediatrics.org/cgi/doi/10.1542/peds.2015-1141

DOI: 10.1542/peds.2015-1141

Accepted for publication Jul 21, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

WHAT'S KNOWN ON THIS SUBJECT: Use of a standard treatment protocol with stringent weaning guidelines for infants with neonatal abstinence syndrome supports improved outcomes including shorter duration of opioid exposure and length of hospital stay.

WHAT THIS STUDY ADDS: We demonstrate generalizability of a protocol-driven weaning strategy for improvement in hospital outcomes for neonatal abstinence syndrome. After adoption, adherent protocol-adopting centers improved outcomes and eliminated differences in outcomes compared with centers with preexisting stringent weaning protocols.

The incidence of neonatal abstinence syndrome (NAS) after an infant's in utero exposure to opioids has risen dramatically in recent years.[1–3] By 2011, 1.1% of pregnant women in the United States abused opioids, including pain relievers and heroin,[4] and up to 12.9% of women were dispensed an opioid at some point during pregnancy.[5] Between 2000 and 2012, corresponding with increases in maternal antepartum opioid use, the incidence of NAS rose from 1.2 to 5.8 per 1000 births.[2,6] Increases in the incidence of NAS have been reported uniformly in community hospitals, teaching hospitals, and children's hospitals, have affected all racial and ethnic groups, and have been described both nationally and internationally.[7–10] Variations in NAS treatment and associated outcomes persist in the absence of a nationally accepted, evidence-based, and generalizable treatment protocol.[11–13] The average length of hospitalization among infants treated for NAS is ∼16 days (23 days for infants receiving pharmacologic treatment of NAS), although longer stays are common.[2,14,15]

In response to the emerging NAS epidemic, a collaborative of neonatology groups representing Ohio's 6 regional perinatal centers aimed to identify treatment strategies associated with optimal hospital outcomes for NAS. We previously reported the development of a consensus protocol that includes standardized guidelines for scoring NAS, nonpharmacologic treatment, triggers for implementation, guidelines for adjunctive therapy, and a stringent weaning protocol.[16] We reported that use of a protocol with stringent weaning guidelines was associated with reductions in the duration of opioid exposure and length of hospital stay regardless of the treatment opioid.[17] Subsequently, 3 study centers without a standardized weaning approach adopted the standardized protocol.

Through multicenter protocol adoption, this study was used to evaluate the generalizability of the stringent protocol-driven weaning strategy in reducing total duration of opioid treatment and length of inpatient hospital stay for NAS treatment. We examined the use of an adjunctive therapy as a secondary outcome.

METHODS

We conducted a retrospective cohort study of neonates who had a diagnosis of NAS (withdrawal subsequent to chronic in utero opioid exposure with a severity of symptoms necessitating pharmacologic treatment with a first-line opioid agent) and who completed weaning with methadone or morphine from January 2012 through August 2014. All infants received nursery care under the direction of regional perinatal 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]). Together the 6 regional groups directed newborn nursery care in 20 maternity and children's hospitals by following guidelines that specified parameters for NAS identification, scoring, and initiation of pharmacologic treatment. Before July 2013, 3 of 6 provider groups directed NAS care by using group-specific treatment protocols containing explicit weaning guidelines. Although each of the 3 centers implemented protocol-driven weaning, protocol details varied from center to center, and none required completion of weaning as inpatients. In July 2013, the 6 provider groups agreed to adopt a single standardized inpatient weaning protocol that included options for use of either morphine or methadone. Before the date of adoption, center leads participated in monthly phone calls to aid in coordination of practices between centers. The multicenter protocol explicitly required completion of opioid weaning in the inpatient setting and compliance with outlined weaning phases to demonstrate adherence.[16] Three centers with preexisting weaning protocols served as a control to 3 protocol-adopting centers. The details of the protocol development, including nonpharmacologic and pharmacologic components, and prestudy training in standardization of Finnegan scoring and NAS treatment have been described previously.[17,18]

Infants born at ≥34 weeks' gestation who were treated pharmacologically for NAS with methadone or morphine were included in the analysis. Infants who received iatrogenic opioid treatment or who had significant medical conditions necessitating surgical intervention or mechanical ventilation were not included in the analysis. Infants treated with buprenorphine (N = 45) under a separate experimental protocol at 1 site with a preexisting weaning protocol were excluded from analysis. Primary outcomes were the number of days of opioid treatment and length of initial hospital stay. As a consequence of incomplete documentation after patient transfer from a birth hospital to a higher-acuity facility, 10 infants had incomplete outcome data. Three infants for whom both length of stay and treatment duration were missing were excluded from analysis. Seven additional infants had a measured length of stay but an incomplete treatment duration measurement. Data for these infants were retained for length of stay analyses. For infants discharged with prescribed opioid for home therapy, actual treatment duration was recorded when known. However, when actual treatment duration was unavailable, we

estimated duration by using the length of opioid course prescribed at discharge. Adjunctive therapy was defined as the use of phenobarbital or clonidine secondary to a weaning opioid. Because the standard protocol included provisions for initiation of and discharge with adjunctive therapy, use of phenobarbital or clonidine was not deemed a failure. However, a necessitated change of first-line treatment opioid (indicated by the use of multiple treatment opioids) was deemed a failed wean.

We conducted statistical analyses by using SAS version 9.3 (SAS Institute, Inc, Cary, NC) software. Data distributions were assessed for normality, and differences in infant and maternal characteristics before and after collaborative-wide adoption of stringent weaning guidelines were tested with χ^2 (for categorical variables) or t tests (for continuous variables). Because 3 centers had preexisting protocols, the unadjusted analysis was stratified to examine the effects of the collaborative-wide protocol adoption on treatments and outcomes at the 3 protocol-adopting centers and the centers with preexisting protocols (which served as a control) separately.

Because infants could be considered as "clustered" or grouped by treatment site, linear mixed models were used to test mean differences in the main outcomes before and after collaborative-wide adoption. Random effects allowed us to account for patients clustered within each treatment site. A variable for whether the center had a preexisting protocol and the interaction between this variable and time (before and after protocol adoption phase) was included. We adjusted P values from prespecified comparisons for multiple testing by using the Holm–Bonferroni method. Model results were reported as least squares means, with 95% confidence intervals for continuous variables. Potential confounders that had clinical or biological plausibility or were reported previously to exhibit statistical relevance in unadjusted analysis (infant gestational age, level of care setting, and type of maternal exposure [ie, buprenorphine vs short-acting opioids only])[17] were assessed in the model. Confounders in the regression models were defined as variables that influenced the relationship between the group and outcome, as indicated by a change in the β estimate. Diagnostics for the linear mixed model included influence analysis. We also conducted a subanalysis including only patients who completed opioid weaning as inpatients. Finally, we measured outcomes among patients who received adherent protocol-driven weaning at any time throughout the study regardless of treatment site; this included patients from control sites during either study phase and from adopting sites during the adoption phase.

A waiver of informed consent for the collection of deidentified data was obtained for each of the 20 hospitals participating in the study either through a reliant institutional review board review based on a primary review from the University Case Medical Center or through completion of an independent institutional review board review. Additionally, a Certificate of Confidentiality was obtained from the National Institutes of Health to further ensure the protection of the participants and their mothers. All data were obtained through manual data abstraction and chart review by clinical staff at each participating nursery using standardized data definitions and study forms. Study data were collected and managed with Research Electronic Data Capture (REDCap Consortium, Vanderbilt University, Nashville, TN) tools hosted at Cincinnati Children's Hospital. Research Electronic Data Capture is a secure, Web-based application designed to support data capture for research studies, providing validated data entry, audit trails, and automated export procedures.[19]

RESULTS

Table 1 presents maternal and neonatal characteristics and clinical measures of 981 infants pharmacologically treated for NAS during the study period. Patients treated at the 3 sites with existing protocols (control) and the 3 protocol-adopting sites are characterized with a univariate comparison before and after multicenter adoption of the stringent weaning protocol in July 2013. The control sites pharmacologically treated 813 infants (454 before multicenter weaning protocol adoption and 359 after), and the adopting sites pharmacologically treated 168 infants (75 before and 93 after adoption).

Over the study period, mean time until onset of NAS symptoms was 43.9 hours (median = 36 hours), with no significant change between study phases. A majority (69.7%) of infants were treated in the level 3 NICU setting, where a significant increase was identified at control sites during the adoption phase. An increase in nonopioid exposures was identified at both control and protocol-adopting sites, indicating an increase in overall maternal drug use during the adoption time period (47.9% for the entire study cohort). The rate of hepatitis C among control sites paralleled increasing regional trends in heroin use. Lastly, a postadoption decline in the collection of race and ethnicity data at adopting sites resulted in a significant difference in race and ethnicity categorization between time periods.

As shown in Table 2, after adoption of the multicenter protocol, 48% of infants treated by the protocol-adopting sites received inpatient protocol-driven weaning. Among infants managed by the control sites, protocol adherence increased to

TABLE 1 Study Demographics and Hospital Outcomes at Sites With Existing Protocols and at Protocol-Adopting Sites With a Univariate Comparison Before and After Multicenter Protocol Adoption

	Overall, *N* = 981	Existing Protocol Sites			Protocol-Adopting Sites		
		Before Multicenter Adoption *N* = 454	After Multicenter Adoption *N* = 359	*P*	Before Multicenter Adoption *N* = 75	After Multicenter Adoption *N* = 93	*P*
Maternal characteristics							
Maternal age, y, mean (SD)	27.0 (4.7)	26.6 (4.5)	27.3 (4.8)	.02	27.1 (4.5)	27.5 (4.8)	.57
Race and ethnicity							
White, non-Hispanic, *N*, %	810, 82.6	377, 83.0	313, 87.2		55, 73	65, 70	
Black, non-Hispanic, *N*, %	44, 4.5	17, 3.7	16, 4.5	.84	8, 11	3, 3	.004
Hispanic, *N*, %	13, 1.3	4, 0.9	3, 0.8		3, 4	3, 3	
Other, non-Hispanic, *N*, %	10, 1.0	3, 0.7	1, 0.3		5, 7	1, 1	
Unknown, *N*, %	104, 10.6	53,11.7	26, 7.2		4, 5	21, 23	
Marital status							
Married, *N*, %	159, 16.2	62,13.7	58, 16.2	.09	16, 21	23, 25	.17
Unmarried, *N*, %	770, 78.5	364, 80.2	290, 80.8		50, 67	66, 71	
Unknown, *N*, %	52, 5.3	28, 6.2	11, 3.1		9, 12	4, 4	
Insurance							
Public, *N*, %	719, 73.3	341, 75.1	267, 74.4		48, 64	63, 68	
Private, *N*, %	107, 10.9	35, 7.7	35, 9.7	.66	15, 20	22, 24	.14
Self-pay, *N*, %	85, 8.7	38, 8.4	31, 8.6		8, 11	8, 9	
Unknown, *N*, %	70, 7.1	40, 8.8	26, 7.2		4, 5	0, 0	
Hepatitis C							
Positive, *N*, %	244, 24.9	110, 24.2	106, 29.5	.005	16, 21	12, 13	.15
Negative, *N*, %	633, 64.5	300, 66.1	199, 55.4		58, 77	76, 82	
Not tested, *N*, %	104, 10.6	44, 9.7	54, 15.0		1, 1	5, 5	
Other maternal drug exposures							
Self-reported SSRI use, *N*, %	91, 9.5	34, 7.5	36 10.0	.25	7, 9	14,15	.38
Self-reported tobacco use, *N*, %	726, 74.0	340, 74.9	274, 76.3	.70	54, 72	58, 62	.25
Any nonopioid by toxicology or self-report, *N*, %	470, 47.9	203, 44.7	187, 52.1	.05	29, 39	51, 55	.05
Infant characteristics							
Gestational age, completed weeks, mean (SD)	38.3 (1.6)	38.3 (1.6)	38.3 (1.6)	.92	38.4 (1.8)	38.2 (1.6)	.63
Preterm, *N*, %	130, 13.3	57, 12.6	47, 13.1	.92	13, 17	13, 14	.70
Birth wt, g, mean (SD)	2990.7 (480.6)	3003.8 (474.9)	2991.0 (456.0)	.70	2990.4 (597.7)	2926.3 (525.5)	.45
Infant gender, male, *N*, %	527, 53.8	239, 52.6	195, 54.5	.65	42, 56	51, 55	.95
Highest level of care setting							
1 or 2, (normal or special care nursery), %	297, 30.3	175, 38.5	63, 17.6	<.001	26, 34.7	33, 35.9	.99
3 (NICU), %	682, 69.7	279, 61.5	295, 82.4		49, 65.3	59, 64.1	
Discharge disposition							
Home with mother, %	624, 63.6	299, 65.9	231, 64.3		40, 53.3	54, 58.1	
Home with other family member, %	163, 16.6	68, 15.0	57, 15.9	.97	18, 24.0	20, 21.5	.94
Foster care or adoption, %	177, 18.0	80, 17.6	65, 18.1		15, 20.0	17, 18.3	
Transfer to another facility, %	17, 1.7	7, 1.5	6, 1.7		2, 2.7	2, 2.2	

96.7% from 87.9% ($P < .001$). Consistent with specifications of the multicenter protocol, there was a decrease in the percentage of infants discharged from control sites with prescribed opioids to be completed at home (0.6% vs 8.6%, $P < .001$). An increase in the percentage of infants discharged with prescribed opioids from the adopting sites was not significant (52% vs 37%, $P = .09$). During the preadoption stage, of 67 infants (12.6%) discharged from the hospital with a prescribed opioid, actual treatment days were captured for 44 and estimated for 23 based on prescription at discharge. During the adoption phase, 50 infants were discharged from the hospital with a prescribed opioid (11.1%). Nine of the infants had a measured duration of treatment, and duration was estimated for the remaining 41. Protocol-adopting sites experienced a reduction in the use of adjunct drug therapy (5% vs 21%, $P = .004$), but no change in adjunct drug therapy was measured at the control sites (41.2% vs 34.6%, $P = .06$). Reductions in the percentage of infants treated with multiple opioids (indicating failed weans) were observed at both site types, although the differences were significant only at the control sites (1.4% vs 5.1%, $P = .008$). Changes in the percentages of infants treated with methadone and morphine at the adopting sites were driven by an

TABLE 2 Comparison of Treatments and Outcomes Before and After Multicenter Protocol Adoption at Existing and Adopting Protocol Sites

	Existing Protocol Sites			Protocol-Adopting Sites		
	Before Multicenter Adoption *N* = 454	After Multicenter Adoption *N* = 359	*P*	Before Multicenter Adoption *N* = 75	After Multicenter Adoption *N* = 93	*P*
Protocol-driven weaning	Yes	Yes	—	No	Yes	—
Adherent to weaning protocol, %	87.9	96.7	<.001	0	48	<.001
Treated with morphine, %	57.3	60.7	.36	60	28	<.001
Treated with methadone, %	47.8	40.7	.05	45	74	<.001
Treated with multiple opioids, %	5.1	1.4	.008	5	2	.49
Home on opioids, %	8.6	0.6	<.001	37	52	.09
Adjunctive therapy, %	34.6	41.2	.06	21	5	.004

—, statistical comparison not applicable.

increased volume at 1 center (resulting from an expanded purview of 1 practice during the second study phase), which typically used methadone as the first-line weaning agent.

Table 3 compares outcomes before and after multicenter adoption. Before adoption, there was a nearly 16-day difference in treatment duration between control and adopting sites (18.3 vs 34.0 days, $P < .001$). After adoption there remained a significant difference in treatment durations at the sites (17.0 vs 23.0 days, $P = .03$), but the gap was narrowed to 6 days. This change represented a significant reduction in duration of treatment and length of stay ($P < .001$) when outcomes were compared between adopting sites before and after adoption. The subanalysis of patients who completed opioid weaning as inpatients also revealed that before multicenter adoption there were differences in both treatment duration (16.4 vs 31.8 days, $P < .001$) and length of stay (22.1 vs 37.3 days, $P = .003$) between control sites and protocol-adopting sites. Significant improvements in both treatment duration (15.7 vs 31.8 days, $P < .001$) and length of stay (21.2 vs 37.3 days, $P < .001$) were identified after multicenter adoption among infants treated at the protocol-adopting sites. In a comparison of control and protocol-adopting sites, differences in outcomes were no longer significant after multicenter adoption. Regardless of study phase or treatment site, 791 patients experienced a significantly shorter opioid treatment duration (17.2 days vs 31.8 days, $P < .001$) but no difference in inpatient length of stay (24.9 days vs 24.6 days, $P = .84$) when care adhered to protocol-driven weaning guidelines, compared with 190 infants whose care was not fully adherent.

DISCUSSION

This analysis demonstrates generalizability of stringent protocol-driven weaning for NAS across a multicenter setting. Collectively, patients at protocol-adopting sites experienced significant decreases in duration of opioid treatment and rates of adjunct treatment after

TABLE 3 Comparison of Treatment Duration and Length of Stay Between Control and Protocol-Adopting Sites Before and After Multicenter Adoption

	Before Multicenter Adoption			After Multicenter Adoption			Comparison of Adopting Site Outcomes (Before vs After Adoption)
	Existing Protocol Sites *N* = 454	Protocol-Adopting Sites *N* = 75	*P*	Existing Protocol Sites *N* = 359	Protocol-Adopting Sites *N* = 93	*P*	*P*
Duration of opioid treatment	18.3 (15.2, 21.4)	34.0 (29.9, 38.2)	<.001	17.0 (13.9, 20.2)	23.0 (18.9, 27.1)	.03	<.001
Length of inpatient hospital stay	21.2 (12.4, 30)	31.6 (22.5, 40.8)	.22	23.3 (14.5, 32.1)	23.7 (14.6, 32.8)	.95	<.001
Completed treatment as inpatients							
	N = 415	*N* = 47		*N* = 357	*N* = 45		
Duration of opioid treatment	16.4 (11.3, 21.5)	31.8 (25.5, 38.1)	<.001	17.3 (12.2, 22.4)	15.7 (9.6, 21.7)	.69	<.001
Length of inpatient hospital stay	22.1 (15.6, 28.6)	37.3 (29.7, 44.9)	.003	23.2 (16.7, 29.7)	21.2 (13.8, 28.5)	.68	<.001

Reported as adjusted means with 95% confidence intervals in parentheses.
All *P* values adjusted for multiple comparisons with the Holm–Bonferroni correction.

adoption of the protocol. When we compared patients at the control and adopting sites who, as directed by the multicenter protocol, completed opioid weaning as inpatients, statistical differences in both treatment duration and length of inpatient stay outcomes were eliminated after multicenter adoption. Because there were fewer affiliated hospitals among the adopting centers, fewer infants were managed by those groups. Nevertheless, adoption of the standard protocol enabled improved outcomes at centers with both large and small patient volumes.

It should be noted that 1 adopting site established a group-specific practice incorporating most of the elements from the multicenter protocol; however, they retained a long-standing practice of discharging infants from the hospital with prescribed opioid therapy after stabilization and several consistent weans. Before discharge, candidates for home therapy also had approval from Social Services, a family support system in place to reliably administer medications, an identified pediatrician willing to manage the outpatient wean, and a schedule for regular home nursing visits. On average, home therapy patients were discharged at 14.7 days of life. Patients treated by this group experienced the shortest length of stay but the longest total duration of opioid treatment. This finding is consistent with previous reports that a shorter length of inpatient stay may be achieved with a longer course of opioid treatment.[20] The extended treatment duration is a consequence of a less aggressive home versus inpatient weaning schedule. Still, implementation of stringent weaning guidelines at the site led to a significant, nearly 1-week reduction in treatment duration (26.3 days vs 32.9 days, $P = .04$). This tradeoff between length of stay and opioid treatment duration explains why differences persisted in the duration of opioid treatment outcome when control and adoption groups that included patients who were discharged with prescribed opioids were compared. When only those who completed weaning as inpatients were compared, no such difference remained after adoption.

Although reductions in length of stay with home therapy can significantly decrease treatment costs, important safety considerations should also be taken into account. The long-term implications of prolonged opioid treatment on neurocognitive development are not well understood, and appropriate safeguards and transition models must be implemented before the administration of opioid weans with limited clinical supervision.[20–23] Concerns about providing morphine or methadone to opiate-addicted parents may be unfounded because the average infant dose is reportedly $<0.2\%$ of the average maternal dose.[21] Nevertheless, social work assessment may aid in the selection of appropriate candidate families to receive treatment in the outpatient setting. Close follow-up and other safety measures may also mitigate potential safety threats for a select subset of patients.[22]

Even among control sites with preexisting group-specific protocols, improvements were observed during the multicenter adoption phase. Among control sites, there was a significant reduction in treatment with multiple opioids, indicating failed weans. Also, control sites collectively experienced a reduction in opioid treatment duration during the multicenter adoption period. Two primary factors are likely to have contributed to these improvements. First, protocol adherence increased among control sites. Second, the practice of prescribing home opioid treatment was almost completely eliminated, a change that also explains an increase in the length of inpatient stay among patients at the control sites. Demonstration of improvement at both control and adopting sites highlights the benefits of protocol standardization. Regardless of treatment site, throughout the study time frame patients whose treatment adhered to protocol-driven weaning guidelines experienced an opioid treatment duration >2 weeks shorter than that of patients whose treatment was not fully adherent.

This study has substantial strengths, including a large number of infants treated with a standardized protocol and rigorously collected data based on standard definitions. There are some limitations to this analysis. This large, prospectively evaluated implementation may be limited by unmeasured practices within or across study sites. For example, because the study scope was limited to infants treated pharmacologically with opioids, we did not measure the number of opioid-exposed infants at each center who were managed with only nonpharmacologic measures or with pharmacologic treatments other than opioids. However, training for standardization of assessment and nonpharmacologic approaches before study initiation were intended to minimize such variation. Although total opioid exposure (in milligrams per kilogram) is a more important outcome measure, treatment duration, a simpler measure to track, was used as a surrogate. In addition, because the study cohort was deidentified, we were not able to comprehensively track NAS-related readmissions that may have occurred at facilities other than those at which initial inpatient treatment was provided. With regard to safety of patients discharged with prescribed opioid therapy, discharging neonatologists had an established relationship with the pediatrician who oversaw outpatient weaning. Discharged infants were seen once or twice weekly by the pediatrician and once weekly by a visiting nurse. The family was also

free to call whenever questions or concerns arose. Pediatricians reported nearly 100% compliance for follow-up and >90% compliance for medication administration. Communication was maintained between the pediatrician and neonatologists after handoff; however, details of care provided by the pediatrician in the outpatient setting were not systematically captured in the hospital electronic records from which the study data originated. Because of this lack of data, length of treatment among the patient subgroup often had to be estimated based on prescribed duration at discharge.

CONCLUSIONS

Adoption of standard opioid weaning guidelines for inpatient NAS treatment, along with protocol adherence, led to reduced duration of opioid exposure and length of inpatient stay outcomes. Reduced length of stay achieved through completion of opioid weaning in the home setting may come as a tradeoff with longer total duration of infant opioid treatment. Results offer promise for additional improvement in NAS outcomes through widespread adoption of evidence-based, protocol-driven weaning. Additional research efforts will focus on the refinement of the weaning protocol.

ABBREVIATION

NAS: neonatal abstinence syndrome

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: REDCap technology was provided through Center for Clinical and Translational Science and Training grant support (grant UL1-RR026314). All phases of this study were supported by funding provided by the State of Ohio Innovation Grant through the Ohio Office of Health Transformation (grant G1213070561).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Massatti R, Falb M, Yors A, Potts L, Beeghly C, Starr S. *Neonatal Abstinence Syndrome and Drug Use Among Pregnant Women in Ohio, 2004–2011*. Columbus, OH: Ohio Department of Mental Health and Addiction Services; 2013
2. Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol*. doi:10.1038/jp.2015.36
3. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med*. 2015;372(22):2118–2126
4. SAMHSA. Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2008–2011. 2012. Available at: http://archive.samhsa.gov/data/NSDUH/2011SummNatFindDetTables/NSDUH-DetTabsPDFWHTML2011/2k11DetailedTabs/Web/HTML/NSDUH-DetTabsSect6peTabs55to107-2011.htm#Tab6.71B. Accessed December 11, 2014
5. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology*. 2014;120(5):1216–1224
6. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000–2009. *JAMA*. 2012;307(18):1934–1940
7. Tetstall E, Liu AJ, An EI, Canalese J, Nanan R. Pregnancy and neonatal characteristics of opioid-dependent Indigenous Australians: a rural and metropolitan comparison. *Aust N Z J Obstet Gynaecol*. 2009;49(3):279–284
8. Carrieri MP, Amass L, Lucas GM, Vlahov D, Wodak A, Woody GE. Buprenorphine use: the international experience. *Clin Infect Dis*. 2006;43(suppl 4):S197–S215
9. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134(2). Available at: www.pediatrics.org/cgi/content/full/134/2/e547
10. Turner SD, Gomes T, Camacho X, et al. Neonatal opioid withdrawal and antenatal opioid prescribing. *CMAJ Open*. 2015;3(1):e55–e61
11. Patrick SW, Kaplan HC, Passarella M, Davis MM, Lorch SA. Variation in treatment of neonatal abstinence syndrome in US children's hospitals, 2004–2011. *J Perinatol*. 2014;34(11):867–872
12. Hudak ML, Tan RC; Committee on Drugs; Committee on Fetus and Newborn; American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics*. 2012;129(2). Available at: www.pediatrics.org/cgi/content/full/129/2/e540
13. U.S. Government Accountability Office. Prenatal drug use and newborn health: Federal efforts need better planning and coordination. 2015. Available at: www.gao.gov/assets/670/668385.pdf. Accessed February 23, 2015
14. Johnson K, Greenough A, Gerada C. Maternal drug use and length of neonatal unit stay. *Addiction*. 2003;98(6):785–789
15. Lainwala S, Brown ER, Weinschenk NP, Blackwell MT, Hagadorn JI. A retrospective study of length of hospital stay in infants treated for neonatal abstinence syndrome with methadone versus oral morphine preparations. *Adv Neonatal Care*. 2005;5(5):265–272
16. The Ohio Children's Hospital Association Neonatal Abstinence Syndrome Committee. Ohio Children's' Hospitals Neonatal Research Consortium enteral morphine or methadone protocol for neonatal abstinence syndrome (NAS) from maternal exposure. 2013.

Available at: https://opqc.net/sites/bmidrupalpopqc.chmcres.cchmc.org/files/NAS/Ohio%20Childrens%20NAS%20Treatment%20Protocol%200822%202013%20%20FINALrev2.pdf. Accessed April 8, 2015

17. Hall ES, Wexelblatt SL, Crowley M, et al; OCHNAS Consortium. A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics*. 2014;134(2). Available at: www.pediatrics.org/cgi/content/full/134/2/e527
18. Lucas K, Knobel RB. Implementing practice guidelines and education to improve care of infants with neonatal abstinence syndrome. *Adv Neonatal Care*. 2012;12(1):40–45
19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377–381
20. Kelly LE, Knoppert D, Roukema H, Rieder MJ, Koren G. Oral morphine weaning for neonatal abstinence syndrome at home compared with in-hospital: an observational cohort study. *Paediatric Drugs*. 2015;17(2):151–157
21. Smirk CL, Bowman E, Doyle LW, Kamlin O. Home-based detoxification for neonatal abstinence syndrome reduces length of hospital admission without prolonging treatment. *Acta Paediatr*. 2014;103(6):601–604
22. Backes CH, Backes CR, Gardner D, Nankervis CA, Giannone PJ, Cordero L. Neonatal abstinence syndrome: transitioning methadone-treated infants from an inpatient to an outpatient setting. *J Perinatol*. 2012;32(6):425–430
23. Gregory KE. Caring for the infant with neonatal abstinence syndrome in a community-based setting. *J Perinat Neonatal Nurs*. 2014;28(3):161–163

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