A Cohort Comparison of Buprenorphine versus Methadone Treatment for Neonatal Abstinence Syndrome

Eric S. Hall, PhD[1], Barbara T. Isemann, BSPharm[2], Scott L. Wexelblatt, MD[1,3], Jareen Meinzen-Derr, PhD[4], Jason R. Wiles, MD[1], Sharon Harvey, BSN[2], and Henry T. Akinbi, MD[1,3]

Objectives To compare the duration of opioid treatment and length of stay among infants treated for neonatal abstinence syndrome (NAS) by using a pilot buprenorphine vs conventional methadone treatment protocol.

Study design This retrospective cohort analysis evaluated infants who received pharmacotherapy for NAS at 6 hospitals in Southwest Ohio from January 2012 through August 2014. A single neonatology provider group used a standardized methadone protocol across all 6 hospitals. However, at one of the sites, infants were managed with a buprenorphine protocol unless they had experienced chronic in utero exposure to methadone. Linear mixed models were used to calculate adjusted mean duration of opioid treatment and length of inpatient hospitalization with 95% CIs in infants treated with oral methadone compared with sublingual buprenorphine. The use of adjunct therapy was examined as a secondary outcome.

Results A total of 201 infants with NAS were treated with either buprenorphine (n = 38) or methadone (n = 163) after intrauterine exposure to short-acting opioids or buprenorphine. Buprenorphine therapy was associated with a shorter course of opioid treatment of 9.4 (CI 7.1-11.7) vs 14.0 (12.6-15.4) days ($P < .001$) and decreased hospital stay of 16.3 (13.7-18.9) vs 20.7 (19.1-22.2) days ($P < .001$) compared with methadone therapy. No difference was detected in the use of adjunct therapy (23.7% vs 25.8%, $P = .79$) between treatment groups.

Conclusion The choice of pharmacotherapeutic agent is an important determinant of hospital outcomes in infants with NAS. Sublingual buprenorphine may be superior to methadone for management of NAS in infants with select intrauterine opioid exposures. *(J Pediatr 2016;170:39-44)*.

The use of opioids has escalated throughout the US, resulting in an epidemic of opioid misuse, overdose, and death.[1,2] Between 2005 and 2011, more than 14% of pregnant women were dispensed an opioid at some time during pregnancy,[3] and by 2011 more than 1% of pregnant women used opioid-based pain relievers or heroin illicitly.[4] Infants born to opioid-dependent women are likely to experience withdrawal symptoms, collectively termed neonatal abstinence syndrome (NAS).[5,6] By 2012, the incidence of NAS in the US reached 5.8 per 1000 live births.[7] As a consequence of increased use of neonatal intensive care units and prolonged hospitalization for the treatment of NAS, average hospital charges for infants with NAS amount to more than 5 times those for healthy infants.[7-9] Multiple factors, including type and extent of in utero exposures, can impact the severity of NAS symptoms and the duration of inpatient treatment which averages 23 days for those requiring pharmacotherapy.[7,10] Strategies that mitigate the incidence and severity of NAS or that shorten the treatment course would ease the impact on affected mothers and babies while simultaneously alleviating related social, economic, and public health burdens.

Previous efforts demonstrated that the use of a formalized treatment protocol improved short-term outcomes after NAS pharmacotherapy[11,12]; however, no consensus has been reached regarding optimal pharmacotherapy procedures, including the selection of first-line opioid agent, threshold for initiating therapy, rates of dose escalation to achieve desired treatment effect, rates of subsequent dose weaning, criteria for adding an adjunctive agent, or the utility of outpatient opioid therapy.[13-16] Although oral morphine and methadone have been the mainstay of pharmacotherapy for NAS, sublingual buprenorphine may offer potential advantages, including a ceiling effect for respiratory depression, limited risk for outpatient misuse, longer half-life compared with morphine, and less cardiovascular effects. On the basis of an initial report by Kraft et al,[17] who pioneered the use of sublingual buprenorphine for the treatment of NAS along with limited neonatal pharmacokinetic data,[18] we developed a buprenorphine-weaning protocol for NAS treatment. The protocol was implemented in the University of Cincinnati Medical Center in June 2011.

Our primary objective in this retrospective analysis was to evaluate short-term outcomes of a pilot sublingual buprenorphine-weaning protocol compared with a standardized oral methadone treatment regimen. Duration of opioid therapy

NAS Neonatal abstinence syndrome

From the [1]Perinatal Institute, Cincinnati Children's Hospital Medical Center; [2]University of Cincinnati Medical Center; [3]University of Cincinnati College of Medicine; and [4]Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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and length of inpatient hospital stay among infants treated pharmacologically for NAS were the primary outcomes of interest. We hypothesized that pharmacotherapy with buprenorphine would shorten treatment courses. We also examined the use of adjunct therapy with phenobarbital as a secondary outcome.

Methods

This retrospective cohort analysis includes neonates treated pharmacologically for NAS with methadone or buprenorphine in Southwest Ohio from January 2012 through August 2014 as part of statewide NAS quality improvement efforts.[12] A single neonatology group directed newborn care in all 6 participating nurseries located at Bethesda North Hospital, Cincinnati Children's Hospital Medical Center, Good Samaritan Hospital, Mercy Health – Anderson Hospital, Mercy Health – Fairfield Hospital, and the University of Cincinnati Medical Center. The neonatology group provided a continuity of best practices and attending physicians across all study sites. As described previously, training was administered at all participating nurseries for standardization of NAS assessment, including scoring and initiation of pharmacologic treatment before the study period.[11,19]

At the pilot site (University of Cincinnati Medical Center), a 5-step sublingual buprenorphine protocol was implemented for the treatment of infants who experienced intrauterine opioid exposures with the exception of chronic exposure to methadone. The 5-step wean was developed with Kraft et al's initial loading dose to capture signs of withdrawal.[17] Next, the taper was designed to support a steadily declining serum drug concentration, taking into consideration the lengthy half-life of buprenorphine,[18,20] at a similar rate provided by the conventional methadone taper. A sublingual formulation of 75 μg/mL buprenorphine was compounded[21] and initiated at a dose of 4.4 μg/kg every 8 hours with a maximum daily dose not to exceed 39 μg/kg. We used this formulation throughout the entire study time frame, using birth weight to determine dosing throughout the duration of treatment. The buprenorphine protocol provided guidelines for escalation, weaning, and use of adjunct therapy (Table I). Before the initiation of buprenorphine treatment at the pilot site, nursing staff received training on appropriate sublingual dosing and administration.

All infants who required opioid treatment at the other 5 nurseries, as well as infants at the pilot site with chronic methadone exposure, received care according to a standardized 8-step methadone protocol (Table II). This methadone protocol was used at all study sites throughout the study timeframe. Parameters for escalation or weaning of dosage and recommendations for the use of adjunct therapy with phenobarbital were similar between the 2 treatment protocols. For both buprenorphine and methadone treatments, opioid weaning was completed before discharge; however, infants who received adjunct therapy were discharged routinely with prescribed phenobarbital and were gradually weaned under clinical direction in the outpatient setting.

Table I. Pilot buprenorphine-weaning protocol

Initiation
- ○ Initiate protocol for infants with 3 consecutive Finnegan scores ≥8, or 2 consecutive Finnegan scores ≥12

	Buprenorphine dose	Dosing interval	Number of doses
Step 1	4.4 μg/kg	Q8	3
Step 2	2.6 μg/kg	Q8	3
Step 3	1.7 μg/kg	Q8	3
Step 4	1.7 μg/kg	Q12	2
Step 5	1.7 μg/kg	Q24	1

Escalation
- ○ If average Finnegan scores >8 after 2 doses (9 h) increase dose by 0.8 μg/kg Q8 × 2 until Finnegan scores are 8 or below (5.2 × g/kg Q8 × 2, 6.0 μg/kg Q8 × 2, etc., max dose of 13 μg/kg Q8)
- ○ If average Finnegan scores <8, wean each day by 0.8 μg/kg until back to 4.4 μg/kg Q8 and advance to step 2

Weaning
- ○ Wean to next step if average Finnegan score is <8 for the past 24 hours.
- ○ If average Finnegan score is 8-12, do not wean
- ○ If average Finnegan score >12, go back one step on taper (backslide)
- ○ If average Finnegan score remains >12 for 48 h go back two steps on taper

Adjunct therapy
- ○ Consider adding phenobarbital if
  Infant at maximum buprenorphine dose of 39 μg/kg/day OR
  Unable to wean after 24-48 h

Discharge
- ○ Observe for 72 h from the last dose of step 5

The retrospective cohort consists of infants who were ≥34 weeks' gestation at birth and who received pharmacotherapy for NAS after chronic in utero exposure to opioids other than methadone. At all sites, participants received treatment with buprenorphine or methadone as a single opioid-weaning agent after receiving 3 consecutive scores

Table II. Standard methadone-weaning protocol

Initiation
- ○ Initiate protocol for infants with 3 consecutive Finnegan scores ≥8, or 2 consecutive Finnegan scores ≥12

	Methadone dose	Dosing interval	Number of doses
Step 1	0.05 mg/kg	Q6	4
Step 2	0.04 mg/kg	Q6	4
Step 3	0.03 mg/kg	Q6	4
Step 4	0.02 mg/kg	Q6	4
Step 5	0.02 mg/kg	Q8	3
Step 6	0.02 mg/kg	Q12	4
Step 7	0.01 mg/kg	Q12	4
Step 8	0.01 mg/kg	Q24	2

Escalation
- ○ If infant fails step 1 (scores >12) consider steps 1A through 1C

	Methadone dose	Dosing interval	Number of doses
Step 1A	0.1 mg/kg	Q6	4
Step 1B	0.075 mg/kg	Q6	4
Step 1C	0.05 mg/kg	Q6	4

Weaning
- ○ Wean to next step if average Finnegan score is <8 for the past 24 h
- ○ If average Finnegan score is 8-12, do not wean

Adjunct therapy
- ○ Consider adding phenobarbital if unable to wean after 24-48 h

Discharge
- ○ Observe for 72 h from the last dose of step 8