

ORIGINAL ARTICLE

Buprenorphine pharmacotherapy for the management of neonatal abstinence syndrome in methadone-exposed neonates

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Abstract

We aimed to compare the outcomes of pharmacotherapy with either buprenorphine or methadone in infants treated for neonatal abstinence syndrome (NAS) secondary to intrauterine exposure to methadone. This is a multi-center, retrospective cohort study to assess length of treatment (LOT), hospital length of stay (LOS), and cumulative opioid exposure between infants treated with either methadone or buprenorphine for NAS secondary to in utero exposure to methadone. Infants delivered at a gestational age ≥ 35 weeks and a maternal history of opioid-use disorder and/or urine drug screen positive for methadone, and postnatal pharmacotherapy for NAS with either buprenorphine or methadone as first-line opioid replacement therapy, were eligible. Median LOT, LOS, and cumulative opioid exposure were compared between buprenorphine- and methadone-treated infants. A total of 156 infants (48 treated with buprenorphine and 108 with methadone) were identified. The median LOT and LOS for buprenorphine-treated infants was 8 and 13 days compared with 15 and 20 days for methadone-treated infants, respectively, $P < .001$ for both outcomes. Median cumulative opioid dose in morphine equivalents was 0.6 mg/kg for buprenorphine-treated infants vs 1.05 mg/kg for methadone-treated infants, $P < .001$. No adverse effects were noted among either group. Of infants treated with buprenorphine, 34 (71%) required the addition of adjunctive pharmacotherapy during the NICU stay, compared with 31 (32%) in the methadone-treated group, $P = .0008$. However, significantly fewer infants treated with buprenorphine required continuation of therapy beyond discharge as compared with those treated with methadone. The difference is most likely a reflection of the protocols used by the sites. In infants that required pharmacotherapy for NAS secondary to intrauterine exposure to methadone, treatment with buprenorphine, compared with methadone therapy, was associated with better outcomes. If confirmed with prospective data, buprenorphine could be considered first-line therapy for the two medication-assisted treatment regimens recommended by the American College of Obstetricians and Gynecologists.

KEYWORDS

buprenorphine, methadone, neonatal abstinence syndrome, opioids, withdrawal

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1 | INTRODUCTION

The incidence of neonatal abstinence syndrome (NAS), infant drug withdrawal secondary to chronic in utero exposure to opioids, including methadone and other psychotropic drugs, has risen dramatically over the past decade.¹⁻³ NAS is associated with prolonged hospitalization in the Newborn Intensive Care Unit and has become a major health burden in the United States.^{4,5} Additionally, infants diagnosed with NAS are more than twice as likely to be readmitted to the hospital compared with uncomplicated term infants.⁶ The American College of Obstetricians and Gynecologists (ACOG) recommends medication-assisted treatment with methadone or buprenorphine in opioid-dependent women during pregnancy.⁷ However, both medications are associated with NAS. The American Academy of Pediatrics (AAP) and a systematic review identified opioid replacement as the ideal treatment of NAS, when pharmacotherapy is indicated.^{8,9} However, choice of agent varies widely between institutions, both with respect to first-line medication and dosage protocol.^{8,10,11} Outside of a recent prospective, randomized clinical trial wherein short-term outcomes were better in infants receiving methadone compared with morphine,²⁸ and there are insufficient data to compare the relative efficacy of the commonly prescribed opioids (morphine, methadone, and buprenorphine) in order to guide therapy.

In retrospective, cohort studies, we and others have shown that buprenorphine is associated with a shorter length of stay (LOS), shorter length of therapy, and minimal side effects when used for the management of all-cause NAS as compared to methadone for infants with in utero exposure to short- and/or long-acting opioids, including methadone and/or buprenorphine.^{10,12-14} Buprenorphine has several advantages over other opioids in the management of NAS. The mechanisms of action of buprenorphine, as a partial *mu* agonist and weak *kappa* antagonist activity in the central nervous system, support its biologic and scientific plausibility for use in NAS.¹⁵ As such, we posit that buprenorphine could be safely used as a first-line agent for all in utero opioid exposures, including intrauterine exposure to methadone.

In this retrospective study, we assessed the relative efficacy of buprenorphine vs methadone as first-line pharmacotherapy for NAS in infants exposed to methadone in utero. Our primary outcome was length of hospital stay. Secondary outcomes included length of opioid therapy and cumulative opioid exposure. We also compared the proportion of infants that required adjunctive pharmacotherapy, including the need for adjunct therapy at discharge.

2 | METHODS

2.1 | Study design

This is a retrospective cohort study performed on infants admitted to four regional hospitals staffed by physicians from Cincinnati Children's Hospital Medical Center. These include the St. Elizabeth Health Care (SEHC) in Edgewood, Kentucky, and three hospitals in Cincinnati, Ohio—The University of Cincinnati Medical Center (UCMC), Mercy Hospital Anderson Nursery (MAN), and Good

Samaritan Hospital (GSH). By protocol, all parturient women are screened with a urine drug test at the point of admission and infants delivered to mothers with a history of opioid-use disorder or positive urine drug test are tested for drugs with either a urine or cord tissue drug test. Infants exposed to long-acting opioids (methadone or buprenorphine) in utero are monitored for NAS for a minimum of 96 hours during birth hospitalization. Eligible infants were those born from March 2015 to March 2017 at a gestational age ≥ 35 weeks and a maternal history of methadone therapy or urine drug screen positive for methadone, and treatment for NAS with either buprenorphine or methadone as first-line opioid replacement therapy. All four sites use the same criteria for initiation, maintenance, and weaning of pharmacotherapy and for addition of adjunct therapy based on modified Finnegan neonatal abstinence scoring.¹⁶ However, the choice of first-line opioid therapy is different between the sites. The sites use similar protocols for both nonpharmacologic management and pharmacologic management of infants with a diagnosis of NAS, as described previously.^{10,12,13} Infants from SEHC are a subset of infants reported in a recent publication of all-cause NAS.¹² The current study, in contrast, focuses on comparing buprenorphine with methadone in exposure-specific NAS (intrauterine methadone exposure).

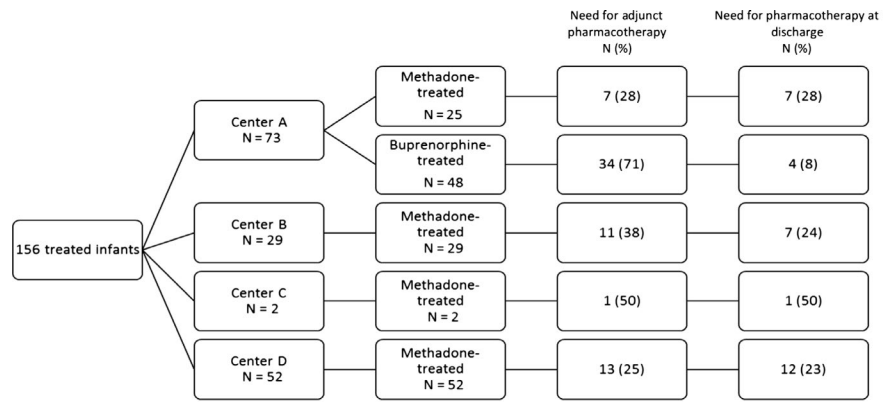
Maternal and infant demographic data, maximum dose of opioid replacement therapy in mg- or mcg/kg/d, length of opioid replacement therapy (LOT), cumulative postnatal opioid exposure, the need for and type of adjunctive pharmacotherapy, LOS, adverse drug effects, and the need for continuation of adjunct therapy at discharge were recorded into a centralized, secure, online database (REDCap—Research Electronic Data Capture) tool hosted at Cincinnati Children's Hospital Medical Center for storage and analysis.¹⁷ As an exploratory endpoint, cumulative opioid exposure was calculated in Morphine Milligram Equivalents (MME) using Opioid Morphine Equivalent Conversion Factors as outlined by the Centers for Disease Control and Prevention.¹⁸ Social parameters and co-morbidities that may result in the prolongation of hospitalization beyond that which was medically indicated per current protocols were recorded to avoid the confounding of data at the time of analysis.

The study protocol was approved by the University of Cincinnati (UC) Institutional Review Board (IRB) with a waiver of informed consent. The other sites relied on the IRB approval by UC.

2.2 | Study patients

Neonates ≥ 35 weeks postmenstrual age that received pharmacologic treatment of NAS secondary to in utero exposure to methadone were classified, based on the first-line therapy, into either the buprenorphine-treated or the methadone-treated arms. Infants with confounding illnesses necessitating therapy with opioids other than for the treatment of NAS and neonates whose only exposure to opioids were narcotics administered during labor were excluded from the study. Pertinent covariates examined included maternal and gestational age, birthweight, and in utero polysubstance exposure.

FIGURE 1 Patient flow: treatment arm, need for adjunct therapy, and need for therapy at discharge



	Therapy at discharge	No therapy at discharge	P
Methadone-treated	27	81	.016
Buprenorphine-treated	4	44	

TABLE 1 Baseline demographic characteristics for patients across participating centers and a comparison between methadone-treated vs buprenorphine-treated infants

(a)	Mean (SD)		
Gestational age in weeks	38.4 (1.6)		
Birthweight in kilograms	2.96 (0.48)		
Maternal age in years	28 (4.8)		
(b)	Methadone-treated	Buprenorphine-treated	P*
Gestational age in weeks (SD)	38.1 (1.8)	38.4 (1.6)	.21
Birthweight in kilograms (SD)	2.89 (0.50)	2.97 (0.50)	.20
Maternal age in years (SD)	28.5 (5.1)	28.4 (4.7)	.92
Infant polysubstance exposure, N (%)	45 (42)	18 (37)	.68

Note: P > .05 for all parameters.

*P for buprenorphine-treated vs methadone-treated infants.

2.3 | Statistical analysis

Comparisons between factors that are dichotomous and continuous outcomes were evaluated using Fisher's exact test, or Mann-Whitney rank sum as appropriate. Associations among categorical variables assessed using chi-square analysis using SigmaPlot Data Analysis software V13.0 (Systat Software Inc).

3 | RESULTS

A total of 156 infants treated solely for NAS secondary to intrauterine exposure to methadone were identified across the participating centers during the study period. Of these, 48 infants were treated with buprenorphine as the primary opioid replacement therapy, while 108 received methadone, Figure 1.

The demographic characteristics of the entire cohort were similar between the participating centers. There were no significant differences in the postmenstrual age, birthweight, and intrauterine polysubstance exposure between buprenorphine- and methadone-treated infants, P > .05 for all variables, Table 1. Similarly, site-specific demographic characteristics (gestational age, birthweight, and maternal age) did not reveal any statistically significant differences between the centers (data not shown).

The median (interquartile range, IQR) LOT and LOS for buprenorphine-treated infants were 8 (5-9) and 13 (9-15) days, respectively, compared with 15 (10-18) and 20 (14-23) days for methadone-treated infants, P < .001 for both. Median (IQR) cumulative opioid dose in morphine equivalents was 0.6 (0.4-1) mg/kg for buprenorphine-treated infants, compared with 1.05 (0.5-3.94) mg/kg for methadone-treated infants, P < .001, Figure 3. Adjustments to LOS for prematurity and social reasons were assessed, but none found. Though all vital signs and nursing records were not examined with the rigor of a clinical trial, no adverse effects were reported in the electronic medical records among either group.

Of infants treated with buprenorphine, 34 (71%) required the addition of adjunctive pharmacotherapy during the NICU stay, compared with 31 (32%) in the methadone-treated group, P = .0008. The adjunct therapy of choice for buprenorphine-treated infants was clonidine, and both clonidine and phenobarbital were used at various time periods in the study in methadone-exposed infants. In contrast, continuation of adjunct pharmacotherapy beyond discharge from the NICU occurred in 4 (8%) of infants treated with buprenorphine compared with 27 (24%) infants treated with methadone, P = .016, Figure 1. Choice of adjunct therapy was dependent on study site and included both clonidine and/or phenobarbital at all sites. Weaning of adjunct therapy was done on both an inpatient and outpatient basis based on the institutional protocols.

To further assess the internal validity of our findings, we performed a post hoc analysis of outcomes on infants from the hospital site (SEHC) where two-thirds of infants received buprenorphine and one-third were treated with methadone, in contrast to the other

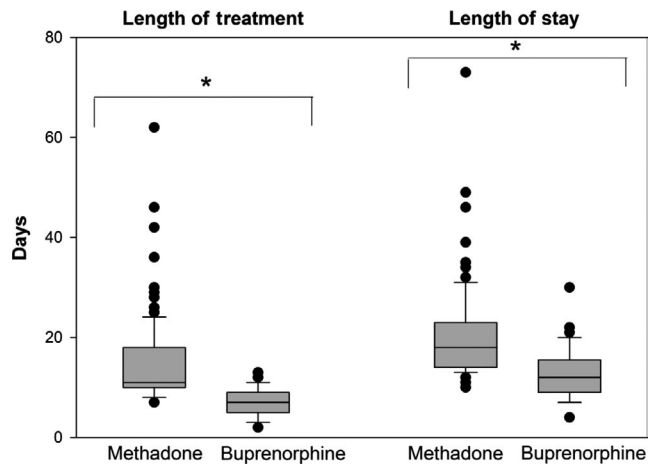


FIGURE 2 Length of stay and length of treatment for methadone- and buprenorphine-treated Infants * $P < .001$

three sites where all infants were treated with methadone. This sub-analysis showed shortened LOS and LOT similar to the entire study population. Specifically, median length of treatment (LOT) and LOS were both shorter in buprenorphine-treated infants (LOT 8 days [range: 4-13] and LOS of 13 days [4-30]) than in those treated with methadone (LOT 10 days [7-22] and LOS of 14 days [12-31]), $P < .001$ for both, Figure 2. Additionally, the post hoc analysis showed that there was no statistically significant difference between the number of patients who required adjunct pharmacotherapy or those who required pharmacotherapy at discharge when comparing the SEHC cohort with the aggregate data from all other centers excluding SEHC (data not shown).

4 | DISCUSSION

The ACOG recommends methadone or buprenorphine as medication-assisted treatment for pregnant women with opioid-use disorder.⁷ In utero exposure to buprenorphine is associated with decreased length of hospital stay in infants with NAS compared with exposure to methadone.²⁵ Outcomes of NAS following therapies for specific intrauterine opioid exposures have not been adequately addressed. In the current retrospective study, we found that in NAS due to intrauterine exposure to methadone, postnatal treatment with buprenorphine is associated with a shorter length of NICU stay, duration of treatment, and lower cumulative opioid exposure, compared with postnatal pharmacotherapy with methadone. To our knowledge, this is the first report of efficacy of methadone vs buprenorphine in exposure-specific NAS. Consistent with previous reports, no adverse effects were identified (data not shown) in either buprenorphine- or methadone-treated infants.¹⁵ Given other reports of the utility of buprenorphine, our data argue for a role for buprenorphine for NAS from all intrauterine opioid exposures including methadone-exposed neonates.

Although oral morphine and methadone remain the most frequently prescribed first-line medications in the treatment of NAS in the United States, sublingual buprenorphine is a treatment modality which has

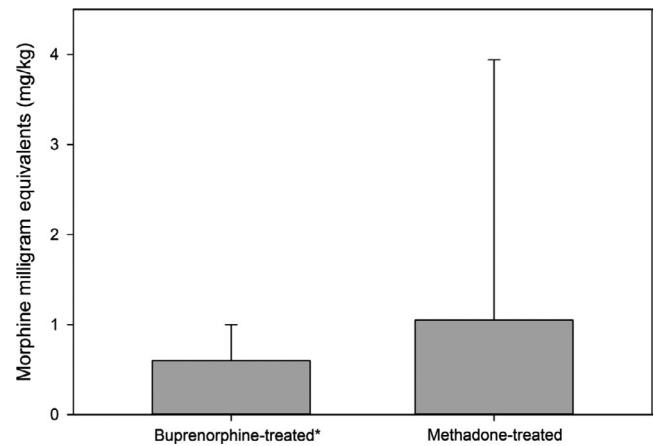


FIGURE 3 Cumulative opioid exposure for methadone- and buprenorphine-treated Infants * $P < .001$. Methadone: median = 1.05 mg/kg (MME), IQR = 0.5-3.94 mg/kg (MME). Buprenorphine: Median = 0.6 mg/kg (MME), IQR = 0.4-1 mg/kg (MME)

gained some traction in recent years.^{8,9,19} Possible advantages of buprenorphine over morphine or methadone include its favorable safety profile given the agonist/antagonist properties of buprenorphine and its action on both *mu* and *kappa* opioid receptors, alleviating withdrawal symptoms due to partial agonist activity at *mu* receptors and mitigating the dysphoria associated with opioid withdrawal through action on *kappa* receptors.²⁰ Agonist effects of buprenorphine at the delta and opioid receptor-like (ORL1) receptors may also play a role.¹⁵

Our findings are consistent with some of the previous reports that buprenorphine therapy in NAS is associated with reduced length of NAS treatment and LOS compared with oral morphine²¹ or with methadone in all-cause NAS. Although no difference was reported in the use of adjunctive pharmacotherapy between buprenorphine- and morphine-treated infants in a recent report,¹⁵ we found that buprenorphine-treated infants required adjunct pharmacotherapy more often. However, significantly fewer infants treated with buprenorphine required continuation of therapy beyond discharge as compared with those treated with methadone. The difference is most likely a reflection of the protocols used by our sites which leverage favorable pharmacokinetics and pharmacodynamics of buprenorphine in a 4-step taper for infants treated with buprenorphine as compared with an 8-step taper for those treated with methadone. Secondary to the duration of the study, the choice of adjunct therapy varied between study sites—sites used either clonidine or phenobarbital, based on their institutional protocols, Appendix 1. This also probably accounts for shorter LOT and LOS than those reported in previous studies.^{15,22} The criteria for initiation, weaning, and addition of adjunct therapy were comparable between all centers. As an exploratory endpoint, cumulative opioid exposure when standardized and expressed in MME was lower with postnatal buprenorphine therapy in our study. The significance of this is unknown.

Strengths of the current study include the involvement of four separate hospitals staffed by a physician group that uses the same treatment algorithms for managing NAS, thus reducing the potential

for heterogeneity and practice variations, well documented in the NAS literature. Another strength of the current study is the ample sample size for this patient population which may support generalizability of our findings to other settings. We also recognize certain limitations of the current study, including the lack of a prospective, randomized comparison of the methadone vs buprenorphine in the treatment of NAS. As designed, the decision to treat with methadone or buprenorphine was dependent on the site. As such, there could be site-specific differences in care for which we could not account, although all sites used the NICU model of care—with rooming in possible at all centers—and have similar practices and policies with regard to breastfeeding. Inter-rater reliability is another limitation and was not assessed, and however, all staff are required to undergo training for Finnegan scoring on a routine basis, in order to mitigate inter-rater variability. Although the demographics are comparable between the two groups, retrospective studies are fraught with unaccounted-for confounders. The sample size precludes adjusting for several important variables such as the percentage of mothers with polypharmacy in each group or concurrent illicit drug use.

Our study addresses a knowledge gap with respect to exposure-specific NAS and may be a first step toward targeted or individualized therapy. This aligns with the position of the Government Accountability Office of the United States—specifically, the treatment of NAS including the effectiveness of different drugs.^{23,24} To the best of our knowledge, this is the first study to date comparing buprenorphine to methadone therapy as primary opioid replacement for methadone-exposed infants who require pharmacotherapy for the management of NAS. Our results demonstrate that methadone-exposed infants who require pharmacotherapy for the management of NAS have a favorable response to buprenorphine therapy despite a potentially more severe presentation of NAS.^{2,25-27} Outside of a recent prospective, randomized clinical trial wherein short-term outcomes were better in infants receiving methadone compared with morphine,²⁸ there are insufficient data to compare the relative efficacy of the commonly prescribed opioids (morphine, methadone, and buprenorphine) in order to guide therapy. Our findings, if broadly adopted after confirmation with a prospective study, may impact the standard of care for pharmacologic management of NAS, in selecting the optimal therapeutic agent which may improve outcomes and potentially decrease overall healthcare costs.

In conclusion, postnatal treatment of infants with NAS secondary to chronic intrauterine exposure to methadone with buprenorphine may be superior to postnatal pharmacotherapy with methadone with respect to LOT, hospital LOS, and cumulative opioid exposure. However, more infants are treated with buprenorphine required adjunctive pharmacotherapy. Using our current protocols, therapy with buprenorphine would result in earlier discharge from the hospital and less disruption for the family. The favorable findings surrounding buprenorphine therapy, combined with novel strategies such as Eat, Sleep, Console, and PRN therapy, could further impact duration of therapy, cumulative opioid exposure, and NAS-related LOS. A randomized prospective study to compare the different treatment modalities for NAS is warranted.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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APPENDIX 1

INSTITUTIONAL PROTOCOLS

METHADONE FOR MANAGEMENT OF NEONATAL ABSTINENCE SYNDROME (NAS)

INITIATION OF THERAPY

Initiate at Step 1 for infants with Finnegan scores >8 on three consecutive scorings (but not $\geq 11 \times 3$).

Initiate at Step 1a for infants with Finnegan scores ≥ 11 on three consecutive scorings.

Initiate at Step 1a for infants with two Finnegan scores >12 within a 24-h period.

Taper step	Methadone dose	Interval
Step 1	0.1 mg/kg	Q 6 h × 4
*If average Finnegan scores continue ≥ 8 after 2 d, proceed to step 1a		
Step 1a	0.1 mg/kg	Q 4 h × 6
Step 1b	0.1 mg/kg	Q 8 h × 3
Step 1c	0.1 mg/kg	Q 12 h × 2
Step 2	0.07 mg/kg	Q 12 h × 2

(Continues)

APPENDIX 1 (Continued)

Taper step	Methadone dose	Interval
Step 3	0.05 mg/kg	Q 12 h × 2
Step 4	0.04 mg/kg	Q 12 h × 2
Step 5	0.03 mg/kg	Q 12 h × 2
Step 6	0.02 mg/kg	Q 12 h × 2
Step 7	0.01 mg/kg	Q 12 h × 2
Step 8	0.01 mg/kg	Q 24 h × 1

BUPRENORPHINE FOR NEONATAL ABSTINENCE SYNDROME (NAS)

Step 1	4.5 mcg/kg	Q 8 h
If average scores ≥ 8 (at starting dose 4.5 mcg/kg) increase by 1.5 mcg/kg/dose every 1-2 doses, to a maximum dose of 7.5 mcg/kg/dose, until 2 scores <8		
Step 1a	6 mcg/kg	Q 8 h
Step 1b	7.5 mcg/kg	Q 8 h
Step 2	3 mcg/kg	Q 8 h
Step 3	1.5 mcg/kg	Q 8 h
Step 4	1.5 mcg/kg	Q 12 h