Buprenorphine for the Treatment of Neonatal Abstinence Syndrome

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Abstract

Objective: To summarize the available data for using buprenorphine in neonatal abstinence syndrome and discuss these data in context of the current standard of care therapies, oral morphine and oral methadone. **Data Sources:** A literature search was conducted using PubMed (1949-May 2018) and EMBASE (1980-May 2018). Combinations of the search terms “buprenorphine,” “neonatal,” and “neonatal abstinence syndrome” were used. **Study Selection and Data Extraction:** All full-length, English-language studies were included in this review. **Data Synthesis:** A total of 4 studies were included in this review including 1 retrospective cohort study, 2 prospective single-center open-label randomized trials, and 1 prospective single-center, double-blind study. Oral morphine was the comparator in 3 studies, and oral methadone was the comparator in one. Buprenorphine was associated with a significant reduction in duration of treatment in 3 of the 4 studies and was associated with a significant reduction in duration of hospital stay in 3 of the 4 studies. In the randomized, double-blinded trial, buprenorphine had a significantly reduced duration of treatment (15 vs 28 days, $P < .001$) and duration of hospital stay (21 vs 33 days, $P < .001$). The requirement of adjunct treatment was similar between groups in all 4 studies, and buprenorphine did not have any significant adverse reactions in comparison with morphine and methadone. **Conclusions:** Buprenorphine appears to be a safe option for treating neonatal abstinence syndrome that is potentially superior to the current standard of care therapies with respect to duration of treatment and hospital length of stay.

Keywords

neonatology, neonatal abstinence syndrome, buprenorphine, withdrawal, opioids

Introduction

Neonatal abstinence syndrome (NAS) is the occurrence of signs and symptoms of withdrawal after in utero drug exposure. Opioids are of particular concern due to the prevalence of opioid abuse as well as the potential for withdrawal to cause severe symptoms in the neonate. NAS can be associated with a wide variety of symptoms, which are listed in Table 1.¹ The severity of NAS is typically assessed and monitored using a scoring system. The Finnegan scoring system (either the original or a modified version) is commonly used, and other scoring systems such as the Rivers Tool and the Lipsitz Neonatal Withdrawal Scale are also available.² The use of these scales in preterm neonates or in infants experiencing polysubstance withdrawal or withdrawal from nonopioid substances has not been properly established. The components and scoring for the modified Finnegan scoring system can be seen in Table 2.³

Management of NAS can consist of both nonpharmacologic and pharmacologic therapy. Nonpharmacologic interventions are typically environmental and include keeping neonates in a quiet area free from external excitatory

stimulus (ie, light and noise). Soothing, gentle handling, and nonnutritive sucking are important interventions. If the neonate is clinically stable, rooming-in should be encouraged to promote infant-mother bonding. Breastfeeding is another important intervention and should be encouraged unless contraindicated (relapsing or actively abusing opioids or other substances). Because buprenorphine and methadone are only minimally excreted in milk, it is safe for a mother on opioid maintenance therapy for their opioid addiction to breastfeed. Nutrition should be closely monitored and milk or formula should be offered frequently and in small amounts.³

Pharmacologic therapies are initiated when nonpharmacologic therapies are insufficient to control NAS symptoms. Opioids are the first-line therapy for NAS. Historically, oral

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Table 1. Neonatal Abstinence Syndrome Signs and Symptoms.¹

System	Signs/Symptom
Autonomic reactivity	Irritability
	Hypertonia
	Yawning
	Sneezing
	Mottling
	Fever
	Vomiting
Skin	Diarrhea
	Mottling
	Increased sweating
Head, eyes, ears, nose, and throat	Nasal flaring
	Nasal stuffiness
Neurological	Sneezing
	Tremors
	Seizures
	Irritability
	High-pitched cry
	Poor sleep
	Frequent yawning (>3-4 times)
	Frequent sneezing (>3-4 times)
	Hypertonia
	Hyperactive deep tendon reflexes
Gastrointestinal	Exaggerated Moro reflex
	Diarrhea
	Dehydration
	Electrolyte abnormalities
	Perianal lesions
	Hyperphagia
	Vomiting

morphine and oral methadone have been used. The advantages of these agents are that they are well established in clinical practice with known dosing and adverse effect profiles. Both can be used as monotherapy. Pharmacologic therapy is often initiated based on modified Finnegan scores; therapy is initiated if the score is >8 on 2 different occasions or ≥ 12 on any occasion. If the score is ≥ 12 on follow-up then the dose of either agent may be increased by 10%. If the score is 9 to 11 then the dose could remain the same. If the score is <8 then a 10% dose reduction over 24 hours could be instituted. Should monotherapy be insufficient to control symptoms, adjunctive treatment with phenobarbital, a γ -aminobutyric acid agonist, can be initiated. Clonidine, an α -2-adrenergic agonist, has also been evaluated for control of autonomic symptoms in NAS. Naloxone, paregoric or tincture of opium, benzodiazepines, and chlorpromazine do not have a role in the pharmacologic management of opioid-related NAS.^{2,3}

Morphine is a full μ -opioid receptor agonist. The pharmacokinetic properties of morphine can be found in Table 3.⁴⁻⁷ Because morphine has a short half-life it must be given

frequently (typically every 3-4 hours) but this has the added advantage of allowing for rapid titration of the dose to achieve symptom control. Methadone, a synthetic full μ -opioid receptor agonist, differs from morphine in several ways (long half-life and more stable blood levels). However, there can be significant interpatient variability in terms of pharmacokinetics, which can make dosing erratic. There are limited data comparing morphine and methadone head-to-head for NAS. In a single-center, prospective, randomized, controlled trial methadone had a statistically significant shorter duration of treatment compared with morphine. Additionally, there was no difference between the two with regard to use of adjunct therapy. However, other important clinical endpoints such as duration of stay in the hospital were not evaluated so no solid conclusions can be drawn from this study.⁸ Two trials are registered at www.clinicaltrials.gov that will compare morphine and methadone head-to-head (ClinicalTrials.gov numbers NCT02851303 and NCT01958476).

In some cases, opioid therapy is not enough to control symptoms of NAS and adjunctive therapies need to be used. Phenobarbital has a long history of being used as both primary and secondary treatments in NAS.⁹⁻¹¹ This γ -aminobutyric acid receptor agonist has a long half-life and requires therapeutic drug monitoring for prolonged use. Clonidine, a centrally acting α_2 -adrenergic agonist, has been recently evaluated in neonates for help controlling autonomic symptoms related to withdrawal, for which it is commonly used in adults.¹²⁻¹⁵

Buprenorphine is a partial μ -opioid receptor agonist with a prolonged half-life that has been used extensively in adults to ameliorate opioid withdrawal. Because buprenorphine undergoes extensive first-pass metabolism, it is given via the sublingual route. Other appealing characteristics of buprenorphine include a ceiling effect for respiratory depression, limited abuse liability, and a well-established safety profile in adults.

Methods

A literature search was conducted using PubMed (1949-May 2018) and EMBASE (1980-May 2018). Combinations of the search terms “buprenorphine,” “neonatal,” and “neonatal abstinence syndrome” were used. Results were restricted to full-length, English-language, human-subject studies. Results were screened for relevance. The reference sections of relevant articles were manually screened for potentially missed citations.

Data

In 2008, Kraft and colleagues published the first of 3 randomized trials evaluating sublingual buprenorphine for the treatment of NAS. The first trial was a single-site,

Table 2. Modified Finnegan Scoring System.³

System	Clinical Indicator	Points
Central nervous system	High-pitched crying	2 Points if present 3 Points if continuously present
	Limited sleep after feeding	1 Point if 2 to 3 hours after feeding 2 Points if 1 to 2 hours after feeding 3 Points if <1 hour after feeding
	Moro reflex	2 Points if hyperactive 3 Points if markedly hyperactive
	Tremors	1 Point if mild when disturbed 2 Points if moderate to severe when disturbed 3 Points if mild while undisturbed 4 Points if moderate to severe while undisturbed
	Hypertonia	2 Points
	Excoriation	1 Point
	Myoclonic jerks	3 Points
	Generalized convulsions	5 Points
Metabolic, vasomotor, and respiratory	Sweating	1 Point
	Fever	1 Point if 37.5°C to 38.3°C 2 Points if >38.3°C
	Frequent yawning (>3-4 times)	1 Point
	Mottling	1 Point
	Nasal stuffiness	1 Point
	Sneezing (>3-4 times)	1 Point
	Nasal flaring	2 Points
	Respiratory rate	1 Point if >60 per minute 2 Points if >60 per minute with retractions
Gastrointestinal	Excessive sucking	1 Point
	Poor feeding	2 Points
	Regurgitation	2 Points if present at all 3 Points if projective
	Loose stools	2 Points if present at all 3 Points if watery

Table 3. Pharmacokinetics of Opioids Used for Neonatal Abstinence Syndrome.⁴⁻⁷

	Buprenorphine	Morphine	Methadone
Clearance	3.5 L/h/kg	75.3 L/h/70 kg	8.94 L/h/70 kg
Half-life	11 hours	9.0 ± 3.4 hours (preterm neonates) 6.5 ± 2.8 hours (term neonates) 2.0 ± 1.8 hours (infants and children)	Highly variable; 3.5 to 60 hours
Bioavailability	7% (sublingual)	48.5%	Variable; 41% to 99%
Metabolism	N-dealkylation via CYP3A4 to norbuprenorphine	Glucuronidation to morphine-3-glucuronide and morphine-6-glucuronide	N-demethylation via CYP3A4, CYP2B6, and CYP2C19 to inactive metabolites

Abbreviation: CYP = cytochrome P450 enzyme.

randomized, open-label trial that enrolled neonates over a 3-year period.¹⁶ Enrollment criteria included exposure to opioids in utero, ≥37 weeks gestation, and demonstration of signs and symptoms of NAS requiring treatment (any 3 consecutive scores on the modified Finnegan scale adding

up to ≥24). Patients were excluded if there were major congenital malformations and/or intrauterine growth retardation, medical illness requiring intensification of medical treatment, concomitant maternal benzodiazepine or severe alcohol abuse, maternal use of benzodiazepine or alcohol

in the 30 days prior to enrollment, concomitant use of CYP 3A4 inhibiting or inducing drugs, seizure or other neurologic abnormality, and breastfeeding.

Patients were randomly assigned to either sublingual buprenorphine 13.2 µg/kg/day in 3 divided doses or to standard-of-care treatment consisting of morphine 0.4 mg/kg/day in 6 divided doses. Dose escalation (20% for sublingual buprenorphine and 10% for morphine) was done when 2 or 3 Finnegan scores totaled 24 or more or there was a single score of 12 or more. Rescue doses were permitted as well for uncontrolled symptoms. Adjunctive phenobarbital was initiated when the total buprenorphine dose reached 39 µg/kg/day or the total morphine dose reached 1 mg/kg/day. Once stabilized the daily dose was weaned every 24 hours and were monitored for 48 hours after discontinuing treatment. Dosing for both medications was based on birth weight. Major endpoints included length of treatment, length of stay, and use of adjunct phenobarbital. This was a pilot study so it was not powered to measure a difference between any of the endpoints.

Twenty-six patients were enrolled in the trial with 13 being randomized to each treatment group. In terms of efficacy outcomes there were no significant differences between groups as seen in Table 4.¹⁶⁻¹⁹ However, the differences between the buprenorphine and morphine groups on length of treatment (32 vs 22 days, respectively) and length of stay (27 vs 38 days, respectively) would be clinically significant keeping in mind this was a pilot trial that did not have power to measure a difference on these efficacy outcomes. Buprenorphine was generally well tolerated with one infant having seizures that an independent review was not able to link to treatment. On the basis of this small, pilot study further studies were deemed warranted.

In 2010, Kraft et al conducted a follow-up trial evaluating a revised dosing regimen of buprenorphine in NAS.¹⁷ In this single-site, randomized, open-label trial buprenorphine was compared with oral morphine. Enrollment criteria included ≥ 37 weeks gestation, any 3 consecutive scores on the MOTHER NAS neonatal abstinence scoring system adding up to ≥ 24 , or a single score ≥ 12 . Patients were excluded for similar reasons as the previous 2008 Kraft trial.

Patients were randomly assigned to either sublingual buprenorphine or oral morphine over a 2-year period. Buprenorphine was initially dosed at 15.9 µg/kg/day in 3 divided doses. Oral morphine was initially dosed at 0.4 mg/kg/day in 6 divided doses. Both treatments could be escalated based on uncontrolled symptoms using the MOTHER NAS scores and all dosing was based on daily weight. Once stabilized on a dose a weaning process was begun, and patients were observed for at least 2 days following discontinuation of treatment. This was a follow-up pilot study evaluating a modified dosing regimen so a sample size calculation was not performed. Major endpoints included

adverse events, length of treatment, length of stay, and use of adjunct phenobarbital.

Twenty-four patients were enrolled in the trial with 12 being randomized to each treatment group. In terms of efficacy outcomes, buprenorphine was shown to be statistically significantly better than morphine for the outcomes of length of treatment (23 vs 38 days, respectively; $P = .01$) and length of stay (32 vs 42 days, respectively; $P = .05$). In terms of safety both treatments were well tolerated. One infant in the buprenorphine group developed a cytomegalovirus infection, prolonged reflux/poor feeding, and elevated transaminases. The poor feed/reflux was initially thought to be a component of the NAS, but a lack of resolution with phenobarbital and no worsening when the agents were withdrawn led to further investigation, which resulted in the detection of cytomegalovirus in the patient's urine. The infant did develop alanine transaminase and aspartate transaminase levels 30 and 20 times the upper limit of normal. An independent review board deemed this unrelated to the study drug but recommended liver function test monitoring for the rest of the study, which were found to be normal in the 6 subsequently enrolled patients (3 in each group).

Kraft and colleagues published a follow-up trial to their 2 previous studies in 2017.¹⁸ In this single-site, double-blind, double-dummy, randomized controlled trial patients were assigned to either sublingual buprenorphine or oral morphine over a 5-year period. Enrollment criteria included gestational age ≥ 37 weeks, exposure to opioids in utero, and signs and symptoms of NAS. Exclusion criteria included a major congenital malformation, birth weight < 2200 g, a serious medical/neurologic illness, a bilirubin level > 20 mg/dL, maternal use of a benzodiazepine 30 days before birth, or seizures. Breastfeeding was initially an exclusion criterion until the study protocol was amended.

Patients were randomly assigned in a 1:1 fashion to either sublingual buprenorphine every 8 hours or oral morphine every 4 hours. Dose adjustments were made based on disease severity using the MOTHER NAS scale. There was a maximum dose of 60 µg/kg/day for buprenorphine and 1.2 mg/kg/day for morphine, which would be reached after 6 dose increases. If disease stability was not achieved then adjunct phenobarbital was initiated. The primary efficacy endpoint was duration of treatment for NAS symptoms starting from the first dose of study drug. Secondary endpoints include length of hospital stay, percentage of infants requiring adjunct phenobarbital, and safety. Pharmacokinetic, pharmacogenomic, neurobehavioral, and feeding dysfunction data were also collected but not reported on.

One hundred and twenty-one infants were screened and 63 were enrolled (33 to buprenorphine and 30 to morphine). Five patients were withdrawn from the trial based on parental concern (3 in buprenorphine group and 2 in morphine group) and were given open-label oral morphine; no withdrawals were due to adverse events. In the intention-to-treat analysis

Table 4. Comparison of Studies Evaluating Buprenorphine in NAS.¹⁶⁻¹⁹

Reference	Design	Population	Intervention	Duration of Treatment (days)	Length of Hospital Stay (days)	Adjunct Therapy N (%)
Hall et al ¹⁹	Retrospective cohort trial	N = 201 (38 BUP; 163 methadone)	BUP or methadone titrated and weaned using Finnegan score	BUP ^a : 9.4 (7.1-11.7) Methadone ^a : 14.0 (12.6-15.4) <i>P</i> < .001	BUP ^a : 16.3 (13.7-18.9) Methadone ^a : 20.7 (19.1-22.2) <i>P</i> < .001	BUP: 23.7% Methadone: 25.8% <i>P</i> = .79
Kraft et al ¹⁶	Single site, randomized, open-label trial	N = 25 (12 BUP; 13 morphine)	BUP or morphine titrated and weaned using Finnegan score	BUP ^b : 22 ± 11 Morphine ^b : 32 ± 16 <i>P</i> = .077	BUP ^b : 27 ± 11 Morphine ^b : 38 ± 16 <i>P</i> = .068	BUP: 3/12 (25%) Morphine: 1/12 (8%)
Kraft et al ¹⁷	Single site, randomized, open-label trial	N = 24 (12 BUP; 12 morphine)	BUP or morphine titrated and weaned using MOTHER NAS score	BUP ^b : 23 ± 12 Morphine ^b : 38 ± 14 <i>P</i> = .01	BUP ^b : 32 ± 24 Morphine ^b : 42 ± 13 <i>P</i> = .05	BUP: 3/12 (25%) Morphine: 1/12 (8%)
Kraft et al ¹⁸	Single site, randomized, double-blind, double-dummy trial	N = 63 (intention-to-treat; 33 BUP; 30 morphine)	BUP or morphine titrated and weaned using MOTHER NAS score	BUP ^c : 15 (3-67) Morphine ^c : 28 (13-67) ^d -13 (-21 to -7) <i>P</i> < .001	BUP ^c : 21 (7-71) Morphine ^c : 33 (18-70) ^d -13 (-23 to -6) <i>P</i> < .001	BUP: 5/33 (15%) Morphine: 7/30 (23%) <i>P</i> = .36

Abbreviations: BUP, buprenorphine; NAS, neonatal abstinence syndrome.

^aMean (95% confidence interval).^bMean ± standard deviation.^cMedian (range).^dDifference (95% confidence interval).

the median duration of treatment was 15 days in the buprenorphine compared with 28 days in the morphine group (95% confidence interval = 7-21; *P* < .001). The median length-of-stay in the hospital was 21 days in the buprenorphine group compared with 33 days in the morphine group (95% confidence interval = 7-22; *P* < .001). This statistically significant difference was also seen in the per-protocol analysis. There were 13 adverse events in the buprenorphine group (in 7 patients) and 10 events in the morphine group (in 8 patients; *P* = .79). There were 2 serious adverse events (inguinal hernia repair in the morphine group and supraglottoplasty associated with Pierre Robin syndrome in the buprenorphine group). There were no elevations in alanine aminotransferase or aspartate aminotransferase in any patient. There was a lower mean respiratory rate (by 4.4 respirations per minute) in the morphine group compared with the buprenorphine group (*P* = .02).

Hall and colleagues conducted a retrospective cohort comparison of buprenorphine versus methadone for NAS at 6 hospitals in southwest Ohio.¹⁹ Patients were included if they were at least 34 weeks' gestation at birth and received pharmacologic therapy for NAS after in utero exposure to opioids other than methadone. One neonatologist group provided care at all 6 institutions and standardized protocols for the assessment and management of NAS were utilized. Thirty-eight neonates were treated with buprenorphine and 163 were treated with methadone. Patients in the buprenorphine group had statistically significant shorter treatment duration (9.4 vs 14.0 days; *P* < .001) and length of stay (16.3 vs 20.7 days; *P* < .001) compared with patients in the methadone group. There was no difference seen between groups with regard to use of adjunct therapy. The retrospective nature and potential for site bias (only 1 of the 6 hospitals used the buprenorphine protocol) limit how generalizable

this study is, though the results are in line with the results from the Kraft series of trials.

Discussion

NAS is a challenging condition associated with prolonged lengths of stay in neonatal intensive care units and hospitals as well as significant and challenging durations of treatment with opioid therapy. Buprenorphine possesses several pharmacokinetic and pharmacologic properties that make it appealing for treatment in this challenging condition, particularly in comparison with the current standards of care, morphine and methadone. The data from these 4 studies confirm that buprenorphine should not just be safe for treating NAS but might actually be more effective than either morphine or methadone. Larger studies would be needed to confirm this though the feasibility of conducting such studies in such a vulnerable patient population may preclude them from being performed.

Buprenorphine is also being studied for use in neonates experiencing withdrawal from benzodiazepines (ClinicalTrials.gov numbers NCT01671410 and NCT02249026) and a randomized controlled trial is also being done comparing buprenorphine with morphine in NAS (ClinicalTrials.gov number NCT01708707).

There are several concerns with using buprenorphine in NAS. Even though buprenorphine has been used in clinical practice for a number of years in adults there are still limited data and experience using it in neonates. Sublingual administration with neonates can be challenging, and to minimize the risk of swallowing doses a pacifier was immediately inserted after placing a dose under the tongue. Additionally, the studies summarized above are mostly single-center studies, which limits the generalizability of these studies. Most hospitals with neonatal care wards across the country likely have limited or no clinical experience using buprenorphine in these patients, and because these patients are so vulnerable there could be resistance to changing the standard of care from oral morphine/methadone to sublingual buprenorphine. The intravenous formulation of buprenorphine does contain ethanol (30%), which presents another concern; however, the volume of medication being administered tends to be very small (~0.2 mL) alleviating this concern.¹⁹ A future area of study would be studying formulations using less ethanol.¹⁶

With regard to safety buprenorphine was associated with no increase in any medication-associated adverse drug events compared with either morphine or methadone in any of the studies. The aforementioned ethanol administration could be a concern in neonates requiring high doses of buprenorphine. Neonates of mothers with polysubstance abuse (ie, opiates and benzodiazepines) were excluded from these studies, and there is theoretical concern that buprenorphine could have a decreased therapeutic index.¹⁶

Conclusion

Buprenorphine appears to be as safe as oral morphine and oral methadone for treating NAS and may be more efficacious than these agents at reducing treatment duration and length of stay in the hospital.

Declaration of Conflicting Interests

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