Journal of Perinatology (2011) 31, 692–701

www.nature.com/jp

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Update on the pharmacologic management of neonatal abstinence syndrome

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Although a statement on Neonatal Drug Withdrawal was published in 1998 by the American Academy of Pediatrics, pharmacologic management of neonatal abstinence syndrome (NAS) remains a challenge. Published clinical trials are limited, restricting treatment decision making to practitioner's experience and preference rather than evidence-based medicine. To optimize withdrawal symptom prevention, drug selection is often based on the offending agent (opioids versus polysubstance exposure), clinical presentation, mechanism of action (agonist versus partial agonist/antagonist, receptor effects), pharmacokinetic parameters and available drug formulations. This review addresses risk factors and pathophysiology of NAS, summarizes parameters of common drugs used for the management of NAS, and reviews published literature of standard therapies as well as newer agents. Based on the current literature, paregoric is no longer recommended and oral morphine solutions remain the mainstay of therapy for opiate withdrawal. Other potential therapies include methadone, buprenorphine, phenobarbital and clonidine with the latter two agents as adjunctive therapies.

Journal of Perinatology (2011) **31,** 692–701; doi:10.1038/jp.2011.116; published online 25 August 2011

Keywords: buprenorphine; methadone; morphine; opioids; tincture of opium

Introduction

Neonatal abstinence syndrome (NAS) is the result of fetal exposure to illicit or prescription drug use by the mother prenatally. Intrauterine exposure of the fetus to drugs may lead to neonatal intoxication or withdrawal depending on the substance, extent of exposure and timing of exposure in relation to delivery. Acute maternal exposure to sedatives or opiates before delivery may result in childbirth complications such as respiratory and/or cardiovascular depression in the neonate.[1] In contrast, acute exposure of stimulants such as cocaine to neonates may cause respiratory distress–transient tachypnea.[2,3] Passive dependence develops in neonates exposed *in utero* to addictive illicit drugs, such as marijuana, or prescription drugs, such as barbiturates, benzodiazepines or opiates, through maternal drug use during pregnancy. NAS is comprised of opioid withdrawal signs including central nervous system (CNS) irritability and gastrointestinal dysfunction. In all, 50 to 90% of neonates born to heroin-dependent mothers compared with ~60% of neonates born to mothers maintained on methadone therapy develop withdrawal.[4,5] Neonates exposed to stimulants (that is, amphetamines, cocaine) *in utero* frequently experience neurobehavioral abnormalities such as hypoarousal and physiologic stress, but are less symptomatic for a shorter duration than opiate-exposed infants.[2,3]

The purpose of this article is to review the management of NAS due to opioid and/or polysubstance exposure. The review will focus on literature published since the 1998 American Academy of Pediatrics (AAP) statement on Neonatal Drug Withdrawal to identify any potential change in practice.[6]

Presentation of NAS

Neonatal characteristics associated with maternal drug use are prematurity, unexplained intrauterine growth restriction, neurobehavioral abnormalities, urogenital anomalies, atypical cerebrovascular accident and necrotizing enterocolitis in otherwise healthy term neonates.[1–3] The presentation of withdrawal signs in the neonate is dependent on the pharmacokinetics of the agent, gestational age and total amount of exposure.[7] Neonates exposed to opioids *in utero* have reduced fetal growth parameters, increased incidence of prematurity and inadequate birth weight.[1,8,9]

Opioid withdrawal manifestations can be divided into three categories: neurological, gastrointestinal and autonomic.[4] Table 1 categories the NAS signs based on the system affected. Withdrawal causes an increase in muscle tone, irritability, potential seizures

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Received 8 February 2011; revised 7 July 2011; accepted 25 July 2011; published online 25 August 2011

Table 1 Opioid-induced NAS manifestations

Neurological	*Gastrointestinal*	*Autonomic*
Irritability	Vomiting/diarrhea	Diaphoresis
Increased wakefulness	Dehydration	Nasal stuffiness
High-pitched cry	Poor weight gain	Fever
Tremor	Poor feeding	Mottling
Increased muscle tone	Uncoordinated and constant sucking	Temperature instability
Hyperactive deep tendon reflexes		Piloerection
Frequent yawning and sneezing		Mild elevations in respiratory rate and blood pressure
Seizures (2−11%)		

Abbreviation: NAS, neonatal abstinence syndrome.

and diarrhea. Manifestations of prematurity and NAS often overlap causing differentiation between the two diagnoses challenging.

Neonatal withdrawal symptoms associated with stimulant exposure (that is, amphetamines, cocaine) *in utero* usually presents with neurobehavioral abnormalities.[2,3] Neonatal effects of prenatal exposure to drugs is difficult to evaluate because few pregnant women only consume one drug during pregnancy.[1,2] Abnormalities associated with specific substances of abuse are less defined compared with opioid effects: cocaine causes low birth weight, preterm delivery, and microcephaly, heroin exposure is associated with low birth weight and amphetamines cause intrauterine growth restriction and cardiac anomalies.[1−3]

The onset of withdrawal signs is dependent on the half-life of the opioid. Prenatal exposure to opioids such as morphine and buprenorphine have a shorter time to onset of withdrawal (average 36 h) compared with methadone (60 h).[10] Similar to the AAP statement, recent studies have not been able to prove the correlation between the rate or severity of NAS and dose of maternal methadone therapy.[5,7] Of note, maternal methadone use has been correlated with transient prolongation of the QTc interval in the first 2 days of life in newborn infants (dosage ranged from 30 to 85 mg per day).[11]

Pathophysiology of NAS withdrawal

Due to abrupt cessation of opioid exposure at birth, an exaggerated rebound from the acute pharmacologic effects occurs resulting in a characteristic withdrawal. The mechanism of this amplified reaction is complex and not fully understood. One theory involves the intracellular secondary messenger, cyclic adenosine monophosphate, which is responsible for signal transduction.[12] The initial activation of the opioid receptor strongly inhibits intracellular adenyl cyclase that prevents the production of cyclic adenosine monophosphate.[12] After subsequent repeated exposure, the inhibition becomes weaker due to increased production of adenyl cyclase. After removal of the opioid, the inhibition of adenyl cyclase is reversed, which results in overproduction of cyclic adenosine monophosphate during subsequent withdrawal exposures.[12] The resultant flux of cyclic adenosine monophosphate is a suspect for the intense withdrawal manifestations, in addition to effects from dysregulation of other neurotransmitters.

Diagnosis of NAS

Conditions that can mimic or confound NAS should be managed, such as hypoglycemia, hypocalcemia, infections, hyperthyroidism, hypomagnesemia and trauma (anoxic brain injury or CNS hemorrhage).[4] Important subjective information to attain from the mother includes a detailed history of prescription and non-prescription medication use, social habits and breastfeeding. Various diagnostic tests of the neonate can be utilized to detect the presence of opioids or other illicit drugs including blood sampling, urine drug screen, hair testing and meconium drug testing. Unfortunately, all these diagnostic tests have limitations. Blood and urine samples have a narrow window of detection as the fetus *in utero* rapidly metabolizes opioids, which leads to a low concentration of opioids at birth that is difficult to detect.[9] Only neonates with recent drug exposure will have a positive blood or urine drug screen, resulting in high false-negative rates due to the lack of sensitivity.[12] Neonatal hair is also limited by the procedures required to quantify the very small amounts of drug present and slow growth of hair.[9] In general, measurement of drug concentrations in hair is beneficial for chronic detection assuming enough hair is present. The best method for detecting drug exposure during pregnancy is meconium drug testing with a specificity of 94.6%.[13]

The tools for assessing withdrawal manifestations associated with NAS are used to quantify severity and determine initiation of pharmacologic therapy and drug titrations when necessary.[6,9] Scores are calculated at regular intervals to assess signs of withdrawal and grade severity of NAS. Treatment threshold is specific to the assessment tool and subsequent score. Tools available are the Finnegan scoring system,[14] Lipsitz Tool,[15]

Neonatal Narcotic Withdrawal Index,[16] Ostrea System[17] and Neonatal Withdrawal Inventory.[18]

Non-pharmacologic management of NAS

Non-pharmacologic techniques are used as adjunct therapy to comfort the neonate and manage withdrawal manifestations, which include swaddling, rocking, minimal sensory or environmental stimulation, and maintaining temperature stability. Due to hyperactivity, poor intake and diarrhea, the increased metabolic demand necessitates high caloric intake and may require intravenous fluids to prevent dehydration.[6,9] Frequent small feedings of hypercaloric formula (24 cal per oz) may be necessary to meet the high caloric requirements of 150 to 250 kcal kg^{-1} per day to ensure proper growth and should be individualized.[6]

Although breastfeeding in postpartum women receiving methadone is considered to be safe for newborns, the clinical management is often individualized. Methadone-dependent women without substance abuse treatment or sufficient counseling are not ideal candidates for breastfeeding.[19] The Centers for Disease Control and Prevention states that mothers with concurrent hepatitis B or C infection are not contraindicated to breastfeeding.[20] However, breastfeeding in other maternal comorbid diseases such as HIV is discouraged.[21]

In a retrospective chart review by Abdel-Latif *et al.*,[22] data from drug-dependent mothers and their infants were reviewed to assess the effects of breast milk on the severity and outcome of NAS. Breast milk feedings significantly reduced the need for withdrawal pharmacotherapy compared with formula-fed infants based on Finnegan scores (52.9 versus 79%, $P<0.001$); even after stratifying for prematurity and exposure to multiple illicit drugs and methadone exposure (from maintenance therapy and/or abuse). Length of hospital stay (LOS) was reduced in the breast milk group by an average of five days. Jansson *et al.*[23] studied eight breastfeeding mothers on methadone therapy doses between 50 and 105 mg per day. Methadone concentrations in breast milk were all low (range: 21 to 462 ng ml^{-1}) and lack correlation to maternal dose. The concentrations of methadone in infant plasma samples ranged from 2.2 to 8.1 ng ml^{-1}. There were no statistically significant associations between infant plasma methadone concentrations and breastfeeding.

Pharmacologic management of NAS

The goals of initiating pharmacotherapy are to stabilize clinical manifestations of withdrawal and restore normal newborn activities. Based on the latest recommendation from the AAP on Neonatal Drug Withdrawal, indications for pharmacotherapy include signs of withdrawal such as seizure, fever, decreased duration of sleep, and weight loss or dehydration due to vomiting, diarrhea or poor feeding. The mainstay of NAS management is opioid therapy due to the advantages of bowel motility inhibition and treatment of seizures secondary to withdrawal.[6,9] In order to determine the most appropriate treatment, many factors must be considered such as pharmacokinetics and drug formulations, refer to Table 2. For opioid-associated NAS, morphine-containing preparations, methadone and buprenorphine are treatment options. Phenobarbital, clonidine and diazepam are used for polysubstance exposure, and may be used in combination with opioid therapy for NAS secondary to opiate withdrawal.

Opioids

Opiates are alkaloids derived from opium, which is the juice of the poppy *Papaver somniferum*, and opioids are derived from opiates.[12] Opioids are classified into three categories: prototypic, semisynthetic or purely synthetic. Morphine and codeine are derived from opium and therefore are prototypic opiates. Hydromorphone, heroin and oxycodone are examples of semi-synthetic opioids.[4] Purely synthetic opioids are meperidine, propoxyphene, fentanyl, buprenorphine, methadone and pentazocine. Even though structural differences are present, all opioids are capable of causing euphoria and dependence.[12]

There are opioid receptors (mu, delta and kappa) and neurotransmitters (enkephalin), which comprise the endogenous opioid system. Activation of this system results in sedation and analgesia among other effects. Exogenous opioids bind to the opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain, and produces generalized CNS depression.[25] Activation of the opioid receptors causes acute effects in the following three systems: CNS, gastrointestinal system and respiratory system. CNS effects include decreased pain perception, euphoria, sedation, nausea and vomiting.[4,12] Opioids decrease the motility of the gastrointestinal system resulting in constipation and anorexia.[4,12] Due to decreased responsiveness to carbon dioxide tension in the brainstem, opioids cause respiratory depression.

Paregoric, tincture of opium and oral morphine solution, are currently manufactured in the United States. Paregoric is an anhydrous solution of morphine (0.4 mg morphine equivalent per ml) that is no longer recommended due to the impurity of the solution. Toxic compounds in the solution includes papaverine and noscapine, which are antispasmodics, camphor which is a CNS stimulant, ethanol at 45%, and benzyl alcohol, which causes severe acidosis and gasping syndrome in infants.[6,8] AAP recommends avoiding the use of paregoric secondary to acidosis, respiratory and CNS depression, hypotension, renal insufficiency, seizure and mortality that is primarily associated with the benzoic acid.[6]

Tincture of opium is an opiate commercially available as 10 mg of morphine per ml that requires a 25-fold dilution to a final concentration of 0.4 mg morphine per ml with sterile water. Diluted tincture of opium (DTO) contains the same morphine concentration as paregoric, but contains less alcohol content (0.19% ethanol after dilution) and harmful additives present in

Table 2 Dosage and pharmacokinetics of medications for the management of NAS

	Morphine preparations[a]	*Methadone*	*Buprenorphine*	*Phenobarbital*	*Clonidine*
Dosage	0.03–0.2 mg of morphine per kg per dose every 3–4 h	Initial: 0.05–0.1 mg kg^{-1} per dose every 6 h, increase by 0.05 mg kg^{-1} until NAS score stabilization; maintenance: total daily dose divided every 12 or 24 h	4.4–5.3 mcg kg^{-1} per dose under the tongue every 8 h	16 mg kg^{-1} load, followed by 2–8 mg kg^{-1} per dose daily for level of 20–30 mcg m^{-1}	0.5–1.0 mcg kg^{-1}, followed by 0.5–1.25 mcg kg^{-1} per dose every 4–6 h
Ethanol content	DTO 0.19% (diluted from 10%); morphine contains zero ethanol	8%	30%	Commercial product 15% (depends on manufacturer); extemporaneous preparation, alcohol free	None
Concentration	Require dilution: 0.4 mg ml^{-1}	1 mg ml^{-1}	60 mcg ml^{-1} (extemporaneous compound)	4 mg ml^{-1} (commercial); 10 mg ml^{-1} (extemporaneous compound)	100 mcg ml^{-1} (extemporaneous compound)
Bioavailability	Variable, <40%	36–100%	NA	70–90%	75–95%
Half-life ($t_{½}$, h)	Preterm: 10–20, neonates: 7.6 (range: 4.5–13.3)	Children: 19 ± 14[b] (range: 4–62)	Premature neonates (27–32 weeks GA): 20 ± 8[b]	Neonates: 45–500 h	Neonates: 44–72 h
Protein binding (%)	<20	85–90	96	35–50	20–40
Metabolic pathway (metabolites)	Hepatic glucuronidation (morphine-6-glucuronide (active) and morphine-3-glucuronide (inactive))	Hepatic N-demethylation via CYP3A4 (2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidene (inactive))	Hepatic N-dealkylation primarily via CYP3A4 (norbuprenorphine (active)) and glucuronidation of active metabolite	Hepatic hydroxylation and glucuronidation (inactive)	Hepatic (inactive)

Abbreviations: DTO, diluted tincture of opium; GA, gestational age; NA, information not available; NAS, neonatal abstinence syndrome.
For reference see Leix-comp.[24]
[a]Morphine preparations include paregoric, tincture of opium and oral morphine solution
[b]Mean ± s.d.

paregoric. A concern with DTO is the additional alkaloid contents with opioid-like activity (that is, codeine), and the alkaloid content is not standardized.[4] Oral morphine solution is a feasible option with no additives or alcohol. The commercially available concentration of 2 mg ml^{-1} should be diluted to the same final concentration as DTO (morphine 0.4 mg ml^{-1}) for accuracy of volume measurements and consistency with opioid therapies to reduce medication error.[6,8]

Methadone has been utilized and studied as a potential alternative opioid to oral morphine-containing solutions for NAS therapy for over three decades, but limitations exist. The long half-life of methadone is $\sim$26 h in neonates compared with 8 h with morphine, which may potentially lead to drug accumulation.[6,24] Additional pharmacokinetic information for methadone is summarized in Table 2.

Buprenorphine has recently been investigated as an option for the treatment of NAS. Buprenorphine is a partial mu opioid receptor agonist/antagonist indicated for opioid withdrawal in adults. Buprenorphine binds to the mu opioid receptor with high affinity but low intrinsic activity resulting in mild analgesia, and blocks the binding of other mu agonists such as morphine. Buprenorphine is commercially available as sublingual (SL) tablets administered once daily to control withdrawal in adults, including pregnant women (not approved by the Food and Drug Administration). Buprenorphine is metabolized by the liver enzyme CYP 3A4 to an active metabolite, norbuprenorphine, which requires glucuronidation for elimination (additional information summarized in Supplementary Information).[8] Buprenorphine is pregnancy category C and enters breast milk (similar to methadone).[8]

Review of comparative trials for opioids. AAP guidelines from 1998 recommend DTO as the drug of choice for NAS.[6] Since the publication of those guidelines, more recent trials have investigated and compared agents for the treatment of NAS (Supplementary Information)[25,27,28,30] Langerfeld *et al.*[25] conducted a randomized, double-blind controlled trial in 38 neonates of opioid-addicted mothers to compare DTO with morphine drops. A total of 33 newborns met the criteria for pharmacological intervention (Finnegan score >8), and were randomized to receive either DTO ($n = 16$) or morphine drops ($n = 17$), both 0.4 mg of morphine per ml. The titration of the pharmacological intervention by number of drops was determined by an algorithm based on Finnegan scores: initial dosage was 2 drops per kg every 4 h, and increased by 2 drops per dose until all scores were $\leqslant$8 or mean of 3 scores $\leqslant$7. The mean duration of therapy was not statistically different compared with the morphine group (95% confidence interval, -12.3 to 4.6 days; $P =$ not significant). The difference in mean LOS was not statistically significant between the DTO group and morphine group (32.4 compared with 37.5 days, respectively; $P =$ not significant). No difference was detected between DTO and morphine in maximum dose requirements, cumulative doses, Finnegan scores or weight gain.

One of the early studies reviewing pharmacotherapy of NAS was by Madden *et al.*[26] in 1977, which observed no statistical difference in therapeutic response between methadone, phenobarbital and diazepam for NAS. Three decades later, methadone's place in therapy remains inconclusive. Lainwala *et al.*[27] conducted a retrospective review to evaluate treatment of NAS with oral methadone compared with an oral morphine preparation (OMP), either DTO or neonatal morphine solution based on LOS. Neonates in the methadone group received a loading dosage of 0.1 mg kg^{-1} per dose, followed by an additional 0.025 mg kg^{-1} per dose given every 4 h for continuing Finnegan scores >8 to a maximum dose of 0.5 mg kg^{-1} per day. The maintenance dose was administered every 12 h. The dosage for OMP was 0.05 mg kg^{-1} per dose, and increased by 0.03 mg kg^{-1} per dose every 4 h for NAS scores >8 to a maximum dose of 0.8 mg kg^{-1} per day. The OMP maintenance was administered every 4 h. A total of 17 infants were treated with methadone compared with 29 patients who received an OMP. All patients were $\geqslant$36 weeks gestational age with similar NAS scores. The median LOS was 40 days for infants treated with methadone and 36 days for those treated with OMP ($P =$ not significant). Infants with high birth weight, requiring larger dosages of NAS treatment, and born from mothers receiving high methadone doses (median 75 mg (range, 20 to 120 mg)), were statistically associated with longer LOS. As opiates are highly fat soluble, the author suspects that infants with higher birth weights may have higher stores of opiates resulting in a longer period of withdrawal and hence longer LOS.

Kraft *et al.*[28] performed a randomized, open-label, active-control trial to compare the safety and feasibility of SL buprenorphine for the treatment of NAS to standard therapy, oral neonatal opium solution (NOS) in term neonates. Breastfed neonates were excluded from the study. Efficacy based on LOS and length of treatment was evaluated. Treatment was initiated when the sum of three consecutive modified Finnegan scores was >24. As a commercial oral formulation of buprenophine is not available, one was extemporaneously compounded to a final concentration of 60 mcg ml^{-1} of buprenorphine and 30% ethanol. The NOS had a final alcohol content of 0.19%. The dosage for buprenorphine was 13.2 mcg kg^{-1} per day in three divided doses, which was administered under the tongue, followed by the insertion of a pacifier to enhance SL absorption. The NOS dosage was 0.4 mg of morphine kg^{-1} per day in six divided doses. A total of 25 term neonates were included: 12 received buprenorphine and 13 received NOS. No statistical difference was detected in LOS (27 versus 38 days) and length of treatment (22 versus 32 days), but the trend favored buprenorphine. The pharmacokinetic data exposed an intrasubject variability of measured buprenorphine and norbuprenorphine plasma concentrations potentially due to swallowing of the dose, less than the adequate dose, or altered

metabolism of buprenorphine in neonates. The buprenorphine plasma concentrations ranged from undetectable to 0.6 ng ml^{-1}, which is less than the concentrations necessary to control abstinence in adults ($\geqslant$0.7 ng ml^{-1}).[24,29] Norbuprenorphine was not present in two-thirds of the plasma samples, suggesting impaired absorption or metabolism, or sub-therapeutic dosing of buprenorphine in the newborns of this study.

Kraft *et al.*'s[30] successive randomized, open-label, active-control trial was a separate cohort of 24 patients treated with a revised, dose-optimized treatment plan for buprenorphine. Rather than the 13.2 mcg kg^{-1} per day dosing of buprenorphine in the previous trial, 15.9 mcg kg^{-1} per day divided in three doses administered SL was compared with oral morphine (same dosing scheme as previous Kraft trial[28]). A total of 12 neonates were included in each group. Both length of treatment and LOS were statistically significant shorter in the buprenorphine group compared with the morphine group (23 versus 38 days, $P = 0.01$, and 32 versus 42 days, $P = 0.05$, respectively). No plasma samples of either buprenorphine or norbuprenorphine were obtained in this trial. None of the adverse effects reported were concluded to be caused by the study medication.

Phenobarbital

Phenobarbital is the drug of choice for sedative-hypnotic withdrawal, and used as adjunct therapy for NAS to suppress the hyperactivity associated with opioid withdrawal.[6.] The sedative activity of phenobarbital may be beneficial, but it has little effect on amelioration of the specific opioid-related withdrawal symptoms, such as diarrhea and poor feeding.[6] Phenobarbital depresses CNS activity by binding to the barbiturate site at gamma-aminobutyric acid receptor complex and enhancing gamma-aminobutyric acid activity.[24] The benefits of phenobarbital therapy include CNS depression, modifies hyperactive behavior, controls irritability and insomnia.[9,31] The limitations of phenobarbital use include oversedation, impaired suck reflex, prolonged half-life (45 to 100 h in neonates), drug interactions (that is, induction of theophylline, beta blockers and corticosteroids), rapid development of tolerance to sedative effects and alcohol content of 15%.[24,31]

Review of the literature for phenobarbital. Coyle *et al.*[31] prospectively compared term infants exposed to heroin or methadone *in utero* who received DTO with phenobarbital with DTO monotherapy in a partially randomized, controlled trial (Supplementary Information). The objective was to compare the severity of withdrawal symptoms, LOS and hospital cost of phenobarbital with DTO to DTO alone. Infants with a Finnegan score greater than 7 were randomized to either DTO and placebo or DTO and phenobarbital. The DTO (0.4 mg of morphine per ml) dosage was 0.05 ml kg^{-1} (0.02 mg kg^{-1} per dose) 6 to 8 times per day. Phenobarbital loading dose was 30 mg kg^{-1} divided in three oral 10 mg kg^{-1} doses administered 12 h apart to avoid emesis. The maintenance dose of phenobarbital was 5 mg kg^{-1} per day divided every 12 h with a goal plasma concentration of 20 to 30 mcg ml^{-1}. The infant remained in the hospital for at least 48 h after discontinuation of the DTO for observation. A total of 10 infants were included in each group. No difference was detected in maternal methadone dose, and no correlation was detected between methadone dose and LOS. No infant experienced any seizures during this study. The maximum daily dose in the DTO only group was 16.8 ml compared with 4.7 ml for infants receiving DTO with phenobarbital ($P = 0.009$). DTO with phenobarbital group had a statistically significant reduction in average LOS compared with DTO alone (38 versus 79 days respectively, $P<0.001$). The average hospital cost for DTO alone was $69 200 versus $33 344 for an infant receiving DTO and phenobarbital ($P<0.001$). The average duration of phenobarbital therapy after DTO was discontinued, was 3.5 months.

In a double-blind, randomized controlled trial by Jackson *et al.*[32], the objective was to compare opiate replacement therapy (morphine) to phenobarbital for the management of NAS. Neonates included had a history of maternal drug use and two sequential scores of >4 using the Lipsitz tool. A total of patients were required to detect a 0.5 s.d. difference in the total duration of treatment, assuming alpha = 0.05. A total of 75 infants were randomized to receive oral morphine 0.05 mg kg^{-1} per dose (dilution not specified) or oral phenobarbital 2 mg kg^{-1} per dose (no load) four times daily. The mean gestational age was 40 (range 32 to 42) and 39 (range 33 to 41) weeks in the morphine and phenobarbital group, respectively. In addition to maternal methadone use, the neonates were exposed to other drugs, predominantly benzodiazepines (22 and 44 patients in the morphine and phenobarbital groups, respectively, $P =$ not significant). Neonates in the morphine group required a median of 4 fewer days of active treatment compared with the phenobarbital group (8 versus 12 days, $P = 0.02$). Maternal methadone dose and use of other classes of non-opioid drugs (that is, benzodiazepines) correlated with total days of treatment (assessed with Spearman's rho). Using these variables as covariates while performing an analysis of covariance, the treatment remained a significant independent predictor of the total duration of treatment ($P = 0.03$), and the maternal methadone dose also independently influenced the duration of treatment ($P = 0.04$). No difference was detected in the requirement for additional drugs for NAS symptoms between the groups (47% of phenobarbital group compared with 35% of the morphine group, $P = 0.11$).

Clonidine

Clonidine is a centrally acting alpha 2-adrenergic receptor agonist used to suppress opiate withdrawal symptoms in older children and adults. Activation of alpha-2-adrenergic receptors results in activating an inhibitory neuron, resulting in reduced sympathetic outflow, producing a decrease in vasomotor tone and heart rate.[24]

Abrupt discontinuation results in a rapid increase in blood pressure and symptoms of sympathetic overactivity (such as increased heart rate, tremors, agitation, sweating, palpitations), and can be prevented by a gradual taper over more than 1 week.

Pharmacokinetics of clonidine in newborn infants is limited at this time (summarized in Table 2). Potts *et al.*[33] combined four published studies with an open-label study to examine the pharmacokinetics of intravenous clonidine 1 to 2 mcg kg^{-1} bolus in children after cardiac surgery. A total of 380 observations from 72 children (mean age of 4 ± 3.6 years, range 1 week to14 years) were included in the analysis. Clearance at birth was 0.116 l kg^{-1} per h and reached 82% adult rate by 1 year of age. In neonates and infants, clearance of clonidine is reduced, which is attributable to immaturity of elimination pathways.

Review of literature for clonidine. A prospective, randomized, double-blind trial to compare infants exposed to opiates *in utero* and NAS who received oral DTO and oral clonidine or DTO and placebo was performed by Agthe *et al.*[34] (Supplementary Information). Infants with gestational age of ⩾35 weeks were included if prenatally exposed to opioids and developed moderate to severe NAS scores defined as two consecutive modified Finnegan scores of ⩾9. The score modification was referenced to a text, but not explained. The commercially available formulation of clonidine for epidural administration (100 mcg ml^{-1}) was diluted to 5 mcg ml^{-1} for oral administration. The fixed dosage of oral clonidine was 1 mcg kg^{-1} every 4 h, and the placebo group received an equal volume of isotonic saline at the same frequency. DTO, 0.4 mg ml^{-1} morphine equivalent, was initiated at 0.2 ml (0.08 mg morphine equivalent) orally every 4 h, and escalated based on a dosing algorithm to a max of 0.9 ml (0.36 mg morphine equivalent) every 3 h, or until withdrawal symptoms were controlled (modified pulmonary score <9). Once symptom control was achieved for at least 48 h, DTO was de-escalated at increments of 0.05 ml per dose every 24 h. Treatment failure was defined as three consecutive modified Finnegan scores of ⩾9 on the max dose of DTO, or withdrawal from the study for management at the discretion of the clinical care team. Both groups consisted of 40 infants and were similar with regard to maternal and infant demographics excluding average birth weight, which was lower in the clonidine/DTO group (2864 g ± 365 versus 3047 g ± 395 in the placebo/DTO group, $P = 0.03$). Three infants in both groups were exposed to benzodiazepines *in utero* based on positive maternal urine screens or maternal history. The median length of therapy was 27% shorter for the clonidine/DTO group (11 days (range 4 to 28) versus 15 days (range 4 to 100) in the placebo/DTO group, $P = 0.02$). Total infants prenatally exposed to methadone had a median length of treatment three times longer than infants exposed to heroin alone (15 days for methadone versus 5 days for heroin, $P = 0.05$). Analysis of methadone-only exposed infants revealed clonidine was associated with a shorter length of stay (12 days versus 17 days for placebo/DTO, $P = 0.01$). The mean total dose of DTO required for treatment was less in the clonidine group (7.7 mg ± 8.0 versus 19.2 mg ± 3.3 in the placebo/DTO group, $P = 0.03$). Five infants with treatment failure and three infants experienced seizures in the placebo/DTO group compared with none in the clonidine/DTO group. Rebound of NAS occurred in seven infants in the clonidine/DTO group necessitating restarting DTO within 12 to 48 h after stopping whereas no infants in the placebo/DTO group experienced rebound. Blood pressures and heart rates were statistically lower in the clonidine/DTO group at 24 and 48 h after protocol initiation, but remained within normal range for newborns, and no interventions were necessary. One infant developed supraventricular tachycardia in the clonidine/DTO group at 5 days of age, 3 days after discontinuing clonidine, requiring one dose of adenosine, without reoccurrence or additional treatment.

Benzodiazepines

Benzodiazepines have also been used to ameliorate symptoms of opioid withdrawal. Neurologic excitability is suppressed by depressing all levels of the CNS by binding to the benzodiazepine site on the gamma-aminobutyric acid receptor and modulating gamma-aminobutyric acid, which is an inhibitory neurotransmitter in the brain.[24] Most benzodiazepines require liver metabolism via the CYP enzyme system and form an active metabolite, which then requires further elimination before being excreted. This complicated metabolic pathway may be problematic in a neonate with limited liver metabolic ability. The most common benzodiazepine studied for NAS is diazepam, which is commercially available as an injectable, oral suspension and rectal gel. The injection formulation of diazepam is not recommended in neonates due to the presence of preservatives and risk of gasping syndrome. Oral diazepam suspension is available in two concentrations, one as a concentrate (5 mg ml^{-1}), which may lead to a fivefold overdose if the concentrate is selected accidentally. The rectal diazepam has not been studied in the neonatal population due to preservatives. The AAP statement recommended diazepam with reservations due to cited evidence of poor suck, sedation and limited metabolic capacity of neonates.[6]

Review of literature for benzodiazepines. The Cochrane Collaboration review[35] analyzed the use of sedatives in neonatal opioid withdrawal to assess the effectiveness and safety of using a sedative versus control (placebo, usual treatment or non-pharmacological treatment) for NAS due to withdrawal from opiates, and to determine which type of sedative is most effective and safe for NAS due to withdrawal from opiates. Six studies were included and two trials (Finnegan 1984 and Madden 1977) analyzed the primary outcome of treatment failure with phenobarbital compared with diazepam as adjunct therapy. The meta-analysis of these two studies included 139 infants and found

a significant reduction in treatment failure using phenobarbital compared with diazepam (typical RR 0.39, 95% confidence interval 0.24, 0.62) favoring the phenobarbital group. Phenobarbital demonstrated beneficial effects in infants exposed to opioids alone and to polysubstances.

Summary

Since the publication of the AAP 1998 statement on neonatal drug withdrawal, seven significant studies have been published that contribute to the pharmacological management of NAS. Three articles compared DTO treatment, which has been recommended by AAP, with other opioid therapies. The studies to date have not demonstrated that other opioid therapies are more efficacious than DTO. However, since the potential for the studies to be underpowered (that is, no power analysis stated), it is inconclusive to state that the opioid therapies studied are not superior to DTO. It is important to consider other characteristics of DTO compared with other opioid therapies, especially in terms of safety. For example, DTO contains alcohol and additional alkaloids and requires 25-fold dilution. The potential safety advantages of using alternative opioid therapy over DTO are addressed below.

Opioid therapy for NAS management

Advantage of oral morphine solution is the lack of alcohol and additional alkaloids. A similar disadvantage for both oral morphine solution and DTO is the need for dilutions to be made, which could lead to potential preparation errors. The administration of undiluted tincture of opium would result in a 25-fold overdose compared with a fivefold overdose with undiluted oral morphine solution ($2\,mg\,ml^{-1}$). As with most medications in the nursery and neonatal intensive care unit, all formulations should be prepared in the pharmacy to minimize dilution errors as a result of double check systems per pharmacy policy and procedures recommended by Joint Commission.[36] In addition, oral morphine solution is commercially available as a highly concentrated formulation, $20\,mg\,ml^{-1}$, which would result in overdose if the dilution procedure is unaltered to compensate for the difference. Both DTO and oral morphine solution require dosing frequency every 4 to 6 h, which is time and resource consuming.

In the retrospective comparison of methadone to OMP, no difference was detected in LOS or NAS scores. As some mothers are exposed to methadone during pregnancy, methadone appears to be the ideal drug to treat the NAS. Another advantage of methadone is the less frequent administration (every 12 or 24 h) compared with OMP based on its long half-life. Although, the extensive half-life is a potential disadvantage, the pharmacokinetic parameters of methadone in the neonatal population have not yet been studied and the potential for accumulation due to the long half-life is a concern. Due to the lack of experience and evidence of methadone use in the neonatal population, further investigation is necessary.

The purpose of both open-label comparisons of SL buprenorphine to NOS was based on safety and feasibility. Although the first trial concluded SL buprenorphine is feasible and 'apparently' safe, the intrasubject variability of buprenorphine metabolism and alcohol content of the extemporaneous solution are concerning. The lack of difference detected in the first trial potentially due to under-dosing was alleviated by the higher dose in the second trial where a statistically and clinically significant difference was detected for both LOS and length of treatment. Future investigations of buprenorphine for the treatment of NAS designed preferably as a double-blind, double-dummy trial would provide conclusive evidence of its efficacy. The concern for buprenorphine in premature neonates may be the inability to clear the active metabolite due to saturation or immaturity of the glucuronide pathway.

Non-opioid therapy for NAS management

In the study by Coyle *et al.*, DTO with phenobarbital for the treatment of NAS compared with DTO alone lessened the severity of withdrawal, decreased the LOS, and reduced hospital cost. The reduction in hospital stay was both statistically and clinically significant with an average difference of 41 days. Long-term neurodevelopmental outcomes have not been reported, and require further studies, in particularly with infants treated with prolonged courses of phenobarbital.

Morphine was determined superior to phenobarbital in reduction of treatment duration for NAS, which was not dependent of other variables. When the primary outcome was adjusted for exposure to multiple drugs, the significance of the shorter duration of therapy was not affected by maternal drug use other than methadone. As the study protocol did not require a phenobarbital load or plasma level monitoring, the time to an 'effective' level of phenobarbital could have been delayed. Based on this study, phenobarbital monotherapy for the management of neonates withdrawing primarily from methadone is not as effective as morphine.

Agthe *et al.* determined that clonidine combined with DTO stabilized infants with moderate to severe NAS more rapidly than DTO alone, lowered DTO requirements, and was not associated with clinically significant changes in heart rate or blood pressure. This study provided evidence that clonidine as an adjunct therapy is safe and effective in term neonates experiencing NAS. As clonidine is not commercially available as an oral suspension, a dilution should be made from the epidural injection formulation as opposed to an extemporaneous compound due to accuracy and homogeneity.[37] Extemporaneous compounding requires meticulous measurement and trituration to produce a precise and non-toxic solution for oral administration.

AAP guideline update

After reviewing the current evidence, paregoric is not recommended. OMP, either oral morphine solution or DTO, remains the standard of care based on experience and efficacy data. Some practitioners may elect to favor OMP over DTO because the latter contains alcohol and non-standardized content of additional alkaloids. Regardless of which OMP therapies are used, practitioners must focus on safety of these therapies. It is critical that standard policies and procedures be created, implemented and enforced to ensure proper commercially available preparations are used and dilutions are prepared properly.

Further investigations with methadone therapy for management of NAS are warranted as this agent may provide some advantages for older infants, including extensive half-life, which may result in more steady serum concentrations and less frequent dosing. However, for neonates and younger infants, the prolonged half-life remains a concern and thus, methadone should be used with caution until additional data are available to address the concerns of methadone accumulation and QT prolongation. SL buprenorphine may also be an alternative option in the future for the management of NAS, but limited experience and data exists to date to support its use as a standard of practice. As for adjunct therapy, future studies comparing phenobarbital to clonidine would be beneficial to determine which adjunctive agent is more safe and effective for the management of NAS.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

We acknowledge Sarah A Spinler for editorial review.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp).