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Pharmacologic Management of the Opioid Neonatal Abstinence Syndrome

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DEFINITION OF NEONATAL ABSTINENCE SYNDROME

Neonatal withdrawal symptoms have been noted following prenatal exposure to several drugs. Examples include opioids,[1,2] benzodiazepines,[3,4] mood-stabilizing medications,[5] selective serotonin reuptake inhibitors,[6] and nicotine.[7] For all drug classes except opioids, these symptoms are usually self-limited and do not require pharmacologic treatment. Infants born to mothers with opioid abuse or receiving methadone maintenance often develop withdrawal symptoms, following the postpartum cessation of in utero exposure to opioids. This complex is known as the neonatal abstinence syndrome (NAS). The full mechanistic basis for the clinical presentation is unclear. Tolerance induced by long-term exposure to opioids is primarily mediated by receptor downregulation coupled with upregulation in the cyclic adenosine monophosphate (cAMP) pathway.[8] Other putative mechanisms include neuroimmune activation, production of anti-opioid peptides, or activation of the spinal dynorphin system. Symptoms of withdrawal are hypothesized to be due to increased adenylyl cyclase activity and an abrupt increase in norepinephrine following removal of the mu opioid ligand. NAS is characterized by signs of central nervous system (CNS) hyperirritability, gastrointestinal dysfunction, respiratory distress, and vague autonomic

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symptoms. Common symptoms in order of frequency includes tremor, high-pitched cry, sneezing, increased muscle tone, regurgitation and vomiting, poor sleep, loose stools, sweating, excoriation, mottling, nasal stuffiness, low-grade fever, and tachypnea. Impaired weight gain and seizures are seen with untreated NAS. All infants with prolonged in utero opioid exposure will develop signs and symptoms of withdrawal of varying severity. However, the disorder encompasses a diverse spectrum, and those with milder symptoms respond well to supportive treatments. NAS symptoms severe enough to require pharmacologic treatment occur in 55% to 94% of infants born to opioid-dependent mothers.[9]

Current use of illicit drugs occurs in 4.4% of pregnant women.[10] Heroin use during pregnancy is associated with fetal death and infant morbidity, including intrauterine growth retardation, placental insufficiency, postpartum hemorrhage, preeclampsia, and premature rupture of membranes.[11,12] In an attempt to counteract these poor outcomes, methadone maintenance in opioid-dependent pregnant women has been used for the past 35 years, and is associated with improved birth weight and improvements in multiple domains.[13–16] A more recent development is the expansion in the use and abuse of prescription opioids. Whereas the use of heroin decreased by 19% between 1998 and 2008, the abuse of prescription opioids during the same period increased by 41%.[17] In 2010, 5.1 million individuals reported nonmedical abuse of prescription pain medications within the previous month, with 71% of abused pain relievers being obtained from friends or family, and either bought or taken without permission.[10] The societal burden of NAS is difficult to assess, as is evident from the wide variations and implausible rates reported to regional authorities for hospitals in the defined geographic area with similar patient populations.[18] Such variation is due to limited self-reporting of drug abuse, and underreporting of NAS using the International Classification of Diseases.[19] In 1996, a survey by the National Institute of Drug Addiction estimated that 7000 cases occur each year, although the report conceded this is potentially an underestimation.[20] More recently, the rate of NAS in the United States has increased from 1.2 to 3.9 per 1000 live births between 2000 and 2009.[21] A similar incidence rate has been estimated in Australia.[22]

PREDICTORS OF NAS SEVERITY

The dose of maternal methadone dose as a covariate of the need for NAS treatment length has been examined extensively. Although a meta-analysis that evaluated studies by methodological quality did not identify a statistically significant difference in outcomes between high-dose and low-dose methadone, there is a suggestion of modest maternal dose dependency on outcomes.[23] However, if such an effect does exist, it is small and not relevant in terms of choosing a maternal dose or differential treatment approaches in the treatment of infants. Lower maternal methadone doses have been associated with higher rates of illicit substitution, and a consensus view is that maternal doses of methadone should not be reduced solely to reduce NAS severity. High-quality randomized, controlled trial evidence from the MOTHER study has demonstrated that compared with methadone use, maternal buprenorphine is associated with a decreased need for morphine treatment in NAS and neonatal length of stay.[24] The maternal study population in this study has been convincingly demonstrated to be similar to the patient population at large, strongly supporting the generalizability of results.[25]

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Whereas Jansson and colleagues[26] described worse NAS symptoms and pharmacotherapy in males, severity, need for therapy, or length of therapy were not influenced by gender in a cohort study by Holbrook and Kaltenbach.[27] Similarly, there was no sex dependency in the large randomized MOTHER study, which compared use of methadone and buprenorphine in pregnant women.[28] Intrapartum variability or decelerations in fetal heart rate do not predict the need for therapy in NAS.[29] However, alternations in autonomic regulation, as measured by analysis of maternal[26] or infant[30] vagal tone, have been noted to be predictors of worse NAS symptomatology. It is postulated that infants who adapt to maternal methadone–induced autonomic changes are maladapted to more severe NAS following birth. Methadone exposure during pregnancy is associated with an approximately 2.5-fold increase in the rate of preterm birth.[31,32] Preterm infants have a well-described natural history of NAS and a need for treatment that differs from term infants. The current NAS scoring instruments have not been examined in this population. Need for therapy[33] and length of stay is shorter in the preterm population.[34,35] The preterm population thus appears to be categorically different in terms of in utero opioid exposure.

Polydrug abuse during pregnancy is associated with impaired fetal markers (heart rate and variability) and greater need for postpartum pharmacologic therapy.[36] A retrospective study by Seligman and colleagues[34] demonstrated that the length of NAS treatment for all opioid only exposed infants between 2000 and 2006 was 31 days, compared with 38 days for polydrug-exposed term infants. Strikingly, a multivariate analysis of infants revealed a significant prolongation of treatment duration for NAS (31 vs 47 days, $P<.01$) of benzodiazepine versus non–benzodiazepine-exposed infants. Benzodiazepine withdrawal symptoms in adults include anxiety, tremors, anorexia, nausea, postural hypotension, and in severe cases seizures, delirium, and hyperpyrexia. The onset of symptoms is 12 to 24 hours for short-acting agents with a peak at 72 hours, whereas longer-acting agents such as diazepam are associated with an onset of 24 to 72 hours and a peak between 5 and 8 days following the last dose.[37] Benzodiazepines cross the placenta,[38,39] but maternal confounders have made it difficult to estimate adverse effects specific to in utero exposure of benzodiazepines.[40] Whereas teratogenicity is unlikely in benzodiazepine-exposed infants,[41–43] decreased birth weight and neonatal withdrawal have been noted,[3] the latter manifested by hypotonia and hypoventilation or tremulousness.[4] The half-life of diazepam in neonates is 31 days.[44] Thus, in contrast to that of adults, initiation of neonatal withdrawal for many benzodiazepines can be delayed with an onset at a week and effects noticeable for weeks.[45,46] There is no specific treatment for neonatal benzodiazepine withdrawal. Tobacco exposure is associated with worse NAS symptomatology.[47,48] Analysis of meconium for tobacco, methadone or its metabolites, cocaine, or opioids other than methadone, however, are not predictive of NAS outcomes.[49]

LONG-TERM AND SHORT-TERM SEQUELAE

Environmental and social factors are more important influences upon childhood development than brief periods of prepartum and peripartum exposure to drugs of abuse.[50,51] Infants exposed in utero to opioids show low birth weights, increased preterm birth, and reduced fetal growth parameters, but investigations have been hampered by the logistical difficulty of controlling for tobacco and other social factors associated with illicit

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drug use.[52] Studies linking in utero opioids to impaired neurodevelopment[53] have been criticized for not accounting for confounding of the child's social and environmental milieu.[54] The database for opioid exposure is less robust than that for cocaine.[55] It is possible that there are subtle neurodevelopmental effects arising from in utero opioid exposure apart from effects caused by environmental and home settings.[56] Even if this is real, however, these associations do not provide guidance about practical therapeutic decisions. For newborns, the benefits of maternal opioid therapy during pregnancy using methadone in a structured program clearly outweigh no therapy. There is evidence that untreated or undertreated women may seek street sources of opioids to treat withdrawal symptoms, which clearly has negative neonatal outcomes. Of importance, there is no evidence of long-term adverse outcomes in children treated with pharmacologic agents in comparison with infants who do not require treatment for NAS, or for treatment with different classes of agents.[57,58] Although the database of information is smaller, in human and animal studies neonatal outcomes with in utero buprenorphine exposure are generally favorable compared with methadone.[59]

CURRENT THERAPIES

Variability of Current Practice Patterns

Few studies have examined NAS prevalence and treatment patterns. Nandakumar and Sankar[60] published a survey of 17 neonatal units in the Northwest Region of the United Kingdom, revealing not only conflicting practices in scoring, identification, and management but also a deficit of reliable data to assist practitioners in determining the best regimen to treat NAS. In a survey conducted by Sarkar and Donn[61] in United States neonatal intensive care units (NICU), the focus was primarily on determining the percentage of respondents using an abstinence scoring system, those with access to formal written policies or educational programs for NAS management, and practitioners using customary pharmacologic agents for withdrawal. The 13-question survey of 102 accredited fellowship programs (which had 75 respondents) did not include questions on NAS incidence or length of hospital stay. O'Grady and colleagues[62] conducted a 15-question questionnaire of 235 neonatal units that sought to survey current NAS practices in the United Kingdom and Ireland. The survey assessed first-line and second-line agents, attitudes to breastfeeding by women on methadone, and the safety of infants discharged on medication. Crocetti and colleagues[63] assessed the number of opiate-exposed neonates identified as having NAS, as well as policies and procedures for treatment in 27 hospitals throughout Maryland. In aggregate, these surveys demonstrate significant heterogeneity in diagnosis and treatment patterns. There are clear information gaps for identification, treatment, and length of hospital stay. Moreover, there is a lack of pharmacoeconomic analyses on costs and cost-effectiveness of treatment for NAS.

Framework for Treatment

The therapeutic framework of treatment begins with the identification of infants at risk for NAS. NAS is graded using a standard checklist that identifies and stratifies severity of disease based on signs and symptoms in multiple domains. Of several scoring systems used to gauge symptom severity and titrate drug dose,[64–66] the Finnegan score (or modifications

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of it)[67] is the most commonly used.[61,62] A modification of the Finnegan score used in the multicenter MOTHER study of buprenorphine use for pregnant women[68,69] is the standard instrument used in other randomized NAS research trials.[70,71] The Finnegan instrument was created to assess severity of disease in those with known opioid exposure. On day 2 of life a score of 7 corresponds with the 95th percentile for nonexposed infants, meaning any score of 8 or greater is highly suggestive of in utero opioid exposure even in those denying opioid use during pregnancy.[72] Nonpharmacologic therapies should be used for all infants with in utero opioid exposure. These treatments include swaddling,[73] the use of small calorically dense formulas, rooming in, breastfeeding, and minimization of excessive external stimulation. Infants with mild symptoms should be observed in the hospital for at least 4 days. For infants with severe symptomatology manifested by seizures, poor weight gain, and elevated values in a NAS-specific scoring instrument, pharmacologic therapy is indicated. Ideal treatment uses a protocol-driven use of drug titration to control symptoms. Both symptom-driven (ie, weight-independent fixed dose titration based on severity of NAS scores) and weight-based dosing regimens have been used, with neither being identified as the standard approach.[74] Regardless of the manner of dose titration, infants who do not have control of symptoms despite high doses of the initial therapy are treated with a secondary drug. After stabilization, symptom scores are used to gradually wean the controlling drug or drugs; this occurs typically in an inpatient setting, as it allows careful observation and dose titration of infants. Some institutions stabilize an infant in an inpatient setting, with terminal weaning done as an outpatient. The use of outpatient treatment in highly selected patients is associated with shorter inpatient stays, but extended total duration of therapy.[75]

The rationale to use pharmacologic therapy is to ensure proper feeding and development, and foster the maternal infant bond. The ideal specific drug used would safely achieve these therapeutic goals, while at the same time minimizing the total duration of therapy and length of hospitalization. The most commonly used initial therapy is an opioid, while phenobarbital or clonidine are the primary adjunctive agents. Although used more commonly, phenobarbital has not been demonstrated to have improved safety or efficacy in comparison with clonidine as an adjunctive therapy. A comparison of these agents as adjuncts is currently being investigated (NCT01175668). The role of initial dual therapy of phenobarbital with an opioid has been described, but has not been compared in a large number of patients.[76] The value of this approach has not been established, but anecdotally may provide benefit in infants with polysubstance use.

Opioids

Cochrane reviews,[77,78] the American Academy of Pediatrics,[9,79] and expert reviews[80,81] identify opioid replacement as the ideal treatment for the withdrawal symptoms associated with in utero exposure to opiates. Opioid replacement as a first-line agent (1) improves weight gain but lengthens hospitalizations compared with supportive care, (2) reduces seizure rates and possibly duration of therapy compared with phenobarbital, and (3) reduces treatment failure compared with diazepam.[77] Although many of the studies cited in the Cochrane review had methodological flaws, the standard of care practice that has developed since the 1970s has generally supported this approach. There is limited evidence from which definitive recommendations can be made regarding differential safety and efficacy of

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specific opioids. Moreover, high-quality data on the optimal dose regimens or comparative effectiveness on use of adjunctive agents are lacking. Current practice patterns for these have been developed empirically, and remain an area that would benefit from investigations of higher quality.

Morphine—Morphine is the most commonly used opioid for replacement therapy. Paregoric, a previously commonly used morphine source, was never subject to any formal evaluation by the Food and Drug Administration, and is no longer available. Diluted, deodorized tincture of opium (DTO) has a morphine concentration of 0.4 mg/mL and an ethanol concentration of 0.19%. This agent has been largely replaced by an ethanol-free morphine solution of 0.4 mg/mL concentration. Preservative-free morphine hydrochloride solution for neonatal administration is stable at 4°C for at least 6 months.[82] Because of the relatively short half-life of morphine, best outcomes have been demonstrated when morphine doses are given no longer than 4 hours apart.[83] Accordingly, infants who are sleeping at the nominal dose time should be awakened for drug administration.

Morphine in humans is metabolized primarily to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) via uridine 5′-diphosphate glucuronosyl transferase (UGT)-2B7. The ontogeny of UGT development is dynamic in the immediate postpartum period, demonstrated by reduced M6G/morphine ratio in neonates younger than 7 days as well as an associated reduced postsurgical morphine requirement in comparison with older neonates.[84] Nonlinear mixed-effects models have been used to estimate active metabolite formation as well as elimination.[85] Clearance generally correlates with glomerular filtration, with minimal fecal elimination or metabolism to normorphine. The large interpatient and intrapatient variability of intravenous morphine pharmacokinetics and pharmacodynamics in neonates is due in part to a dynamic acquisition of metabolic enzymes, renal function, and changes in fat and extracellular fluid balance.[84–86] Of note, the pharmacokinetics profile of orally administered morphine in neonates is currently unknown. An area of therapeutic need would be the characterization of the concentration-response relationship. Such a relationship, created with modeling and simulation, would be of use in designing an optimized dose regimen.

The initial dose of morphine was 0.12 to 0.6 mg/kg/d in a survey of 17 pediatric units in the United Kingdom.[60] These investigators had the opinion that a higher initial dose may be associated with better control of symptoms, but acknowledged that evidence to support this intuition was lacking. A dose of 0.24 mg/kg/d was recommended by the 1998 report of the American Academy of Pediatrics (AAP),[9] although this protocol outlined drop-unit doses that would make fine titration difficult. Neither the 2012 AAP Committee on Drugs NAS report[79] nor the Cochrane review of the topic identified a favored specific dose.[77] There is no generally accepted maximum dose of morphine used for NAS. A survey of neonatal units in the United Kingdom revealed that typical maximum doses were up to 1.3 mg/kg/d, and that one-third determined dose according to symptom control rather than a maximum predefined level.[62] Specific protocols for dose titration are based either on a weight-based increase in dose based on scores above a specific NAS score, or a weight-independent dose based on a graded severity of NAS score. Table 1 outlines these 2 commonly used approaches.

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Methadone—Methadone is a long-acting opioid commonly used for abstinence treatment. The longer half-life of methadone provides less of a flux between peak and trough levels, while also providing ease of administration at less frequent intervals. Oral bioavailability in adults is high, but variable.[87] The pharmacokinetics of methadone in the pediatric and neonatal populations has been simulated using physiologic-based pharmacokinetic modeling that suggests significant interpatient and developmental variability, but decreased systemic exposure with age.[88] This model has not been validated by rich patient-level data. There is scant published clinical trial evidence to guide its use in the neonatal population. In a single small study, outcomes with methadone were similar to those for phenobarbital or diazepam.[89] Comparisons with oral morphine are limited to a single retrospective review of 46 patients, in which there was no significant difference in length of stay between treatments.[90] A standard dose has not been established, but the protocol used by Lainwala and colleagues[90] is provided in Box 1. Methadone use remains relatively uncommon, ranging from fewer than 2% of units in the United Kingdom[62] to as many as 20% in the United States.[61] The long dosing interval has led some sites to use methadone as extended outpatient dosing. Compared with full inpatient treatment, infants discharged home on methadone have shorter hospitalizations but longer duration of therapy, though at least in one study having a similar total of methadone administered.[91] Because of the likely variability of pharmacokinetics, frequent outpatient follow-up is required to allow careful monitoring and dose titration based on symptoms.

Buprenorphine—Buprenorphine is a long-acting partial μ opioid receptor agonist that in adults is more effective for withdrawal symptoms than clonidine, and possibly methadone.[92] Use of buprenorphine in this population has gained favor, in part because of its properties of improved safety, particularly with regard to respiratory depression. Buprenorphine has compared favorably with methadone for use in pregnant women.[24] In NAS, the use of buprenorphine has been explored in 2 open-label, placebo-controlled trials.[70,93] A total of 50 infants were randomized in a 1:1 ratio to oral morphine every 4 hours or sublingual buprenorphine administered every 8 hours. The optimized initial dose was 15.9 μg/kg/d, with a maximum of 60 μg/kg/d. Doses were increased 25% until control of symptoms was obtained, and decreased by 10% until cessation of therapy when the dose was 10% of the initial dose. Doses were not adjusted for actual weight, and were instead based on the weight at initiation of therapy. Although the initial goals of this phase 1 investigation was the feasibility and safety of buprenorphine to treat NAS, an efficacy advantage over morphine was demonstrated. When the results from both cohorts were combined, treatment with buprenorphine revealed a mean length of treatment of 23 days, compared with a mean length of 34 days using standard of care oral morphine (Fig. 1). Following log transformation to satisfy normality assumptions, the length of treatment was on average 36% shorter (95% confidence interval [CI]: 17%–51%; $P = .001$) in the buprenorphine arm than in those administered oral morphine, and the length of stay was on average 29% shorter (95% CI: 10%–44%; $P = .006$). Caveats to these findings are an open-label study design and that, while consistent with retrospective studies at the same institution,[34] the duration of treatment and length of stay in both arms was somewhat longer than has been reported at other institutions.

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Adjunctive therapy with phenobarbital was required in 6 of 25 infants in the buprenorphine group compared with 2 of 25 randomized to morphine. It is unclear whether this finding is due to a ceiling effect of buprenorphine as a partial agonist in a subset of patients with more severe disease, or if the predefined maximum dose of buprenorphine was set too low. Pharmacokinetic sampling in this trial unexpectedly revealed amelioration of withdrawal symptoms at plasma concentrations of buprenorphine below the 0.7 ng/mL threshold, estimated for relief of symptoms in adults.[94] This finding could be due to a different volume of distribution of the drug in the neonate, or a pharmacodynamic profile of withdrawal that fundamentally differs from that in adults.

Drugs for sublingual administration are formulated using buprenorphine for injection (Buprenex or equivalent generic) at a concentration of 0.075 mg/mL in a 30% ethanol solution. Buprenorphine is stable at room temperature for at least 30 days in glass vials and for at least 7 days in plastic syringes. Buprenorphine is absorbed by the sublingual route within 2 minutes in adults.[95] There was no evidence of aspiration in neonates after more than 1600 individual doses were administered in the phase 1 investigation. There were 2 serious adverse events. One infant developed cytomegalovirus in the immediate postpartum period and another had idiopathic seizure. Both events were judged to be unrelated to study treatment by the investigator, institutional review board, and data safety monitoring board.

Adjuncts

Phenobarbital—The use of phenobarbital (identified as phenobarbitone in the British nomenclature) is often used as a rescue therapy when maximum dose of opioid replacement therapy is reached without adequate resolution of symptoms, although it has also been used as an initial adjunct in combination therapy with an opioid[76] or as initial monotherapy.[96] Phenobarbital use has been examined in a Cochrane review, which concluded that opioids had a comparative advantage concerning incidence of seizures, duration of treatment, and nursery admissions, but not necessarily in the rate of treatment failure.[78] The half-life of phenobarbital in neonates decreases from 115 hours after 1 week to 67 hours after 4 weeks.[97] This prolonged half-life explains the improved outcomes through the use of a loading dose compared with dosing without a load.[98] The typical loading dose is 20 mg/kg, followed by 5 mg/kg. Phenobarbital anecdotally seems to have particular utility in those infants with polydrug exposure in utero. Phenobarbital causes increased metabolism of many drugs metabolized by the cytochrome P450 system for patients of all agents, a finding confirmed in NAS infants cotreated with phenobarbital and buprenorphine.[99] Questions raised about the potential for deleterious neurodevelopmental effects will be addressed by the ongoing PROPHENO trial (NCT01089504), scheduled to be completed in late 2014.

Clonidine—Clonidine is a centrally acting a-agonist that reduces global sympathetic tone and has been used in adult withdrawal syndromes. Clonidine is less efficacious in adults in comparison with opioids in the management of withdrawal symptoms.[92] Several small retrospective examinations had suggested clonidine as a useful adjunct therapy in NAS (Table 2). Agthe and colleagues[71] described a high-quality, randomized controlled trial of clonidine, 1 μg/kg every 4 hours compared with placebo as a parallel adjunct to oral morphine therapy (in the form of DTO). Clonidine solution for epidural injection (100

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μg/mL) was diluted to 5 μg/mL and administered orally. The dual morphine/clonidine arm had a statistically significant shorter length of stay (11 days [95% CI: 8–15] vs 15 days [95% CI: 13–17]). In addition, the total dose of morphine was 7.7 mg with dual therapy compared with 19.2 mg with monotherapy ($P = .03$). Clonidine was generally well tolerated, with no serious hypotension or bradycardia. An episode of supraventricular tachycardia occurred in one patient 3 days after cessation of clonidine. Based on the mechanism of action of clonidine and potential for post-cessation sympathetic surge, it is plausible that this was causally related to cessation of the study drug. Three infants in the clonidine-treated group died of autopsy-verified myocarditis, sudden infant death syndrome, and homicide (methadone overdose). Each occurred at least 22 days after the cessation of the study drug and were assessed to be unrelated to the study drug.[71] Xie and colleagues[100] performed nonlinear mixed-effects modeling of clonidine pharmacokinetics and noted a rapid increase in clearance in the first month of life. A dose adjustment of 1.5 μg/kg every 4 hours starting the second week of life, based on modeling and simulation, was proposed. This dose adjustment has not been tested in a clinical trial setting.

Breastfeeding

The number of women in methadone programs who choose to breastfeed their newborns has been traditionally low, with more than half of those who start stopping after 6 days.[101] However, it is expected that this number will increase both locally and nationwide as a result of specific campaigns. In 2011, the United States Surgeon General released *A Call to Action to Support Breastfeeding*, which calls for expansion of breastfeeding for American infants. This standpoint is supported by the Department of Health and Human Services in Healthy People 2020, as well as major medical societies.[102] Methadone is passed on to neonates through breast milk, although the absolute amount is small (<0.2 mg/d) and does not appreciably change neonatal serum methadone concentrations.[103] However, a pharmacodynamic effect is suggested, as breastfed infants have decreased severity of NAS or need for treatment with pharmacologic agents.[104,105] Based on the small doses of drug transferred to the infant, it is not clear if this effect reflects the calming effect of the act of breastfeeding or the effect of drug.[106] For mothers maintained on usual abstinence doses, the amount of buprenorphine transferred through breast milk is 0.1 to 1.2 μg/kg/d, which represents approximately 0.02% of the maternal dose.[107–110] The bioavailability of buprenorphine transferred in breast milk is not characterized, but appears low based on measurement in neonatal blood and urine,[110] and by minimal effects in suppression of NAS symptomatology.[111–113] There are no reported safety concerns associated with breastfeeding, therefore despite the product insert that advises against breastfeeding, current national guidelines advocate breastfeeding for mothers prescribed buprenorphine.[114]

Pharmacogenetics

The interpatient variability seen in severity of withdrawal symptoms or response to therapies cannot be reduced to a monogenic etiology in either newborns or adults. However, several single-nucleotide polymorphisms (SNPs) in candidate genes have been identified that appear to determine response to opioids for pain or replacement abstinence therapy in adults, for predilection to substance abuse disorder,[115] and social hedonic capacity.[116] The μ opioid receptor (OPRM1) gene A118G SNP has been associated with differential morphine

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sensitivity, with decreased pain and morphine requirements with the AA genotype.[117] An exploratory examination by Wachman and colleagues[101] in 28 term infants with in utero opioid exposure revealed a significantly lower need for pharmacotherapy, lower doses, and shorter lengths of stay in patients with the AA variant compared with those with the GG variant. Catechol-*O*-methyltransferase (COMT), an enzyme that degrades catecholamines, was also examined. In adults, the COMT SNP (Val158Met) is associated with a lower required morphine dosage in patients with cancer,[118] although the association with addiction is much less clear.[119] Wachman and colleagues[101] reported that COMT (Val158Met) was associated with a decreased need for therapy, dose of medications, and length of stay. Variants of *p*-glycoprotein (MDR1) were not associated with differential NAS outcomes. These intriguing findings, if verified in a larger cohort, may have implications for identifying those most at risk for the need of therapy. Enthusiasm is tempered, however, by the example of pharmacogenetic approaches to warfarin therapy in adults, in which there is limited practitioner uptake despite evidence of efficacy and easy-to-use algorithms.

FUTURE DIRECTIONS

Future directions may include the examination of the existing scales, particularly those based on the Finnegan scale, to discern whether there it is possible to simplify the scales to include those elements most closely correlated with clinical outcomes in the management of infants with known opioid exposure. A 3-point scale consisting of hyperactive Moro reflex, mild tremors when undisturbed, and increased muscle tone has been described as discriminative between opioid-exposed and non-opioid-exposed infants, but this has not yet been validated in a large sample.[24]

Dexmedetomidine is chemically similar to clonidine, but with a greater α2-receptor specificity.[120] Dexmedetomidine has been proposed as a potential alternative for the treatment of iatrogenic pediatric opioid withdrawal syndromes, but has not been evaluated in the treatment of NAS.[121] Lofexidine and guanfacine are other α2-agonists that have been investigated for the treatment of adult withdrawal but not pediatric withdrawal, but the size and quality of studies have been limited.[122] These agents have no theoretical advantage over clonidine.

It is not clear whether a short-acting agent such as morphine, compared with longer half-life drugs such as buprenorphine or methadone, will provide better outcomes for infants who require pharmacologic therapy. Extrapolation from adult abstinence and control of withdrawal symptoms would suggest that longer-acting agents, by reducing the flux in drug concentration, would provide more uniform control of symptoms and a smoother transition to the postcessation period of therapy. However, it is also possible that morphine would provide more flexibility in titrating to a dynamic symptom complex by allowing quicker dose titration and attainment of steady state after dose adjustment. A double-blinded, double-dummy trial currently under way (NCT01452789) may provide insight into this question. The lack of published pharmacokinetic and outcomes data make methadone dosing empiric and non-evidence based.

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The majority of treatment for NAS takes place in an inpatient setting, but there are institutions in which home management with phenobarbital and methadone are used. A formal comparison between these approaches would be useful. The correct location for treatment also needs to take into consideration not only the pharmacology of the replacement agent but also the dynamics of mother-infant dyad and of the social situation. In this way, any investigation should take these considerations into account in structuring a study, as well as in defining end points for examination.

Pharmacogenetics may assist in identifying infants at risk for requiring pharmacologic therapy for NAS, but will likely be only one of many covariates that would feed into a predictive disease-state model. Such a model could effectively link demographics, in utero exposures, disease severity, genetic factors, pharmacodynamic responses, pharmacokinetics, and other variables. It is likely that such a model would be actuated optimally in an electronic system that had system inputs from an electronic medical record. Modeling also will play an increasing role in the realm of quantitative methods, allowing use of the sparse data sets available in neonates. In such a fashion, pharmacometric simulations can predict dose response and help to inform the formulation of new dosing regimens or combination therapy. Using a “learn and confirm” paradigm, these models can be refined and optimized.[123]

SUMMARY

There is clearly an unmet medical need to develop improved pharmacologic treatment for infants with NAS. The mean hospital cost for an NAS admission in 2009 was $53,400.[21] Ideally such treatment would provide improved symptom control without compromising safety, and would shorten treatment duration and length of hospital stay. If widely adopted, treatment with these features would have the potential to decrease resource utilization and costs of treating NAS, as well as to improve psychosocial and developmental outcomes in infants exposed to opioids in utero. Lastly, treatment protocols should be standardized per institution, and re-evaluated as new outcomes data become available.

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KEY POINTS

- All infants with in utero exposure to opioids demonstrate signs and symptoms of withdrawal. Two-thirds of infants require pharmacologic therapy to ensure proper feeding and development.
- Opioid replacement is the optimal primary therapy. The current standard is morphine, although there is significant heterogeneity in treatment regimens, with many centers using methadone.
- Of predictive factors, lack of polysubstance exposure, prematurity, and maternal use of buprenorphine are most strongly associated with less severe withdrawal symptoms and need for pharmacologic therapy.
- Emerging therapies include the use of buprenorphine for primary therapy, and clonidine as an adjunct.
- Pharmacogenetic profiling of infants and the use of modeling and simulation to optimize dosing are emerging, but not fully developed, technologies that may change the treatment of the neonatal abstinence syndrome.

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Box 1

Methadone protocol for inpatient use

- Initial loading dose 0.1 mg/kg/dose
- Additional 0.025 mg/kg/dose given every 4 h for continuing NAS scores greater than 8 until symptoms are controlled or a maximum dose of 0.5 mg/kg/d reached
- Maintenance dose determined by calculating the total methadone dose given over previous 24 hours
- Maintenance dose administered in 2 divided doses every 12 hours

Data from Lainwala S, Brown ER, Weinschenk NP, et al. A retrospective study of length of hospital stay in infants treated for neonatal abstinence syndrome with methadone versus oral morphine preparations. Adv Neonatal Care 2005;5(5):265–72.

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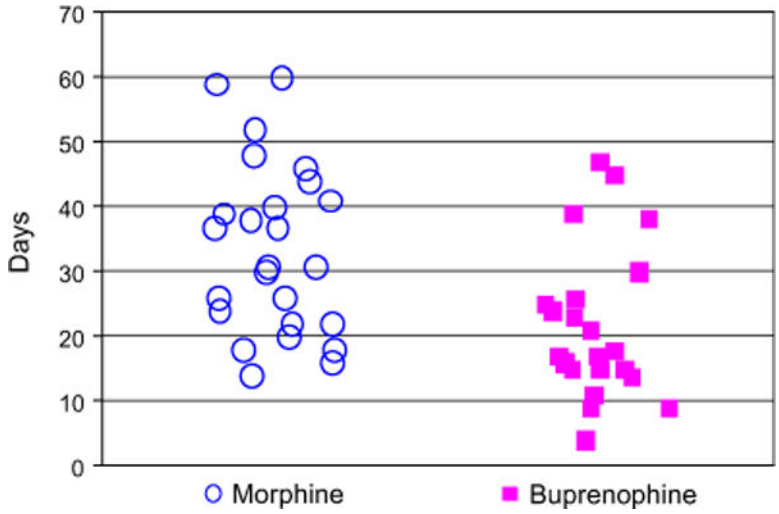

Fig. 1.
Length of treatment: open-label morphine versus buprenorphine by patient.

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Table 1

Morphine regimens, based on Finnegan scoring every 4 hours

Weight Based	Symptom Based
Initial Dose:	*Initial Dose:*
0.4 mg/kg/d in 6 divided doses	For first elevated score >8, rescore in 1 h to verify. If still elevated
Dose Increase:	
20%/d for NAS scores >24 total on 3 measures, or a single score >12	Single NAS score: Dose every 4 h (mg)
Weaning Dose:	9–12: 0.04
After 48 h of clinical stability, reduce dose by 10% every 24–48 h	13–16: 0.08
Reduce dose when the sum of the previous 3 scores is <18 and no single score is >8	17–20: 0.12
Cease therapy when dose is 0.15 mg/kg/d	21–24: 0.16
Rescue Dose:	≥25: 0.20
Administer additional morphine at previous dose for inadequate symptom control between scheduled dose intervals	Doses are fixed and not based on infant weight
Adjunctive Treatment:	Dose Increase:
At dose of morphine 1.25 mg/kg/d initiate second medication[a]	Single NAS score: Increase Dose (mg)
	0–9: None
	9–12: 0.02
	13–16: 0.04
	17–20: 0.06
	Weaning Dose:
	After 48 h of clinical stability, reduce dose by 0.02 mg every 24 h if scores ≤8
	For first elevated score >8, rescore in 1 h to verify. If still elevated
	Two NAS scores: Increase Dose (mg)
	9–12: 0.01
	13–16: 0.02
	17–20: 0.04
	Cease therapy when dose is 0.02 mg Adjunctive Treatment:
	At dose of morphine 1.6 mg/d initiate second medication[a]

[a]Phenobarbital loading dose of 20 mg/kg followed by 5 mg/kg/d, or clonidine.

Data from Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after metha-done or buprenorphine exposure. N Engl J Med 2010;363(24):2320–31; and Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag 2009;5(1):47–55.

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Table 2

Clonidine use

Authors,[Ref.] Year		n	Clonidine Dose (μg/kg)	Outcome in Length of Stay (LOS) or Length of Treatment (LOT)
Hoder et al,[124] 1984	Case Series	7	0.5–1.0 by mouth every 6 h	13 d LOS
Leikin et al,[125] 2009	Case Series	14	0.5–1.0 by mouth every 6 h	7 d LOT In utero exposures = 3 Iatrogenic NAS = 11
Esmaeili et al,[126] 2010	Case Series	29	0.5–3.0 h intravenous	14 d LOT 32 d LOS Chloral hydrate rescue
Agthe et al,[71] 2009	Randomized controlled trial	40	1.0 by mouth every 4 h (+ morphine)	11 d LOT vs 15 for placebo