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Pharmacologic Management of the Opioid Neonatal Abstinence Syndrome

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Keywords

Neonatal Abstinence Syndrome
Opioids
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Clonidine

Abbreviations:

NAS = Neonatal Abstinence Syndrome

AAP = American Academy of Pediatrics

DTO = Diluted Tincture of Opium

C = Celsius

CNS = Central Nervous System

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, though there is significant heterogeneity in treatment regimens with many centers using methadone.
- Of predictive factors, lack of poly-substance 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.

Synopsis

Opioid use in pregnant women has increased over the last decade. Following birth, infants with in utero exposure demonstrate signs and symptoms of withdrawal known as the neonatal abstinence syndrome. Infants express a spectrum of disease, with most requiring the administration of pharmacologic therapy to ensure proper growth and development. Treatment is generally as an inpatient and often involves prolonged hospitalization. There is a general lack of high quality clinical trial data to guide optimal therapy, and significant heterogeneity in treatment approaches. The balance of evidence favors morphine therapy titrated to symptom control and gradually weaned. Therapy with phenobarbital or clonidine is used as an adjunct in severe disease, or occasionally as initial therapy. Poly-substance exposure in utero is associated with more severe symptoms and longer hospitalizations. Breastfeeding is associated with better outcomes and should be strongly encouraged for all infants. Emerging trends in the treatment of infants with the neonatal abstinence syndrome include the use of sublingual buprenorphine, transition to outpatient therapy, and pharmacogenetic risk stratification.

Definition of NAS

Neonatal withdrawal symptoms have been noted following prenatal exposure to a number of 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 medicated by receptor downregulation coupled with upregulation in the cyclic adenosine monophosphate (cAMP) pathway. [8] Other mechanisms may include neuro-immune activation, production of anti-opioid peptides, or activation of the spinal dynorphin system. Symptoms of withdrawal are are hypothesized to be due to increased adenylyl cyclase activity and an abrupt rise in norepinephrine following removal of the mu opioid ligand. NAS is characterized by signs of central nervous system (CNS) hyper-irritability, gastrointestinal dysfunction, respiratory distress, and vague autonomic symptoms. Common symptoms in order of frequency include tremors, 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 55-94% of infants born to opioid-dependent mothers. [9]

Current use of illicit drug 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 counter these poor outcomes, methadone maintenance in opioid-dependent pregnant females 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. While the use of heroin decreased by 19% between 1998 and 2008, 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] This is due to limited self-reporting of drug abuse, and underreporting of NAS using ICD classifications. [19] In 1996, a National Institute of Drug Addiction (NIDA) survey estimated 7,000 cases occur each year, although the report conceded this is potentially an underestimation.[20] More recently, the rate of NAS in the US has increased from 1.2 to 3.9 per 1,000 live births between 2000 and 2009. [21] A similar incident 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. While a meta-analysis which evaluated studies by methodological quality did not identify a statistically significant difference in outcomes between high 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 maternal buprenorphine compared to methadone use is associated with 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 population at large, strongly supporting the generalizability of results. [25]

While Jansson described worse NAS symptoms and pharmacotherapy in males, [26] severity, need for therapy or length of therapy were not influenced by gender in a cohort study by Holbrook. [27] Similarly, there was no sex dependency in the large randomized MOTHER study, which compared use of methadone and buprenorphine in pregnant females. [28] Intrapartum fetal heart rate variability or decelerations 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 and [33] 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 demonstrated that the length of NAS treatment for all non-benzodiazepine exposed infants between 2000 and 2006 was 31 days, compared to 38 days for polydrug-exposed term infants. [34] Strikingly, a multivariate analysis of infants revealed a significant

prolongation of treatment duration for NAS (31 vs 47 days, P<0.01) of benzodiazepine vs. 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 12-24 hours for short acting agents with a peak at 72 hours, while longer acting agents such as diazepam are associated with an onset of 24-72 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] While 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 the 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 and Short Term Sequelae

Environmental and social factors are more important factors affecting childhood development than brief periods of pre-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 drug use. [52] Studies which have linked 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 outside of effects due to environmental and home settings. [56] Even if 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 un- or undertreated women may seek street sources of opioids to treat withdrawal symptoms, which clearly has negative neonatal outcomes. Importantly, there is no evidence of long term adverse outcomes in children treated with pharmacologic agents vs. infants who do not require treatment for NAS, or for treatment with different classes of agents. [57, 58] While the database of information is smaller, neonatal outcomes with in utero buprenorphine exposure are generally favorable compared to methadone in human and animal studies. [59]

Current therapies

Variability of current practice patterns

Few studies have examined NAS prevalence and treatment patterns. Nandakumar published a survey of 17 neonatal units in the Northwest Region of the United Kingdom (UK) 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. [60] While Sarkar conducted a U.S. survey in 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. [61] 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 conducted a 15 question questionnaire of 235 neonatal units that sought to survey current NAS practices in the UK and Ireland. [62] The survey assessed first and second line agents, attitudes to breastfeeding by

women on methadone, and the safety of infants discharged on medication. Crocetti and colleagues assessed the number of opiate-exposed neonates that were identified having NAS, as well as policies and procedures for treatment in 27 hospitals throughout Maryland. [63] There are clear information gaps both for identification, treatment, and length of hospital stay. Moreover, there is lack of pharmaco-economic analyses on costs and cost effectiveness of treatment in 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 upon signs and symptoms in multiple domains. Of a number of scoring systems used to gauge symptom severity and titrate drug dose, [64-66] the Finnegan score (or modifications 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. However, on day 2 of life a score of 7 corresponds with the 95th percentile for non-exposed 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] Non-pharmacologic therapies should be employed for all infants with in utero opioid exposure. These 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 four 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 employs a protocol-driven use of drug titration to control symptoms. Both symptom driven (i.e., weight-independent fixed dose titration based upon severity of NAS scores) as well as weight-based

dosing regimens, have been employed, 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 will 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. Most commonly employed initial therapy is an opioid, while commonly used adjunctive therapies are phenobarbital or clonidine. Though used more commonly, phenobarbital has not been demonstrated to have improved safety or efficacy compared to 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 poly-substance use.

Opioids

Cochrane reviews, [77, 78] the American Academy of Pediatrics, [9, 79] and expert review [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 to supportive care, 2) reduces seizure rates and possibly duration of therapy compared to phenobarbital, and 3) reduces

treatment failure compared to diazepam. [77] While many of the studies cited in the Cochrane review had methodological flaws, the standard of care practice which has developed since the 1970s has generally supported this approach. There is limited evidence with which definitive recommendations can be made regarding differential safety and efficacy of 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 higher quality investigations.

Morphine

Morphine is the most commonly employed replacement therapy opioid. Paregoric, a previously commonly used morphine source, was never subject to any formal FDA evaluation 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 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 degrees C for at least 6 months. [82] Due to 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'-diphisphate glucuronosyl transferase (UGT)-2B7. The ontogeny of UGT development is dynamic in the immediate postpartum period. This is demonstrated by reduced M6G/morphine ratio in neonates younger than 7 days, as well as an associated reduced postsurgical morphine requirement compared to older neonates. [84] Non-linear mixed effects models have been used to estimate both active metabolite formation as well as elimination. [85] Clearance generally correlates with glomerular filtration, with minimal fecal elimination or metabolism to normorphine. The large inter- and intrapatient variability of

intravenous morphine pharmacokinetics (PK) and pharmacodynamics (PD) 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 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 utility in designing an optimized dose regimen.

The initial dose of morphine is 0.12-0.6 mg/kg/day in a survey of 17 pediatric units in the United Kingdom. [60] The authors of this report 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/day was recommended by the 1998 report of the American Academy of Pediatrics (AAP), [9] though this protocol outlined drop unit doses which would make fine titration difficult. Neither the 2012 AAP Committee on Drugs NAS report [79] nor the Cochrane review of the topic identify a favored specific dose. [77] There is no generally accepted maximum dose of morphine used for NAS. A survey of neonatal units in the UK revealed that typical maximum doses were up to 1.3 mg/kg/day, 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 upon scores above a specific NAS score, or a weight-independent dose base upon a graded severity of NAS score. Table 1 provides two commonly employed approaches.

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 which suggests

significant inter-patient 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 use in the neonatal population. In a single small study, outcomes with methadone were similar to 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 employed by Lainwala is provided in Table 2. Methadone use remains relatively uncommon, ranging from <2% of units in the UK, [62] to as high at 20% in the US. [61] The extended dosing interval has led some sites to use methadone as extended outpatient dosing. Compared to full inpatient treatment, infants discharged home on methadone have shorter hospitalizations, but longer duration of therapy, though at least in one study had similar total mg 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 upon symptoms.

Buprenorphine

Buprenorphine is a long acting partial mu 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 due to properties of improved safety, particularly with regard to respiratory depression. Buprenorphine has compared favorably to methadone for use in pregnant women. [24] In NAS, the use of buprenorphine has been explored in two open label, placebo controlled trials. [70, 93] A total of 50 infants were randomized in a 1:1 ratio to oral morphine every four hours or sublingual buprenorphine administered every 8 hours. The optimized initial dose was 15.9 mcg/kg/day, with a maximum of 60 mcg/kg/day. 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 upon the weight at initiation of therapy. While 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, as compared with a mean length of 34 days using standard of care oral morphine (Figure 1). Following log transformation to satisfy normality assumptions, the length of treatment was on average 36% shorter (95% CI: 17%, 51%; p=0.001) 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=0.006). 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.

Adjunctive therapy with phenobarbital was required in 6 of 25 infants in the buprenorphine group compared to 2 of 25 randomized to morphine. It is unclear if 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 could be a factor of a different volume of distribution of the drug in the neonate, or a pharmacodynamic profile of withdrawal that fundamentally differs from that in adults.

Drug for sublingual administration are formulated using buprenorphine for injection (Buprenex or equivalent genetic) 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. (Anagnostis, article in press) Buprenorphine is absorbed by the sublingual route within two minutes in adults. There was no evidence of aspiration in neonates

after > 1,600 individual doses were administered in the Phase 1 investigation. There were two serious adverse events. One infant developed cytomegalovirus in the immediate post partum period, and another had idiopathic seizure. Both events judged to be unrelated to study treatment by the investigator, IRB 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 opioid replacement therapy dose is reached without adequate resolution of symptoms, though it has also been used as an initial adjunct in combination therapy with an opioid [76] or as initial monotherapy. [95] Phenobarbital use has been examined in a Cochrane review, in which the conclusion was that opioids had a comparative advantage incidence of seizures, duration of treatment and nursery admissions, but not necessarily in the treatment failure rate. [78] The half-life of phenobarbital in neonates decreases from 115 hours after 1 week to 67 hours after 4 weeks. [96] This prolonged half-life explains the improved outcomes through the use of a loading dose compared dosing without a load. [97] The typical loading dose is 20 mg/kg, followed by 5 mg/kg. Phenobarbital anecdotally appears to have particular utility in those infants with poly-drug exposure in utero. Phenobarbital causes increased metabolism of many drugs metabolized by the cytochrome P450 system for patients of all agents, a finding which was confirmed in NAS infants co-treated with phenobarbital and buprenorphine. [98] Questions raised about the potential for deleterious neurodevelopmental effects will be addressed by the ongoing PROPHENO trial (NCT 01089504), scheduled to be completed in late 2014.

Clonidine

Clonidine is a centrally acting alpha agonist that reduces global sympathetic tone and has been used in adult withdrawal syndromes. Clonidine is less efficacious in adults as compared to an opioid in the management of withdrawal symptoms. [92] A number of small retrospective examinations had suggested clonidine as a useful adjunct therapy in NAS. (Table 3) Agthe described a high quality, randomized controlled trial of clonidine1 µg/kg every 4 hours compared to placebo as a parallel adjunct to oral morphine therapy (in the form of DTO). Clonidine solution for epidural injection (100 µg/mL) was diluted to 5 µg/mL and administered orally. The dual morphine/clonidine arm had statistically significantly shorter length of stay (11 days [95% CI: 8–15] vs 15 days [95% CI: 13–17]). In addition, total dose of morphine was 7.7 mg with dual therapy compared to 19.2 mg with monotherapy (p=0.03). Clonidine was generally well tolerated, with no serious hypotension or bradycardia. An episode of supraventricular tachycardia occurred in one patient three days after cessation of clonidine. Based upon the mechanism of action of clonidine and potential for post cessation sympathetic surge, it is plausible that this was causally related to cessation of study drug. Three infants in the clonidine treated group died of autopsy verified myocarditis, SIDS, and homicide (methadone overdose). Each occurred at least 22 days after the cessation of study drug and were assessed to be not related to study drug. Xie 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 upon modeling and simulation, was proposed. [99] This dose adjustment has not been tested in a clinical trial setting.

Breast feeding

The number of females 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. [100] It is however, expected that this number will increase both locally and nationwide

due to 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 is a position supported by the Department of Health and Human Services in Healthy People 2020, as well as major medical societies. [101] Methadone is passed on to neonates through breast milk, though the absolute amount is small (<0.2 mg/day) and does not appreciably change neonatal serum methadone concentrations. [102] However, a pharmacodynamic effect is suggested, as breastfed infants have decreased severity of NAS or need for treatment with pharmacologic agents. [103, 104] Based upon 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 drug effect. [105] For mothers maintained on usual abstinence doses, the amount of breast milk transferred buprenorphine is 0.1-1.2 mcg/kg/day, which represents ~0.02% of the maternal dose. [106-109] The bioavailability of buprenorphine transferred in breast milk is not characterized, but appears low based upon measurement in neonatal blood and urine, [109] and by minimal effects in suppression of NAS symptomatology. [110-112] There are no reported safety concerns associated with breastfeeding, and so, despite the product insert which advises against breastfeeding, current national guidelines advocate breastfeeding for mothers prescribed buprenorphine. [113]

Pharmacogenetics

The inter-patient 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 particular 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, [114] and social hedonic capacity. [115] The mu opioid receptor (OPRM1) gene A118G SNP has been associated with differential morphine sensitivity, with decreased pain and morphine requirements with the AA

genotype. [116] An exploratory examination by Wachman 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 to GG. [100] 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 cancer patients, [117] although the association with addiction is much less clear. [118] Wachman reported that COMT (Val158Met) was associated with 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 upon the Finnegan, to see if there is an ability 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 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 alpha 2 receptor specificity. [119] 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. [120] Lofexidine and guanfacine are other alpha 2 agonists which have been

investigated for the treatment of adult but not pediatric withdrawal, but the size and quality of studies have been limited. [121] These agents have no theoretic advantage over clonidine.

It is not clear if a short acting agent such as morphine compared to 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 post-cessation of therapy period. 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 underway may provide insight into this question. (NCT01452789)

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 employed. 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 endpoints for examination.

Pharmacogenetics may assist in identifying infants at risk for requiring pharmacologic therapy for NAS, but likely be only one of many covariates which 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 bringing quantitative methods allowing to use the sparse data sets available in neonates. In such a fashion, pharmacometric simulations can predict dose response and help to inform

formulation of new dosing regimens or combination therapy. Using a “lean and confirm” paradigm, these models can be refined and optimized. [122]

Conclusions

Clearly, there is 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, a 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.

Table 1. Morphine Regimens

Regimens are based upon Finnegan Scoring every 4 hours.

<table>
<tr><th>Weight based</th><th>Symptom based [69, 123]</th></tr>
<tr>
<td>
Initial dose:
0.4 mg/kg/day in 6 divided doses
Dose Increase:
20%/day for NAS scores > 24 total on three measures, or a single score ≥ 12.
Weaning Dose:
After 48 hours of clinical stability, reduce dose by 10% every 24-48 hours
Reduce dose when the sum of the previous three scores is < 18 and no single score is > 8.
Cease therapy when dose is 0.15 mg/kg/day.
Rescue dose:
Administer additional morphine at previous dose for inadequate symptom control between scheduled dose intervals.
Adjunctive treatment:
At dose of morphine 1.25 mg/kg/day initiate second medication *
</td>
<td>
Initial dose:
For first elevated score >8, rescore in one hour to verify. If still elevated:
<table>
<tr><th>Single NAS score</th><th>Dose q4hr</th></tr>
<tr><td>9-12</td><td>0.04 mg</td></tr>
<tr><td>13-16</td><td>0.08 mg</td></tr>
<tr><td>17-20</td><td>0.12 mg</td></tr>
<tr><td>21-24</td><td>0.16 mg</td></tr>
<tr><td>≥25</td><td>0.20 mg</td></tr>
</table>
Doses are fixed and not based upon infant weight
Dose Increase:
<table>
<tr><th>Single NAS score</th><th>Increase Dose</th></tr>
<tr><td>0-9</td><td>none</td></tr>
<tr><td>9-12</td><td>0.02 mg</td></tr>
<tr><td>13-16</td><td>0.04 mg</td></tr>
<tr><td>17-20</td><td>0.06 mg</td></tr>
</table>
Weaning Dose:
After 48 hours of clinical stability, reduce dose by 0.02 mg every 24 hours if scores ≤8
For first elevated score >8, rescore in one hour to verify. If still elevated
<table>
<tr><th>Two NAS scores</th><th>Increase Dose</th></tr>
<tr><td>9-12</td><td>0.01 mg</td></tr>
<tr><td>13-16</td><td>0.02 mg</td></tr>
<tr><td>17-20</td><td>0.04 mg</td></tr>
</table>
</td>
</tr>
</table>

	• Cease therapy when dose is 0.02 mg **Adjunctive treatment:** At dose of morphine 1.6 mg/day initiate second medication*

*phenobarbital loading dose of 20 mg/kg followed by 5 mg/kg/day OR clonidine

Table 2: Methadone protocol for inpatient use

● Initial loading dose 0.1 mg/kg/dose
● Additional 0.025 mg/kg/dose given every 4 hr for continuing NAS scores >8 until symptoms controlled or maximum dose of 0.5 mg/kg/day 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

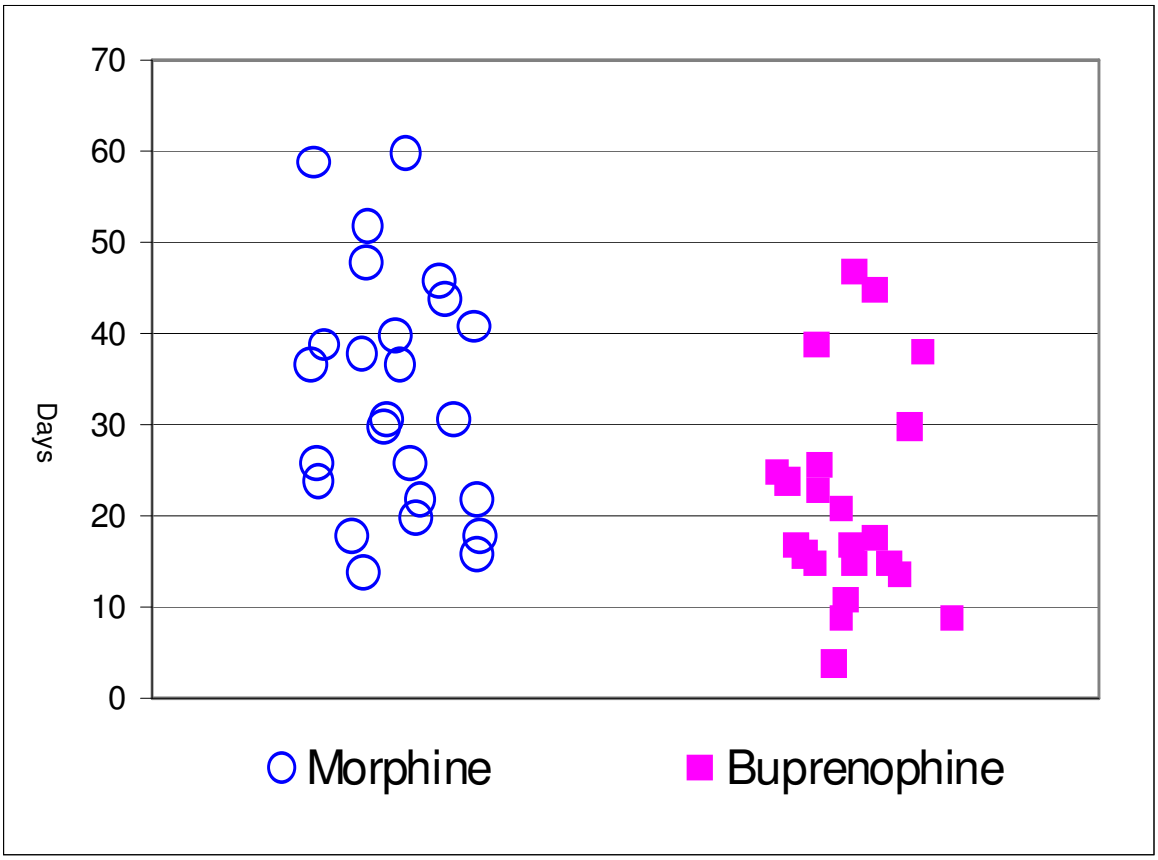
Source: [90]

Table 3: Clonidine Use

Year		**n**	**Clonidine dose (mcg/kg)**	**Outcome in Length of Stay (LOS) or Length of Treatment (LOT)**
Hoder, 1984 [124]	Case Series	7	0.5–1.0 po Q 6 hr	13 day LOS
Leikin, 2009 [125]	Case Series	14	0.5–1.0 po Q 6 hr	7 day LOT In utero exposures = 3 Iatrogenic NAS = 11
Esmaeili, 2010 [126]	Case Series	29	0.5–3.0 hr IV	14 day LOT 32 day LOS Chloral hydrate rescue
Agthe, 2009 [71]	Randomized Controlled Trial	40	1.0 po Q 4 hr (+ morphine)	11 day LOT vs. 15 for placebo

Figure Legend

Length of Treatment: Open Label Morphine vs. Buprenorphine by Patient



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