9-28-2010

Neonatal Abstinence Syndrome: A Retrospective Review of Clonidine as an Adjunct to Opioid Treatment

Joanna Schatz

Neonatal Abstinence Syndrome: A Retrospective Review of Clonidine as an Adjunct to Opioid Treatment

A Thesis Submitted to the

Yale University School of Medicine

In Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

Joanna J. Schatz

2010

NEONATAL ABSTINENCE SYNDROME: A RETROSPECTIVE REVIEW OF CLONIDINE AS AN ADJUNCT TO OPIOD TREATMENT. Joanna J. Schatz (Sponsored by Matthew R. Grossman). Department of Pediatrics, Yale University, School of Medicine, New Haven, CT.

This was a retrospective medical record review of treatment for neonatal abstinence syndrome (NAS) due to *in utero* exposure to opioids. The purpose of our study was to determine if there was a difference in the duration of treatment between infants who received morphine alone compared to infants who were treated with both morphine and clonidine. We hypothesized that there would be a decrease in the duration of treatment in infants treated with both morphine and clonidine compared to infants treated with morphine alone. The primary outcome was duration of treatment for NAS. Medical records of infants born at Yale New Haven Hospital (YNHH) between January 2003 and December 2009 were reviewed. 117 infants met the inclusion criteria. 59 were treated with morphine, and 58 were treated with morphine and clonidine. The mean length of stay of infants treated with morphine and clonidine was significantly shorter than the mean length of stay of infants treated with morphine alone, 19.57 days (SD 9.896) and 25.14 days (SD 12.738) respectively ($p<0.05$). Both groups were similar with regard to infant demographic factors, and there was no significant difference in the maximum dose of diluted morphine in either treatment group ($P=0.410$). These results suggest that infants treated with morphine and clonidine for NAS have decreased lengths of pharmacotherapy compared to infants treated with morphine alone.

Acknowledgements

I would like to thank Dr. Grossman for his patience, encouragement and mentorship throughout this process. I would also like to thank my husband, Luke, and son, William, for their understanding, love and support.

Table of Contents

Introduction

Illicit drug abuse and prescription drug use during pregnancy results in neonatal exposure potentially leading to physical dependence of the infant after birth. Moreover, illicit drug use among women of childrearing age is not an uncommon problem. National estimates from the NSDUH combined data for 2007 and 2008 found that 5.1 percent of pregnant women ages 15 to 44 years had used illicit drugs in the past month, which is similar to the rates from 2004-2005 (4.0 percent) and 2003-2004 (4.6 percent). Although this is a conservative estimate that uses the prevalence of illicit drug use at a specific point any time during a pregnancy, it illustrates that *in utero* exposure to illicit substances is both a significant clinical and a significant social problem. (1-3) In the United States an estimated 7000 infants are born every year having been exposed *in utero* to opioids. (4) Of these infants, 55-94 percent may subsequently develop signs and symptoms of opioid withdrawal know as neonatal abstinence syndrome (NAS). (5-8) NAS is characterized by a constellation of central nervous system (CNS), gastrointestinal (GI), and autonomic symptoms that neonates exposed to opioids *in utero* are at risk of developing. NAS is a complex clinical syndrome that varies widely in presentation and clinical course. The complexity and variability of NAS, as well as the population that is at risk for developing NAS, make it a difficult entity to study.

Clinical manifestations of NAS include: neurologic hyperexcitability with high-pitched crying, yawning, sneezing, skin excoriation, tremors, irritability, disruption of the sleep-wake cycle, hypertonicity, hyperreflexia, and seizures; enteric symptoms with poor feeding, vomiting, diarrhea, increased sucking and dehydration; and autonomic

dysregulation with increased sweating, increased temperature/fever, nasal congestion, tachypnea, and mottling of the skin. These symptoms usually develop within the first 72 hours following birth but can be delayed for several days and up to four weeks. *In utero* exposure to heroin generally presents within 48 hours and methadone within 48-72 hours. (9, 10)

Assessment and treatment of this complex clinical syndrome varies widely across the country and throughout the world. (11, 12) This variability persists in part because the increasing body of literature regarding the characterization and management of NAS has yielded conflicting results, and the studies are often limited by both design as well as by the study population. There have been studies that have attempted to systematically review the literature and offer clarification and guidance to physicians treating this complex clinical syndrome. The guidelines set forth by the American Academy of Pediatrics (AAP) Committee on Drugs in 1998 for the management of neonatal drug withdrawal made the following recommendations:

1. Screening for maternal substance abuse using multiple methods (i.e. history, toxicology screening etc.)
2. Drug withdrawal should be considered in infants with signs and symptoms consistent with the diagnosis, although other diagnoses in the differential should be evaluated and treated if present.
3. Withdrawal should be scored using an appropriate scoring tool which should be used to help govern treatment decisions in a more objective and quantitative way.

4. Withdrawal-associated seizures should be treated, and other possible etiologies should be ruled out.
5. Vomiting, diarrhea, dehydration and poor weight gain are indications for treatment even in the absence of a high withdrawal score.
6. The pharmacologic treatment for withdrawal should match the type of agent causing the withdrawal (i.e. opiates for opiate withdrawal).
7. Severity of withdrawal has not been proven to be associated with differences in long term outcome after intrauterine drug exposure. Additionally, treatment for neonatal drug withdrawal may not alter long-term outcome.
8. Naloxone is contraindicated in infants born to mothers who are known to be opioid-dependent. (13)

Although there are guidelines such as the aforementioned AAP guidelines, subsequent studies have shown that having guidelines does not directly translate into incorporating those guidelines in every day clinical practice. One study done by Sakar *et al*. surveyed neonatal intensive care units (NICU) across the country. They found that only about half of the NICUs had a written policy governing the management of NAS. Additionally, 65 of the 75 sites that responded to the survey reported using some sort of scoring tool, such as the Finnegan Score, to quantify the severity of withdrawal, although ten sites reported not using a scoring tool at all. Despite using a scoring tool, only 70 percent of sites, 53 respondents, reported consistently using a scoring tool to govern treatment (i.e. using the scores to dictate when treatment was initiated, as well as when medication doses were increased or weaned). Eighty-three percent of the sites that responded to the survey reported routinely obtaining either urine or meconium for

toxicology screening before starting pharmacologic intervention for NAS. Finally, 63 percent of respondents, 47 sites, used opioids as the first line treatment for opioid withdrawal. (11) Examination of the AAP recommendations and the results of the study done by Sakar *et al*. highlights the difficulty of adopting and implementing evidence-based clinical practice guidelines. Not only has passive dissemination of information been found to be largely ineffective in promoting implementation of research findings, but the data with regards to NAS is vast and varied which further complicates implementation of evidence-based practices. (14)

The research on NAS is varied in part because it is an entity that is difficult to study due to the heterogeneity of the clinical presentation and course, as well as the heterogeneity of the population in which the syndrome occurs. NAS is manifested clinically as a broad spectrum of presentations influenced by maternal, fetal and environmental factors. These factors include but are not limited to the type and dosage of drug(s), timing and amount of last maternal use of the drug(s), as well as maternal and infant metabolism and excretion of the drug(s). (8, 11) In addition to multiple factors playing a role in the manifestation of NAS, the dynamic nature of maternal-fetal dyad throughout pregnancy with continuous morphological and physiological changes not only in the mother and fetus, but also in the placenta, further complicates matters. Although one of the key elements in understanding the dynamic presentation of NAS is understanding the pharmacologic properties of a drug in the maternal-fetal dyad including the mechanism action, the kinetics, and the dynamics, studies that aim to elucidate the effect of prenatal exposure are limited by both ethical as well as technical factors. (15)

Defining and understanding neonatal abstinence syndrome becomes further complicated by the myriad of drugs an infant may have been exposed to *in utero*. Often maternal use of opioids such as heroin, methadone, morphine or dilaudid is not independent of maternal use of other substances including but not limited to tobacco, alcohol, barbiturates and benzodiazepines. (16-18) One study that examined the drug use patterns of pregnant women in two inner city sites found that cocaine use is associated with an increase in tobacco, alcohol and marijuana use. (16) Although NAS is typically associated with prenatal opioid exposure and much of the research on NAS focuses on heroin and methadone, in every day clinical practice, infants with signs and symptoms of withdrawal will often have been exposed to multiple illicit substances at various points during gestation. Additionally, obtaining a reliable history of *in utero* exposure is incredibly difficult. Maternal self-report is often plagued by under-reporting and can be unreliable, thus it has a low sensitivity and high false negative rates. Toxicology studies done on urine at the time of delivery or meconium only capture the very recent history of substance use, although they are more sensitive and specific as well as cost effective. Finally, hair analysis has the benefit of giving a longitudinal view of substance exposure in addition to having a high sensitivity. However, hair analysis is not only costly, but it can also have false-positive results for passive exposure (19, 20)

Methadone maintenance programs have become the standard of care for opioid-dependent pregnant women and have, in part, alleviated some of the polysubstance use and other psychosocial issues associated with opioid-dependence during pregnancy. These types of programs include comprehensive services that increase access to and usage of prenatal care as well as psychosocial support services. This, in turn, has led to

increased stability of lifestyle, reduced risk-taking behavior, as well as reduction in the number of preterm births and infants with intrauterine growth restriction. (21, 22)

The evidence regarding the prevalence of continued heroin use and concurrent polysubstance use of pregnant women in methadone maintenance programs is consistent with the evidence in other areas of research on NAS: it is varied. There is evidence to support that some opioid-dependent pregnant women treated in methadone maintenance programs continue to use heroin as well as other illicit substances which ultimately impacts the postnatal outcomes of their infants.

One study done by Leifer *et al*. looked specifically at the extent of polysubstance abuse among female pregnant patients in a methadone maintenance program, the Family Center Program in Philadelphia. The study population had been in the program for at least four months. Researchers collected urine samples upon admission to the program, once a week at random, upon admission to the hospital for delivery, and at any point that a subject missed one or more consecutive doses of methadone. Upon admission to the program, subjects were stabilized on a methadone dose that prevented withdrawal symptoms. Within their study population of 100 subjects, 98 percent were multi-drug users. This was consistent with a study done by Chambers in 1972 that found that 97 percent of methadone-maintained patients at Philadelphia General Hospital were multi-drug users. (23) They reported that 74 percent of their patients continued to use heroin despite methadone maintenance treatment and only rare physician refusals of patient's requests to increase the methadone dose. (24) Harper *et al*. reported that women in the Family and Maternal Care Program (FMCP) at the State University of New York Downstate Medical Center enrolled 51 women between the ages of 21 and 25. All of

these women were addicted to heroin when enrolled in the study and started on methadone detoxification therapy. Urine toxicology studies showed that 23 of 51 women used no other illicit substances after joining the FMCP, 27 women used heroin at least once after entering the program, eight of the 27 women used barbiturates at least once, and five women had a positive test for either barbiturates alone or other drugs. Of note, the incidence of heroin use decreased markedly the longer a woman remained in the program. (6) The implications of these studies are that polysubstance use during pregnancy continues to be an important issue in the evaluation and treatment of NAS despite advances made by methadone maintenance programs.

As stated previously, there is a large and heterogeneous body of literature on the treatment of NAS. The main goals of treatment are to ameliorate symptoms of NAS, promote neuromaturation and self-organization of the infant, and to reduce morbidity. (28) The first line of treatment is supportive care which includes but is not limited to holding, swaddling, minimal stimulation, and rooming-in. (13, 17, 18, 25-28)

Supportive care may be adequate for mild withdrawal, but infants with NAS often require treatment beyond supportive care with opiates and/or sedatives, and should be assessed with the aid of a NAS scoring tool such as the Finnegan Neonatal Abstinence Scoring System, Lipsitz Tool, or Neonatal Withdrawal Inventory. (30-33) In one study done by Zelson *et al.*, 68.7 percent of infants that manifested signs of withdrawal required pharmacologic intervention. (9) In another study done by van Baar *et al.*, 80 percent of infants born to drug dependent mothers required pharmacologic intervention. (29) Pharmacologic intervention should aim to quell hyperactivity and autonomic instability and promote feeding, weight gain and normal sleep patterns. The choice of

pharmacotherapy is less straightforward, and many different agents have been used over the years, including several different opioids (methadone, morphine, diluted tincture of opium, and paregoric), clonidine, chloral hydrate, chlorpromazine, diazepam, and phenobarbitone. (34)

There have been two recent Cochrane reviews that examined pharmacologic treatment, specifically sedatives and opiates, for opiate withdrawal in newborn infants. (35, 36) One review aimed to assess the safety and efficacy of sedative treatment for NAS compared to non-opiate control. It also sought to determine the safest and most effective sedative for the treatment of NAS. The review included six studies with a total of 305 subjects. Based on their review, Osborn *et al*. concluded that trials of sedatives have generally been of poor quality. When a sedative is needed for the treatment of NAS, the preferred agent is phenobarbitone. Even though phenobarbitone alone has not been shown to reduce treatment failure, when it is compared to supportive treatment, it may reduce the daily duration of supportive care needed, and it may also reduce the severity of withdrawal in infants who are also treated with an opioid. (35) The second review sought to assess the efficacy of opioid treatment for NAS and included seven studies with 585 total subjects. Based on this review, Osborn *et al*. concluded that opioids, when compared to supportive care, appear to reduce the time it takes an infant to regain birth weight, reduce the duration of supportive care, but increase the duration of hospital stay. Also, opioids, when compared to sedatives such as phenobarbitone, may reduce the incidence of seizure and duration of treatment, although no overall effect was found on treatment failure rate. In comparison to diazepam, opioids do reduce the incidence of treatment failure. (36)

A third review by Johnson *et al*. also supports the findings of the Cochrane review as well as the AAP guidelines that opioids should be used as the first line treatment for infants exposed to opioids *in utero* who subsequently develop NAS. (34) These findings are consistent with what one might expect when examining at the pharmacologic actions of opioids on the central nervous system. Opioids act on the opiate receptors, mu, delta, and kappa, throughout the brain and more specifically in one of the brain's major noradrenergic centers, the locus ceruleus, a nucleus in the dorsal pons that projects diffusely to the forebrain, brainstem and spinal cord. On a molecular level, binding to the receptors of these transmembrane proteins leads to the activation of second messengers within the cell and decreases the activity of adenylate cyclase leading to the reduction of cyclic AMP (cAMP). (37, 38) The reduction of cAMP is inhibitory and subsequently leads to potassium efflux and calcium influx into the noradrenergic neurons and decreased norepinephrine release. (39) Chronic exposure to opioids leads to increased release of norepinephrine to overcome the inhibitory effects on noradrenergic neurons. Abrupt discontinuation of opioid exposure, as is the case with infants transitioning to extrauterine life, leads to the loss of this inhibitory effect and to significant increases in noradrenergic activity. Increase in noradrenergic activity in the brain is manifested clinically as symptoms of withdrawal. (40) Thus, by administering opioids, this noradrenergic hyperactivity is reduced, leading to amelioration of withdrawal symptoms. (34)

Clonidine hydrochloride has also been suggested as a potential treatment for NAS in the literature. It is an α-2-adrenergic receptor agonist often used for its antihypertensive properties. (41) In the central nervous system, it acts presynaptically in

the locus ceruleus on α-2-adrenergic receptors decreasing catecholamine, specifically norepinephrine, release. (34, 41, 42) Thus, clonidine acts on α-2-mediated inhibition rather than opioid-mediated inhibition of brain noradrenergic activity with similar reductions in withdrawal symptoms. Although the action of clonidine suppresses the symptoms associated with opioid withdrawal, it has limitations as a single agent, especially due to its side effects of hypotension and bradycardia. (43)

Studies in older children and adults have shown clonidine to be efficacious in the treatment of opioid withdrawal. (43-48) In one study done by Gold *et al*. clonidine was found to produce a rapid and statistically significant decrease in opiate withdrawal signs and symptoms in ten adult patients who underwent abrupt discontinuation of methadone in an inpatient setting. (44) A double-blind, placebo-controlled, cross-over trial done by Gold *et al*. found that clonidine eliminated signs and symptoms of opiate withdrawal in eleven patients in a hospital setting for a period of 240-360 minutes. (45)

Although there is clear evidence to support the use of clonidine for the treatment of opioid withdrawal in older children and adults, the data on the use of clonidine in infants with NAS has been limited to only a few studies. (35, 49-51) A pilot study done by Hoder *et al*. reported that clonidine effectively ameliorated the symptoms of neonatal narcotic withdrawal in six out of seven infants. They also did a retrospective review of 13 infants treated with phenobarbitone and found that the length of treatment in the clonidine group was significantly less than that of the phenobarbitone group, six to 27 days with a mean of 13 days and 15 to 55 days with a mean of 27 days respectively ($t = 2.93$, $df = 18$, $p < 0.05$). Even though the few studies of clonidine seem to indicate that clonidine is a reasonable and useful treatment for NAS, larger reviews have found that

there is insufficient data to support the use of clonidine for NAS. (13, 34-36) However, the reviews that cited insufficient data for the use of clonidine for the treatment of NAS were all published prior to the publication of a study done by Agthe *et al*. which clearly indicated that clonidine in addition to opioid therapy is more efficacious than opioid therapy alone (35, 49-51)

The study done by Agthe *et al*. is the largest prospective double-blind, randomized trial of any kind in NAS. It is also the first randomized, controlled trial of clonidine. It enrolled 80 infants with intrauterine exposure to either heroin or methadone and NAS as defined by two consecutive modified Finnegan scores of ≥ 9, and followed them throughout their hospital course until discharge. Infants were randomly assigned to receive either oral clonidine or placebo in addition to treatment with diluted tincture of opium. The primary outcome of the study was duration of treatment with opioid therapy. (51)

They found that the group of infants treated with both diluted tincture of opium and clonidine had a significantly shorter duration of treatment (27 percent shorter) as compared to those who received diluted tincture of opium and placebo, median of 11 days and 15 days respectively. In addition to a longer duration of treatment, the placebo group required higher doses of opioids in 40 percent of infants as compared to the clonidine group which required higher doses of opioids in only 20 percent of infants. Additionally, there were no treatment failures in the clonidine group, and treatment failures occurred in 12.5 percent of the placebo group. In the clonidine group, however, seven infants required recommencement of opioid therapy after initial discontinuation, whereas none of the infants in the placebo group required opioid therapy to be restarted

after discontinuation. Despite seven infants requiring recommencement of opioid therapy, the duration of treatment was still significantly shorter in the clonidine group as compared to placebo. In addition, neither group experienced adverse cardiovascular outcomes including hypertension, hypotension, bradycardia or oxygen desaturations. (51)

Illicit drug use during pregnancy has been and remains an important issue in the United States and throughout the world. (1-3) Historically, the characterization of withdrawal in and treatment of infants exposed to opioids and other illicit substances *in utero* has been challenging. Furthermore, there has been no clear consensus on the optimal treatment regimen for this population, and the vast majority of studies are limited by either study design, study population or both. Although organizations have attempted to clarify this complex entity, recommendations and guidelines do not directly translate into clinical practice and further clarification is needed. (11-14) Recommendations suggest the use of opioids for opioid detoxification with the addition of sedatives if additional intervention is needed. (13, 35, 36)

More recent reviews and studies have suggested the addition of an α-2-adrenergic receptor agonist such as clonidine, which has clearly been shown to be efficacious in the treatment of opioid withdrawal in older children and adults, may also be efficacious in the treatment of infants with NAS. (43-47) It has been shown to reduce duration of treatment as well as reduce the amount of opioid required to ameliorate the symptoms of NAS. (49-51) The promising results of a small number of trials looking at clonidine as a potential pharmacologic intervention for NAS indicate the need for additional studies to corroborate and further characterize the potential benefits as well as long-term safety of clonidine.

Purpose

The purpose of this study was to look retrospectively at the medical records of infants treated postnatally for neonatal abstinence syndrome at Yale New Haven Hospital (YNHH) to determine if there was a difference in the duration of treatment between infants who received diluted oral morphine sulfate alone compared to those who were treated with both diluted oral morphine sulfate and diluted oral clonidine hydrochloride. We hypothesized that there would in fact be a decrease in length of hospital stay in those infants treated with both morphine and clonidine compared to those treated with morphine alone. The primary outcome of this study was duration of treatment, which was defined as the total number of days an infant received morphine with or without clonidine for the treatment of NAS. Additionally, this study examined factors that could potentially influence duration of treatment in infants with NAS such breastfeeding, gestational age, birth weight, gender, Apgar scores, mode of delivery, and attending physician.

Methods

A retrospective review of medical records was undertaken. The study was reviewed and approved by the Yale Human Investigation Committee. Records of infants born at Yale New Haven Hospital (YNHH) between January 2003 and December 2009 were identified using CPT codes for the diagnosis of NAS. Data was obtained by thorough manual review by the investigator of both hardcopy paper medical records as well as electronic medical records. The data collected included birth, admission and discharge dates, gestational age, birth weight, gender, race, mode of delivery, Apgar scores at one and five minutes, maximum dose of medication required to control

symptoms of NAS, results of toxicology screening tests, history of intrauterine exposure to illicit substances when available, and attending physician.

Criteria for inclusion in the study were:

- Diagnosis of neonatal abstinence syndrome
- Gestational Age ≥ 36 weeks
- Treated at YNHH between January 2003 to December 2009
- *In utero* exposure to opioids as determined by maternal history, toxicology or infant toxicology
- Symptoms of NAS requiring pharmacologic intervention

Diagnosis of NAS was determined initially by CPT code and subsequently by review of the medical record. Gestational age was determined by medical record review. *In utero* exposure to opioids was confirmed by toxicology results when available and otherwise maternal history as recorded in the infant's medical record was used. Symptoms of NAS requiring pharmacologic intervention were determined by three consecutive modified Finnegan scores with a total score of ≥ 24 over a period of 24 hours as assessed by nursing staff every eight hours and subsequent initiation of treatment per report in the medical record.

Criteria for exclusion from the study were:

- Transferred to another facility during treatment
- Diagnosis of iatrogenic NAS due to postnatal exposure to opioids

- Major concomitant medical illness i.e. sepsis, congenital anomalies, prematurity < 36 weeks, and the presence of seizures as part of the infant's presenting symptom complex

The standard treatment protocol for NAS at YNHH prior to 2006 was to monitor infants at risk of developing NAS every eight hours for a total of three assessments in a 24 hour period of time (day, evening and night) using a modified Finnegan scoring algorithm which includes scoring of withdrawal symptoms in three major areas, central nervous system disturbances, metabolic/vasomotor/respiratory disturbances, and gastrointestinal disturbances (Appendix A). Pharmacologic intervention with diluted oral morphine sulfate was initiated when the total withdrawal score was 24 or greater over a 24 hour period of time. The starting dose of diluted oral morphine sulfate was 0.08-0.12 mg/kg/dose every four hours or the total 24 hour dose could be divided into every three hour dosing if the infant was receiving feedings that frequently. This dose was increased by 0.04 mg/dose every eight hours until signs of withdrawal were controlled (i.e. a score less than ten over an eight hour period of time) or until a maximum dose of 0.4 mg/dose. After signs of withdrawal were controlled for two to three days, infants were weaned by ten percent decrements of the maximum dose of morphine sulfate every one to three days with a goal of maintaining withdrawal scores less than ten over a 24 hour period of time. Diluted oral morphine sulfate was discontinued when the dose had been weaned to 0.06 mg/dose. (See Figure 1)

The standard treatment protocol for NAS from 2006 to December 2009 was to assess infants at risk of developing NAS every eight hours using the modified Finnegan

algorithm and initiate pharmacologic intervention with both diluted oral morphine sulfate and oral clonidine when the total withdrawal score was 24 or greater over 24 hours. The starting dose of diluted oral morphine sulfate was 0.08-0.12 mg/kg/dose every three to four hours depending on the feeding schedule. The morphine dose was increased by 20 percent of the initial dose every eight hours until the signs of withdrawal were controlled with a withdrawal score less than ten over eight hours or a maximum dose of 0.2 mg/kg/dose was reached. Oral clonidine was administered at a dose of 1 mcg/kg/dose every four hours or 0.75 mcg/kg/dose every three hours based on the infant's feeding schedule. If the maximum dose of morphine was reached, clonidine could be increased by 25 percent to a maximum of 2 mcg/kg/dose every four hours or 1.5 mcg/kg/dose every three hours.

After signs of withdrawal were controlled for two days with withdrawal scores less than ten over each eight hour period of assessment, weaning of morphine by ten percent of the maximum dose was begun. If there were two scores of ten or greater in a 24 hour period of time, consideration was given to increasing the morphine dose to the last stable dose and extending the weaning interval back to two days. Diluted oral morphine could be discontinued when the dose had been weaned to 0.06 mg/dose. Twenty-four hours after the discontinuation of morphine, the clonidine dose could be decreased by 50 percent if the infant had been stable. Heart rate and blood pressure were monitored for rebound elevations, and then if there was no rebound tachycardia or hypertension and withdrawal scores remained stable for 12 hours, the clonidine could be discontinued altogether. (See Figure 2)

All infants included in the study were treated at YNHH using the aforementioned standard treatment protocols. Withdrawal symptoms were monitored by trained pediatric nursing staff using a modified Finnegan neonatal abstinence scoring algorithm every eight hours (Appendix A). The Finnegan scoring algorithm is a clinical tool used to measure the severity of neonatal withdrawal. Twenty signs and symptoms most often observed with neonatal withdrawal are ranked from one to five, with one being mild and five being severe. These scores are then summed to give a total score that aims to quantify the severity of withdrawal. (31)

Based on treatment for NAS, infants were divided into two groups: morphine alone or morphine and clonidine. Infants who failed clonidine due to bradycardia or hypotension were included in the morphine group. Continuous data was analyzed using the Mann-Whitney *U* test due to the non-normal distribution of data and small sample size. Adjustment for potential confounding factors was made using a multivariate regression analysis. For descriptive statistics, means and standard deviations were reported for normally distributed data, and medians and interquartile ranges for non-normally distributed data. Continuous variables were analyzed using independent-samples t-test for between groups comparisons with equal variances not assumed. All tests were two-tailed, and statistical significance was defined as a P value < 0.05. All data were analyzed using SPSS version 18.0.

Figure 1. NAS Treatment Algorithm for Diluted Oral Morphine Sulfate

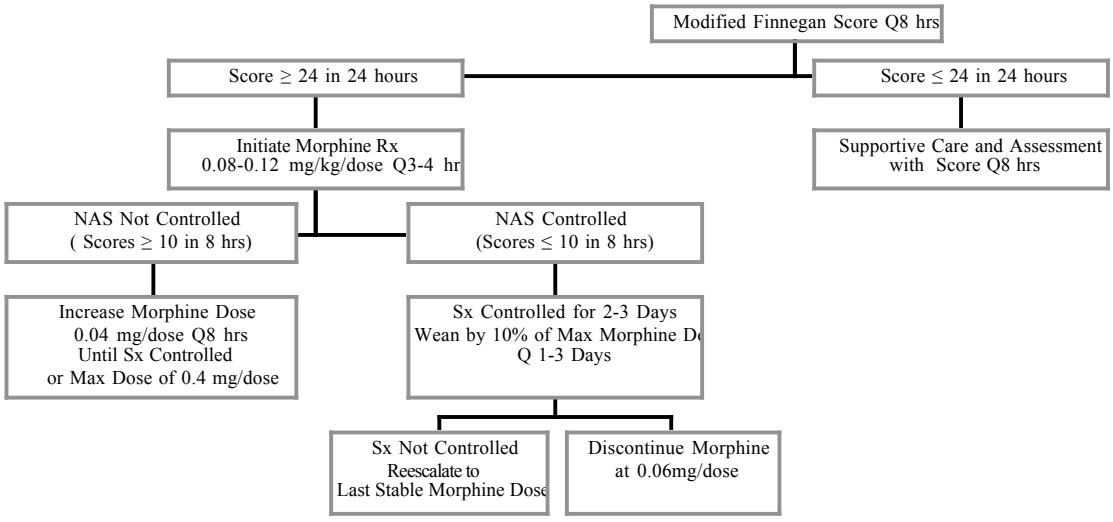
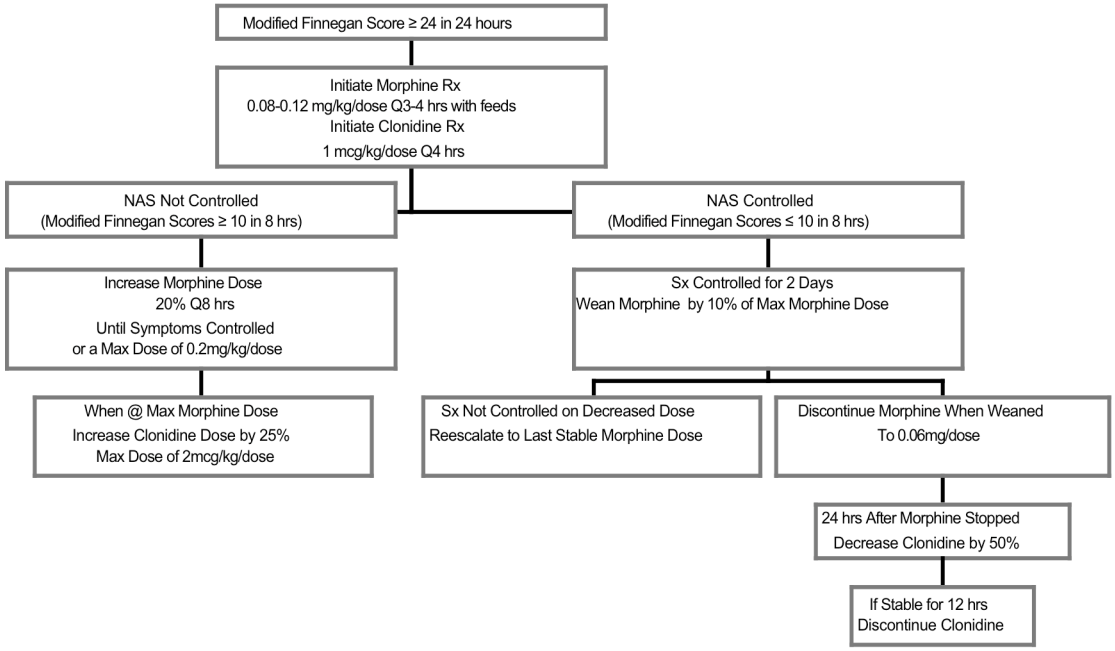


Figure 2. NAS Treatment Algorithm for Diluted Oral Morphine Sulfate and Diluted Oral Clonidine Hydrochloride



Results

One hundred and ninety four infants were identified by CPT code for NAS during the study period. Of those, 77 were ineligible: eight transferred to other hospitals, eight had NAS due to postnatal exposure to opiates, eleven had NAS but did not require treatment, and 50 were less than 36 weeks gestation. One hundred and seventeen infants met the inclusion criteria and were included in the analysis.

Both groups were similar with regard to infant demographic factors. There were no significant differences in birth weight, gestational age, gender, mode of delivery, Apgar scores at one and five minutes, type of feeding, or maximum diluted oral morphine sulfate dose. Descriptive statistics and p values for these variables are listed in Table A.

All infants included in the study were exposed *in utero* to opioids, heroin, methadone, or a combination of these. Fifty-nine were treated with morphine, and fifty-eight were treated with morphine and clonidine. The mean number of days of treatment for the morphine group was 25.14 days (SD 12.738). The mean number of days of treatment for the morphine and clonidine group was 19.57 days (SD 9.896). Mann-Whitney *U* rank sum test found the difference between these two groups to be significant ($p<0.05$). (See Figure 3)

The ten subjects who failed treatment with clonidine due to bradycardia were included in the morphine group. We did, however, do additional analyses with these subjects included in the morphine and clonidine group to assess whether or not an intention to treat design would be necessary. The results remained statistically significant when a Mann-Whitney *U* rank sum test was done ($p<0.05$).

Unstandardized β coefficients and 95% confidence intervals computed by linear regression are as described in Table B. Additionally, there was no significant difference in the maximum dose of morphine in either the morphine treatment group or the morphine and clonidine treatment group (P=0.410).

Characteristics	**Morphine Treatment Group**	**Morphine/Clonidine Treatment Group**	P Value
N=117	59 (50.4%)	58 (49.6%)	
Gestational Age	38.8 (SD 1.31)	38.78 (SD 1.64)	0.843
Birth Weight	2954 (SD 441.32)	3117.6 (SD 662.57)	0.120
Male Gender	31 (52.5%)	25 (43.1%)	0.311
Apgar at 1 minute	8.52 (SD 0.8)	8.44 (SD 1.25)	0.690
Apgar at 5 minutes	8.91 (SD 0.28)	8.81 (SD 0.58)	0.215
Type of Feeding -Breastfeeding -Formula -Both -Unknown	 1 (1.7%) 52 (88.1%) 5 (8.5%) 0 (0%)	 6 (10.3%) 46 (79.3%) 4 (6.9%) 2 (3.4%)	 0.111
Max Morphine Dose (mg/kg/dose)	0.12 (SD 0.079)	0.14 (SD 0.167)	0.389

Table A. Descriptive Characteristics and Comparisons Between Treatment Groups. Values in parentheses represent percentages for categorical data. Independent Samples T-test with equal variances not assumed was used.

Factor	**β Coefficient (Unstandardized)**	**95% Confidence Interval**	**P Value**
Clonidine	-4.733	-9.09 to -0.367	0.034
Birth weight (Grams)	-0.001	-0.006 to 0.004	0.710
Gestational Age	1.576	-0.071 to 3.224	0.061
Feeding (Breastfeeding vs. Formula)	-2.194	-6.408 to 2.020	0.304

Table B. Factors Associated with Duration of Treatment in Infants Treated for NAS as Described by Regression Analysis. Vaginal delivery (VD). Cesarean Section (C/S).

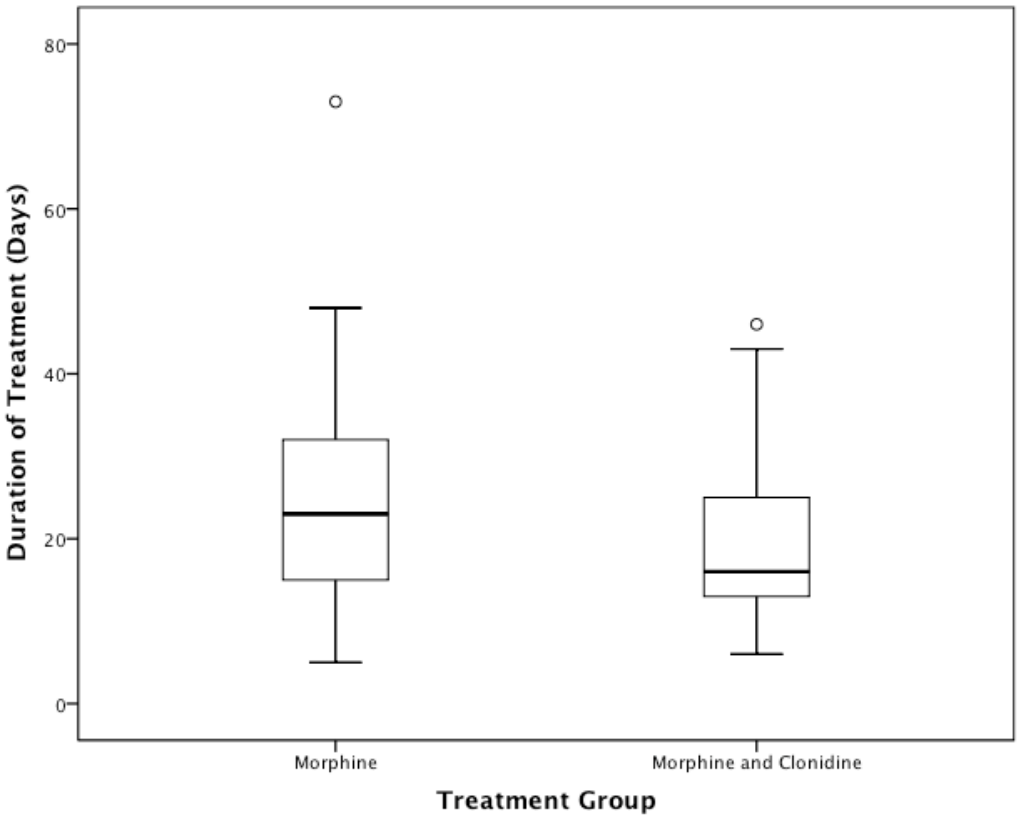


Figure 3. Duration of treatment in infants treated with diluted oral morphine sulfate or diluted oral morphine sulfate and diluted oral clonidine hydrochloride. Infants treated for NAS with morphine alone had a median duration of treatment of 22 (IQR: 13) and those with morphine and clonidine had a median duration of treatment of 16 (IQR: 13). These differences were statistically significant (p=0.011, Mann-Whitney *U*)

Discussion

Neonatal abstinence has been described and studied at length, yet the body of literature regarding its assessment and treatment has yielded conflicting and somewhat confusing results. As a result, clinical assessment and treatment of NAS varies widely. (11, 12) Several classes of drugs including opioids, benzodiazepines, barbiturates, and phenothiazines, have been studied and used alone or in combination for the treatment of NAS. (34, 52)

Clonidine, which had previously been used successfully in older children and adults for treatment of opioid withdrawal, has more recently been found to be useful in the treatment of infants with NAS. (43-51) Our finding that treatment with clonidine and morphine ameliorated symptoms of NAS and led to detoxification of infants more rapidly than treatment with morphine alone further supports the data that clonidine is an appropriate choice for the treatment of NAS when used as an adjunct to opioid therapy.

Clonidine is a desirable pharmacologic agent to use in the treatment of NAS because it is neither a sedative nor an opioid. By acting centrally on α-2-adrenergic receptors and inhibiting sympathetic outflow, clonidine works in parallel systems in the same neurons as opioids. (34, 41, 42) Additionally, clonidine is well absorbed after oral administration, and it is readily distributed in the central nervous system due to its lipid solubility. (53)

Clonidine, however, is not without side effects. The more common side effects of clonidine include hypotension, rebound hypertension, atrioventricular block, and bradycardia. In our study ten subjects failed treatment with clonidine due to bradycardia. Although rebound hypertension was not one of the data points we chose to specifically

examine, none of the infants treated with clonidine had rebound hypertension. There were also no incidences of rebound symptoms of NAS as seen in the Agthe *et al*. study. (51) This could be due, in part, to the stepwise reduction of clonidine over 48 hours, as well as weaning morphine completely before decreasing and subsequently discontinuing clonidine as part of our standard treatment protocol for NAS at YNHH.

The use of clonidine as an adjunct to opioid treatment for infants with moderate to severe NAS has larger social and economic implications. (54) Illicit drug use, and more specifically opioid use, remains a significant social problem in the United States. (1-8) Infants born with NAS require increased care including NICU observation, protracted treatment courses, prolonged postnatal hospital stays, and often extensive social work services while in the hospital. This increased need for and use of resources is also not without impact on cost. A study done by Dryden *et al*. investigated the factors associated with the development of NAS and assessed the implications for healthcare resources of infants with prenatal exposure to illicit substances. They found that 48.4 percent of infants born to women on methadone maintenance were admitted to the NICU. Infants born to drug-misusing mothers represented 2.9 percent of hospital births, but they occupied 18.2 percent of the total NICU spots for the period of the study. Furthermore, almost all women in the study were assigned a social worker during their pregnancy, and all families were assessed by the social work department prior to discharge from the hospital. (54) Thus, finding a treatment regimen that decreases the amount and duration of treatment for NAS could potentially alleviate at least some of the impact infants with prenatal exposure to illicit substances has on healthcare resources.

The study by Agthe *et al*. suggested a decreased need for opioids with the addition of clonidine for the treatment of opioid withdrawal. (51) Our analysis found no difference between the maximum doses of morphine required to control symptoms of NAS in either treatment group ($p > 0.05$). Our study looked retrospectively at infants treated over a six year period of time, and there was substantial variability in the attending physicians treating the infants and the pediatric nursing staff assessing the infants over that time period. This variability could have led to differences in scoring and treating NAS that impacted the overall quality of our data. Given the limitations of our study design as well as the paucity of data regarding the use of clonidine as an adjunct to opioid therapy for neonatal withdrawal, additional studies designed to specifically look at dosing requirements of opioids are needed to further clarify this. Additionally, not all opioids have the exact same mechanism of action in the brain, so even with the guidelines and recommendations that specify the use of opioids for NAS, randomized controlled trials looking at different opioid therapies with or without clonidine also need to be done.

All infants included in our study were exposed *in utero* to opioids, mainly heroin and/or methadone. This was confirmed by either maternal history as recorded in the medical record or toxicology studies if results were available in the medical record. Overall, doses of methadone that the mothers were taking at the time of delivery as reported in the medical records of their infants, ranged from 15mg to 195mg. Additionally, some of the women on methadone maintenance also had urine toxicology studies or their infants had urine toxicology studies that were positive for substances other than methadone, including but not limited to other opioids, cocaine and barbiturates. Due to the limitations of our chart review and the quality of data available

for the maternal history of drug use, data obtained regarding amounts of methadone and polydrug exposure was not subject to statistical analysis. There are studies to suggest that maternal self-report alone can be unreliable and often under-reports the extent of *in utero* exposure an infant has had, which is consistent with the small amount of data that we were able to collect during our review. (19, 20) An important thing to note, however, is that the subject population included in our study is heterogeneous with respect to prenatal exposures. Although having a subject population that is heterogeneous in prenatal exposure to illicit and prescribed substances complicates the characterization, treatment, and response to treatment of infants with NAS, it is more representative of the true patient populations that physicians are treating on a daily basis.

In addition to duration of treatment and maximum dose of morphine required to ameliorate symptoms of NAS, we secondarily examined birth weight, gestational age, gender, mode of delivery, Apgar scores at one and five minutes, and type of feeding. None of these additional factors were found to have a statistically significant relationship to the duration of treatment in either group. We also examined race, but 33 out of 117 subjects (28 percent) did not have this data available in their paper medical record, and thus due to the large portion of missing data, this was not included in our analysis.

Although we did not find a significant relationship between duration of treatment and gestational age, this is consistent with what we would expect given that gestational age was one of the factors that we controlled for in our study design. Gestational age of 36 weeks or greater was chosen because there is some data that suggests that preterm infants have a different neonatal course than infants born at term. (55, 56) One retrospective cohort study looking at 53 preterm and 66 term infants with similar *in utero*

exposure to methadone and other illicit substances found that preterm infants required lower doses of opioid and shorter courses of treatment to control symptoms of NAS. (55) Possible explanations for this differential course of NAS have been suggested and include the relative maturity or immaturity of the central nervous system in premature infants, or simply a decrease in length of *in utero* exposure of infants leading to a less severe clinical course.

Additionally, we did not see a significant impact on duration of treatment with mothers who breastfed. This could be in part due to the small numbers of mothers in our study population who breastfed. Only one mother (1.7 percent) in the morphine group breastfed exclusively, and five mothers (8.5 percent) supplemented breastfeeding with formula. Six mothers (10.3 percent) in the morphine/clonidine group exclusively breastfed, and four mothers (6.9 percent) supplemented breastfeeding with formula. The low numbers of mothers who breastfeed in this population could be due in part to the almost immediate separation of the mother and infant as the infant is taken to the NICU for observation and possible treatment initiation. Another reason could be the often complicated social situations of this patient population and not infrequent need for placement of the infants in foster care or in the care of a relative other than the mother.

Studies have been done that look specifically at the impact of breastfeeding on the severity of NAS and the duration of treatment of NAS. (54, 57, 58) One study by Abdel-Latif *et al*. found that breast milk intake was associated with reduction in severity of NAS and need for pharmacologic intervention regardless of gestational age or type of drug exposure. (57). Moreover, breastfeeding in mothers on methadone maintenance has been shown to be both beneficial and safe. (58).

Although our data did show a significant decrease in the duration of treatment for infants treated with both morphine and clonidine, our study was limited by design and sample size. Our data was limited to the information recorded in the medical records we reviewed which was varied. Not all subjects had urine toxicology studies, and maternal histories were limited to what was recorded at the time of delivery or obtained in the history from the mother. Race was often not recorded in the paper medical records, but could be found on result reports for the newborn screening test.

The study period of January 2003 to December 2009 was chosen specifically to capture both infants treated with morphine alone which was the standard treatment protocol at YNHH prior to 2006, and infants treated with both morphine and clonidine as was the standard treatment protocol from 2006 to the present. The study period spans six years. This was necessary in the design of the study to capture the desired data, however, it increases the potential for increased variability and less consistency in the data. Specifically, within the six years, the standard treatment protocol changed significantly, resident and attending physicians changed, and medical records changed from paper to electronic. Although there is increased potential for variability, the modified Finnegan scoring algorithm has remained the same, and the treatment protocol with morphine has also remained the same.

This retrospective medical record review supports the small but growing body of literature supporting safety and efficacy of clonidine for opiate detoxification in infants exposed *in utero* to opioids. Additional studies are indicated to look at long-term safety of clonidine, and randomized controlled trials are needed to further characterize the use of clonidine with different opioids.

Appendix A:
NEONATAL ABSTINENCE ASSESSEMENT SCORING
(MODIFIED FINNEGAN SCALE)

DATE:_____
DOSE: _____

		D	E	N
CENTRAL NERVOUS SYSTEM DISTURBANCES				
Irritability				
Which interferes with the infant's ability to sleep at least 2 hours after feeding	1			
Which interferes with the infant's ability to bottle feed (requiring gavage)	2			
Inconsolable while being held	3			
Mild Tremors Undisturbed	3			
Moderate-Severe Tremors Undisturbed	4			
Mild Tremors Disturbed	1			
Moderate-Severe Tremors Disturbed	2			
Increased Muscle Tone	2			
Excoriation (Describe location/size)	1			
METABOLIC/VASOMOTOR/RESPIRATORY DISTURBANCES				
Sweating	2			
Fever < 101 (37.2 - 38.3)	1			
Fever > 101 (≥ 38.4)	2			
Frequent Yawning	1			
Mottling	1			
Nasal Stuffiness	1			
Sneezing	1			
Nasal Flaring	1			
Respiratory Rate				
> 60/min	1			
> 60/min with retractions	2			
GASTROINTESTINAL DISTURBANCES				
Excessive Sucking	1			
Poor Feeding	2			
Regurgitation	2			
Projectile Vomiting	3			
Loose Stools	2			
Watery Stools	3			
	TOTAL			

24 HOUR TOTAL

Bibliography

1. Substance Abuse and Mental Health Services Administration. (2009). *Results from the 2008 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09-4434). Rockville, MD.

2. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. (October 4, 2007). *The NSDUH Report: Substance Use Treatment among Women of Childrearing Age*. Rockville, MD.

3. Schempf AH. Illicit drug use and neonatal outcomes: a critical review. *Obstet Gynecol Surv*. 2007 Nov;62(11):749-57. Review.

4. Luty J, Nikolau V, Beam J.. Is opiate detoxification unsafe in pregnancy? *J Subst Abuse Treat*. 2003;24:363–367.

5. Fricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. *Am J Dis Child*. 1978;132 (4):360 –366.

6. Harper RG, Solish GI, Purow HM, Sang E, Panepinto WC. The effect of a methadone treatment program upon pregnant heroin addicts and their newborn infants. *Pediatrics*. 1974;54 (3):300 –305.

7. Madden JD, Chappel JN, Zuspan F, Gumpel J, Mejia A, Davis R. Observation and treatment of neonatal narcotic withdrawal. *Am J Obstet Gynecol*. 1977;127 (2):199 –201.

8. Ostrea EM, Chavez CJ, Strauss ME. A study of factors that influence the severity of neonatal narcotic withdrawal. *J Pediatr*. 1976;88 (4pt1):642 –645.

9. Zelson C, Rubio E, Wasserman E. Neonatal narcotic addiction: 10 year observation. *Pediatrics*. 1971 Aug;48(2):178-89.

10. Kandall SR, Gartner LM. Late presentation of drug withdrawal symptoms in newborns. *Am J Dis Child*. 1974 Jan;127(1):58-61.

11. Sakar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national survey. *J Perinatol*. 2006 Jan 1;26(1):15-7.

12. O'Grady MJ, Hopewell J, White MJ. Management of neonatal abstinence syndrome: a national survey and review of practice. *Arch Dis Child Fetal Neonatal Ed*. 2009 Jul;94(4):F249-52.

13. American Academy of Pediatrics Committee on Drugs. Neonatal Drug Withdrawal. *Pediatrics*. 1998;101:1079-1088

14. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. *BMJ*. 1998 Aug 15;317(7156):465-8. Review.

15. Zagon IS. Opioids and development: new lessons from old problems. *NIDA Res Monogr*. 1985;60:58-77.

16. Bendersky M, Alessandri S, Gilbert P, Lewis M. Characteristics of pregnant substance abusers in two cities in the northeast. *Am J Drug Alcohol Abuse*. 1996 Aug;22(3):349-62.

17. Blinick G, Wallach RC, Jerez E, Ackerman BD. Drug addiction in pregnancy and the neonate. *Am J Obstet Gynecol*. 1976 May 15;125(2):135-42.

18. Levy M, Spino M. Neonatal withdrawal syndrome: associated drugs and pharmacologic management. *Pharmacotherapy*. 1993 May-Jun;13(3):202-11. Review.

19. Kuschel C. Managing drug withdrawal in the newborn infant. *Semin Fetal Neonatal Med*. 2007 Apr;12(2):127-33. Epub 2007 Feb 23. Review.

20. Ostrea EM Jr, Knapp DK, Tannenbaum L, Ostrea AR, Romero A, Salari V, Ager J. Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. *J Pediatr*. 2001 Mar;138(3):344-8.

21. Kandall SR, Doberczak TM, Jantunen M, Stein J. The methadone-maintained pregnancy. *Clin Perinatol*. 1999 Mar;26(1):173-83. Review.

22. Gottheil E, Sterling RC, Weinstein SP. Diminished illicit drug use as a consequence of long-term methadone maintenance. *J Addict Dis*. 1993;12(4):45-57.

23. Chambers, CD, Taylor A. 1972. Patterns of "Cheating" among methadone patients. In *Drug Abuse: Current Concepts and Research*. Kewp, W Ed, Thomas Pub., Springfield, Ill.

24. Leifer ED, Goldman J, Finnegan LP. Prevalence and implications of multi-drug abuse in a population of methadone-maintained women. *NIDA Res Monogr*. 1983 Apr;43:322-8.

25. Finnegan LP. Discussion: dilemmas in research in perinatal addiction—intervention issues. *NIDA Res Monogr*. 1992;117:344-8. Review.

26. van Sleuwen BE, Engelberts AC, Boere-Boonekamp MM, Kuis W, Schulpen TW, L'Hoir MP. Swaddling: a systematic review. *Pediatrics*. 2007 Oct;120(4):e1097-106. Review.

27. Abrahams RR, Kelly SA, Payne S, Thiessen PN, Mackintosh J, Janssen PA. Rooming-in compared with standard care for newborns of mothers using methadone or heroin. *Can Fam Physician*. 2007 Oct;53(10):1722-30.

29. Velez M, Jansson LM. The Opioid dependent mother and newborn dyad: non-pharmacologic care. J Addict Med. 2008 Sep 1;2(3):113-120

29. van Baar AL, Fleury P, Soepatmi S, Ultee CA, Wesselman PJ. Neonatal behavior after drug dependent pregnancy. *Arch Dis Child*. 1989 Feb;64(2):235-40.

30. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2(1-2):141-58.

31. Finnegan L, Connaughton JJ, Kron, R. 1995. A scoring system for evaluation and treatment of the neonatal abstinence syndrome: a new clinical and research tool. In *Basic and Therapeutic Aspects of Perinatal Pharmacology*. Marselli P, Garanttini S, Sereni F, eds. New York, NY: Raven. 139-152.

32. Lipsitz PJ. A proposed narcotic withdrawal score for use with newborn infants. A pragmatic evaluation of its efficacy. *Clin Pediatr (Phila)*. 1975 Jun;14(6):592-4.

33. Zahorodny W, Rom C, Whitney W, Giddens S, Samuel M, Maichuk G, Marshall R. The neonatal withdrawal inventory: a simplified score of newborn withdrawal. *J Dev Behav Pediatr*. 1998 Apr;19(2):89-93.

34. Johnson K, Gerada C, Greenough A. Treatment of neonatal abstinence syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2003 Jan;88(1):F2-5. Review.

35. Osborn, DA, Jeffery, HE, Cole, MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database Syst Rev 2005; CD002053

36. Osborn, DA, Jeffery, HE, Cole, M. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database Syst Rev 2005; CD002059

37. Beitner DB, Duman RS, Nestler EJ. A novel action of morphine in the rat locus coeruleus: persistent decrease in adenylate cyclase. *Mol Pharmacol*. 1989 May;35(5):559-64.

38. Duman RS, Tallman JF, Nestler EJ. Acute and chronic opiate-regulation of adenylate cyclase in brain: specific effects in locus coeruleus. *J Pharmacol Exp Ther*. 1988 Sep;246(3):1033-9.

39. Di Chiara G, North RA. The neurobiology of opiate abuse. *Trends Pharmacol Sci*. 1992 May;13(5):185-93. Review.

40. Little PJ, Price RR, Hinton RK, Kuhn CM. Role of noradrenergic hyperactivity in neonatal opiate abstinence. *Drug Alcohol Depend*. 1996 May;41(1):47-54.

41. Houston MC. Clonidine hydrochloride. *South Med J*. 1982 Jun;75(6):713-9. Review.

42. Sica DA. Centrally acting antihypertensive agents: an update. *J Clin Hypertens* (Greenwich). 2007 May;9(5):399-405. Review.

43. Fishbain DA, Rosomoff HL, Cutler R. Opiate detoxification protocols. A clinical maual. *Ann Clin Psychiatry*. 1993 Mar;5(1):53-65.

44. Gold MS, Pottash AC, Sweeney DR, Kleber HD. Opiate withdrawal using clonidine. A safe, effective, and rapid nonopiate treatment. *JAMA*. 1980 Jan 25;243(4):343-6.

45. Gold MS, Redmond DE Jr, Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet*. 1978 Sep 16;2(8090):599-602.

46. Gold MS, Redmond DE Jr, Kleber HD. Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Am J Psychiatry*. 1979 Jan;136(1):100-2.

47. Fishbain DA, Rosomoff HL, Rosomoff RS. Detoxification of nonopiate drugs in the chronic pain setting and clonidine opiate detoxification. *Clin J Pain*. 1992 Sep;8(3):191-203. Review.

48. Yaster M, Kost-Byerly S, Berde C, Billet C. The management of opiod and benzodiazepine dependence in infants, children, and adolescents. *Pediatrics*. 1996 Jul;98(1):135-40. Review.

49. Hoder EL, Leckman JF, Poulsen J, Caruso KA, Ehrenkranz RA, Kleber HD, Cohen DJ. Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res*. 1984 Nov;13(3):243-51.

50. Leikin JB, Mackendrick WP, Maloney GE, Rhee JW, Farrell E, Wahl M, Kelly K. Use of clonidine in the prevention and management of neonatal abstinence syndrome. *Clin Toxicol (Phila)*. 2009 Jul;47(6):551-5

51. Agthe AG, Kim GR, Mathias KB, Hendrix CW, Chavez-Valdez R, Jansson L, Lewis TR, Yaster M, Gauda EB. Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. *Pediatrics*. 2009 May; 123(5):e849-56.

52. Theis JG, Selby P, Ikizler Y, Koren G. Current management of the neonatal abstinence syndrome: a critical analysis of the evidence. *Biol Neonate*. 1997;71(6):345-56. Review.

53. Timmermans PB, Brands A, van Zwieten PA. Lipophilicity and brain disposition of clonidine and structurally related imidazolidines. *Naunyn Schmiedebergs Arch Pharmacol*. 1977 Nov;300(3):217-26.

54. Dryden C, Young D, Hepburn M, Mactier H. Maternal methodone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *BJOG*. 2009 Apr;116(5):665-71. Epub 2009 Feb 10.

55. Dysart K, Hsieh HC, Kaltenbach K, Greenspan JS. Sequela of preterm versus term infants born to mothers on a methodone maintenance program: differential course of neonatal abstinence syndrome. *J Perinat Med*. 2007;35(4):344-6.

56. Doberczak TM, Kandall SR, Wilets I. Neonatal opiate abstinence syndrome in term and preterm infants. J Pediatr. 1991 Jun;118(6):933-7.

57. Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. *Pediatrics*. 2006 Jun;117(6):e1163-9.

58. Jansson LM, Choo R, Velez ML, Harrow C, Schroeder JR, Shakleya DM, Huestis MA. Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics*. 2008 Jan;121(1):106-14.