

Neonatal Abstinence Syndrome



- The well being of the infant is improved with the well being of the mother

Neonatal Abstinence Syndrome

- n NAS was first described in the 1950's as the narcotic abstinence syndrome
- n NAS is the occurrence of opioid withdrawal at birth after the discontinuation of opioid exposure in-utero
- n Concomitantly, as treatment for opioid dependent pregnant women emerged, so also did treatment for NAS

Neonatal Abstinence Syndrome



- Central nervous system hyperirritability
hyperactivity, irritability, sleep disturbance, tremors

- Gastrointestinal dysfunction
uncoordinated sucking/swallowing, vomiting

- Autonomic Signs
fever, sweating, nasal stuffiness



Treated baby

Neonatal Abstinence Syndrome

- n Due to the significant increase in prescription opioid use and misuse over the past decade, there has been an unprecedented focus on NAS in the past 5 years.
- n Policies often reflect a lack of understanding of the factors that impact both the presentation and severity

NAS as a Reportable Disease

- n For example, some states have begun to include NAS as a reportable disease
- n The criteria for reporting NAS in Georgia requires **one** of the following
 - ❖ Baby born to a mother with a history of substance abuse during pregnancy
 - ❖ Newborn with withdrawal symptoms
 - ❖ Newborn with a positive drug screen

Context of NAS

- n We tend to think of NAS **only** as a linear effect

Prenatal opioid exposure → NAS → Consequences

- n However, although the withdrawal is an outcome of opioid exposure, **the presentation and severity of NAS** is related to a number of factors that must be taken into consideration in our understanding of NAS

Confounding the Issue of NAS is Context

- n Illicit vs. appropriate use of prescribed medication
- n Role of non-opioid drug exposure
- n Gestational age
- n Genetics
- n Role of the treatment environment

Illicit vs. Appropriate Use of Treatment Medications

n Illicit opioid use:

- ❖ Heroin, prescription misuse which may include methadone, buprenorphine, oxycodone, hydrocodone

n Appropriate opioid use:

- ❖ Methadone and buprenorphine for the treatment of women with opioid use disorders who are pregnant
- ❖ The use of oxycodone, hydrocodone for pain management when necessary

Illicit vs. Appropriate Use of Treatment Medications

- Presentation and severity differ within opioids:
 - ❖ Heroin: onset 4-24 hours, NAS less severe than methadone (Zelson et al., 1971)
 - ❖ Methadone*: 48-72 hours
 - ❖ *Buprenorphine**: on average almost 24 hrs. later than methadone, NAS less severe than methadone (Jones et al., 2010)
 - ❖ Oxycodone/hydrocodone: No data

*Has not been found to be related to maternal dose

Consequences of Illicit Use

n Illicit opioid use

- ❖ Fetus subjected to repeated episodes of maternal withdrawal increasing morbidity and mortality
- ❖ Mother may receive little/no prenatal care and have untreated medical/obstetrical complications
- ❖ Increased risk of prematurity, morbidity and mortality

Consequences of MAT

- n The use of methadone and buprenorphine for the treatment of opioid dependent pregnant women
 - ❖ Prevents erratic maternal opioid levels and protects the fetus from repeated episodes of withdrawal
 - ❖ Associated with improved obstetrical care, increased fetal growth, and reduced fetal and neonatal mortality and morbidity
 - ❖ Supports and sustains recovery
 - ❖ Maternal dose has not been found to be related to NAS

Presentation and Severity of NAS

- n Presentation and severity of NAS is also related to:
 - ❖ Other prenatal drug exposure both illicit (cocaine), licit (**alcohol, nicotine**) and prescription medications (**SSRI's and benzodiazepines**)
 - ❖ Genetics
 - ❖ Maternal physiology
 - ❖ Gestational age

Non-opioid Drugs Which May Impact NAS Severity

- n Cause behaviors consistent with NAS but do not require treatment
 - Alcohol
 - Benzodiazepines
 - SSRI's
- n Combined with opioid exposure can exacerbate NAS
 - Alcohol
 - Benzodiazepines
 - SSRI's
 - Nicotine

MOTHER Secondary Analysis

Secondary analysis study:

Predicting Treatment for Neonatal Abstinence Syndrome in Infants Born to Women Maintained on Opioid Agonist Medication (Kaltenbach et al., 2012)

Purpose:

To delineate factors, in addition to buprenorphine or methadone, which predict the expression of NAS severity in infants

Predictor Variables

Predictor variables selected for examination included:

- Maternal maintenance dose at delivery
- Number of days mother received study medication
- Mother's use of anxiolytics or hypo-sedative medications
- Mother's use of psychiatric medications including antidepressants, serotonin reuptake inhibitors (SSRIs), and/or antipsychotic medications during pregnancy
- Number of cigarettes smoked 24 hours prior to delivery
- Maternal weight at delivery
- Delivery type (vaginal or cesarean)
- Estimated gestational age (EGA) at delivery
- Infant birth weight

Predictors of NAS

Predicted higher peak NAS scores

- Lower maternal weight at delivery p=0.03
- Later estimated gestational age p=0.04
- Maternal use of SSRIs p=0.002
- Vaginal delivery p=0.05
- Higher infant birth weight p=0.0002

Predicted receipt of NAS treatment for infants

- Higher infant birth weight p=0.009
- Greater maternal tobacco use at delivery p=0.03

Predictors of NAS

Predicted total dose of medication required to treat NAS symptoms

- Maternal use of SSRIs (p=0.02)
- Higher tobacco use (p=0.05)
- Fewer days of study medication received (p=0.008)

Benzodiazepines and NAS

Benzodiazepine use in methadone and buprenorphine maintained pregnant women have been found to be related to **prolonged length of stay for infants requiring treatment for NAS**

- ❖ Seligman et al., 2008
- ❖ Wachman et al., 2011
- ❖ Pritham et al., 2012

SSRI's and NAS

- n SSRI use in pregnant women maintained on methadone or buprenorphine have been found to be related to:
 - ❖ Higher peak NAS scores (Kaltenbach et al., 2012)
 - ❖ Higher doses of medication for infants requiring treatment (Kaltenbach, et al., 2012; Jansson et al., 2010)
 - ❖ Unrelated to length of treatment (Kaltenbach et al., 2012; Wachman et al., 2011) (Dryden et al., 2009; Seligman et al., 2008 methadone only)

Tobacco and NAS

- n Heavy smoking in pregnant women maintained on methadone or buprenorphine has been found to be related to:
 - ❖ Peak NAS score and amount of time to reach peak NAS score (Choo et al., 2004)
 - ❖ Increased severity of NAS (Winklbaur et al., 2009)
 - ❖ Longer duration of treatment for methadone exposed infants but not buprenorphine exposed infants (Bakstad et al., 2009)
 - ❖ Past 30-day daily average number of cigarettes smoked related to total amount of morphine needed to treat NAS, duration of treatment, and length of hospitalization (Jones, et al., 2013)

Gestational Age and NAS

- n Effect of preterm delivery on the course of NAS:
 - ❖ First reported in 1991 by Doberczak et al., who found that preterm infants born to women maintained on methadone required treatment for NAS less often and displayed less CNS symptoms compared to term infants
 - ❖ Dysart et al., 2007 found differences in NAS treatment outcomes for preterm and term infants born to methadone maintained women. Preterm infants had shorter treatment courses, required less medication and had shorter length of stay
 - ❖ Ruwanpathirana et al., 2014 reported low NAS scores and less treatment among preterm infants compared to term infants.

Genetics and NAS

- n Recent work by Dr. Elisha Wachman and colleagues has been progressively examining whether genetic factors play a role in the incidence and severity of NAS and have found:
 - ❖ Among infants prenatally exposed to methadone or buprenorphine, variants in the OPRM1 and COMT genes were associated with shorter length of hospital stay and less need for treatment (Wachman et al., 2013)
 - ❖ Higher methylation levels within the OPRM1 promoter were found in infants requiring ≥ 2 medications to treat NAS (Wachman et al., 2014)
 - ❖ SNPs in opioid receptors and PNOC genes are associated with severity of NAS (Wachman et al., 2015)

Genetics and NAS

- n Emerging findings require further study but suggest that genetic factors play an important role in the presentation of NAS

Postnatal Factors that Affect NAS

- n Treatment of NAS impacted by:
 - ❖ Assessment protocol
 - ❖ Medication used for treatment, weaning protocols
 - ❖ Breastfeeding
 - ❖ Treatment environment
- n There is **significant variability** in hospital policies and practices that determine both the diagnosis and treatment of NAS

Assessment of NAS

- n Finnegan LP, Kron RE, Connaughton JF, Emich JP (1975). A scoring system for evaluation and treatment of the neonatal abstinence syndrome: A clinical research tool.
- n Lipsitz PJ (1975) A proposed narcotic withdrawal score for use with newborn infants.
- n Green M, Suffet F (1981) The neonatal narcotic index: A device for the improvement of care in the abstinence syndrome.
- n Ostrea EM (1976/1993) Infants of drug-dependent mothers

NAS Scoring Systems

- n Zahorodny W, Rom C, Whitney W, et al. (1998)
The Neonatal Withdrawal Inventory: A simplified score of newborn withdrawal
- n MOTHER NAS scale (2010)
A modification of the Finnegan Score (some items were removed due to overlap with other items or because they do not respond to treatment with opioids and 2 items were added)

Finnegan Scoring Tool

- n Majority of NICUs in the USA use the Finnegan Score
- n The Lipsitz Neonatal Drug Withdrawal Scoring System is used in some institutions but is not represented in the current literature. THE MOTHER NAS Scale is the standard instrument used in a number of clinical trials
- n However the majority of those that used the Finnegan 67% used “**the modified version**”
(Sarkar and Doun, Journal of Perinatology, 2006)
- n Confusion exists regarding “the” and “a” modified Finnegan

Use of Assessment Tool

- n Most important elements:
 - ❖ Use of operational definitions for items
 - ❖ Maintain high inter-rater reliability

Use of Standardized Weaning Protocols

- n Recent studies have found:
 - ❖ Utilizing a standard NAS treatment and weaning protocol for either morphine or methadone reduced duration of treatment and length of hospital stay
(Hall et al., Pediatrics, 2014)
 - ❖ Staff education and the use of a standardized morphine protocol reduced length of stay
(Asti et al., Pediatrics, 2015)
 - ❖ Use of explicit weaning guidelines resulted in shorter duration of treatment, length of stay and lower rate of adjunctive drug therapy
(Hall et al., Pediatrics, 2015)

Treatment for NAS

- Pharmacological Management

- Paregoric
- Tincture of opium
- Morphine
- Methadone
- Phenobarbital
- Clonidine
- Chlorpromazine
- Diazepam

Pediatrics, Vol. 101 No.6 June 1998

- Very few studies compare the efficacy of different medications in the treatment of NAS

Current Recommendation

- AAP 2012
 - “Limited evidence from controlled trials supports the use of morphine and methadone”
- Available efficacy evidence from controlled trials is extremely limited

Clinical Trial Data for Treatment for NAS

n Buprenorphine vs. morphine

Double blind, double dummy RCT

Duration of treatment significantly shorter with buprenorphine (*NEJM, 2017*)

n Methadone vs. morphine

Multisite RCT, expected completion date Dec, 2017

n Clonidine vs. morphine

Small pilot trial

Duration of treatment significantly shorter with Clonidine

Breastfeeding and NAS

- n Breastfeeding has been found to **decrease NAS scores, need for treatment, length of treatment, and length of hospital stay**

(Abel-Latif et al., 2006; Pritham et al., 2012, Wachman e al., 2013, Welle-Strand et al., 2013)

- n The presence of drug in breast milk is minimal and the effect is thought to be due to the interactive and comforting aspects of breastfeeding

Breastfeeding in Methadone Treated Mothers in Recovery



- Methadone detected in breast milk in very low levels
- Methadone concentrations in breast milk are unrelated to maternal methadone dose
- The amount of methadone ingested by the infant is low
- Hepatitis C is not a contraindication for breastfeeding
- **Contraindications: HIV+, illicit drug use, unstable recovery**
- AAP 2012; McQueen et al., 2011; Jansson et al., 2007; Jansson et al., 2010

Breastfeeding in Buprenorphine Treated Mothers in Recovery

- Buprenorphine is found in breast milk 2 hours post-maternal dosing
- Concentration of buprenorphine in breast milk is low
- Amount of buprenorphine or norbuprenorphine the infant receives via breast milk is only 1%
- Most recent guidelines: “the amounts of buprenorphine in human milk are small and unlikely to have negative effects on the developing Infant”

Atkinson et al., 1990; Marquet et al., 1997; Johnson, et al., 2001; Grimm et al., 2005; Lindemalm et al., 2009; Jansson et al., 2009; Müller et al., 2011

Breastfeeding and MAT

- n Mothers receiving methadone or buprenorphine for the treatment of OUD who are engaged in treatment and do not have any contraindications should be encouraged and supported in breastfeeding
 - ❖ Academy of Breastfeeding Medicine, 2009 and 2015
 - ❖ The American Society of Addiction Medicine, 2012 and
 - ❖ The World Health Organization 2014

Summary

- n There are a number of factors that impact the severity of NAS including the in-utero interaction of opioids and non-opioids
- n Genetic and epigenetic factors appear to play a role in the variability of NAS
- n There are a number of postnatal caretaking and environmental factors that may minimize NAS
- n NAS is a complex phenomenon and it's use as an indicator of neonatal harm should be considered prudently