Neonatal Abstinence Syndrome: Understanding the Variations in Expression and Mitigating Them

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Disclosures

• To the best of my knowledge, I have no relevant disclosures.
• Information presented derives from relevant research within the literature and accepted protocols based on research accomplished by me and others.

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.
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Accreditation Statement

- The American Society of Addiction Medicine (ASAM) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
Designation Statement

- The American Society of Addiction Medicine (ASAM) designates this enduring material for a maximum of one (1) AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

- Date of Release March 17, 2015
- Date of Expiration July 31, 2016
System Requirements

• In order to complete this online module you will need Adobe Reader. To install for free click the link below:
  ▪ http://get.adobe.com/reader/
Target Audience

• The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.
Educational Objectives

At the conclusion of this activity participants should be able to:

- Know the symptoms of neonatal abstinence syndrome (NAS)
  - Be aware of which vital functions are disrupted by neonatal abstinence symptoms
- In unrecognized/untreated NAS, issues that can lead to death in the baby
  - Conditions that could affect the onset of NAS?
  - The persistent symptoms of NAS
  - Effect of dose of methadone on expression of NAS
  - The challenges of methadone dosing in pregnant women
  - The causes of variability in NAS expression
Tommy was born to Janet who had been dependent on heroin and prescription opioids for a long time. As soon as she realized that she was pregnant, she was motivated to enroll in a comprehensive drug treatment program. The clinic was very user friendly especially for women and those that are pregnant. The entire pregnancy treatment plan was dedicated to assure a healthy pregnancy with the outcome to be a healthy baby. Janet was ordered methadone once daily, but also counseling concerning her addiction, as well as numerous classes on mothering, child development and practical management of the family after the child was born. The doctor explained that methadone was the best medication for her because of her history of addiction even though a medication called buprenorphine was found to be efficacious.
Baby Tommy (con’t)

- The pregnancy went smoothly and Janet delivered at term a healthy 3500 gram little boy that she named Tommy. Since about 60-80% of babies exposed to methadone experience abstinence in the neonatal period, Tommy was at risk for this condition. On the second day of life, he began to demonstrate symptoms that soon necessitated treatment. His withdrawal was fairly severe and prolonged but the doctors were able to control the symptoms and eventually wean Tommy off morphine. Janet was very attentive to the baby while he was in the hospital and visited daily after her discharge. Tommy came home when he was 3 weeks old but he still had some of the symptoms to a mild degree. Since Janet had received training in how to use supportive measures for these symptoms, the baby did well.
In spite of serious morbidities in opioid exposed neonates, the issue that is of most concern for the mothers, caretakers and nursery staff is Neonatal Abstinence Syndrome.
Psychoactive drugs easily pass from mother to fetus…Cutting the umbilical cord interrupts the drug supply creating the chance for neonatal abstinence
Neonatal Abstinence Syndrome: a potentially serious medical condition

- Affects vital functions in the neonatal period that permit growth and normalcy such as:
  - feeding
  - elimination
  - sleep
- Symptoms mimic other serious neonatal conditions
Serious neonatal conditions that may present with symptoms similar to NAS…

- Septicemia, encephalitis, meningitis
- Post-anoxic CNS irritation
- Hypoglycemia
- Hypocalcemia
- Cerebral hemorrhage
What Neonatal Abstinence is NOT!

- “Born Addicted”
- “Hooked Newborns”
- “Littlest Victims”
- “Heroin Babies”
- “Addicted Babies”
- “Oxy Babies”
- “Oxy Tots”
- “Tiny Addict”
- “Methadone or Bup Babies”
• To call babies "addicted" is stigmatizing and incorrect
• Babies don't have compulsive substance seeking behavior in spite of adverse consequences.
• They do have a transient but potentially serious physiologic disturbance from abrupt discontinuation of prenatal opioid exposure when the umbilical cord is cut.
Can Neonatal Opioid Abstinence cause death of a newborn infant?

Unrecognized/untreated NAS can result in death from:

- excess fluid losses
- hyperpyrexia, seizures
- respiratory instability
- aspiration and apnea
- But NOT in 2014
Signs and Symptoms of Neonatal Opioid Abstinence

- **Central Nervous System** (irritability, high pitched cry, tremors, hypertonia, hyperreflexia, sleep disturbances)
- **Gastrointestinal System** (regurgitation, loose stools, dysrhythmic sucking and swallowing, poor intake with weight loss)
- **Respiratory System** (excessive secretions, nasal stuffiness, tachypnea)
- **Autonomic Nervous System** (sweating, sneezing, yawning, hyperthermia)
Factors Affecting ONSET of Neonatal Opioid Abstinence

- Type of drug utilized by the mother (*heroin vs methadone*)
- Maternal poly-drug use (*variable onsets*)
- Timing of the dose of opioid before delivery (*sooner or later*)
- Character of the labor (*short vs. long*)
- Type and amount of anesthesia and analgesic given during labor and delivery (*epidural-less interference*)
- Maturity of the infant (*term vs. preterm*)
- Nutritional status of the infant (*term vs. intrauterine growth restriction*)
- Presence of intrinsic disease (*the sick infant*)
Can a Newborn Have Opioid Abstinence Symptoms at Birth?

Administration of opioid antagonists in the delivery room is followed by very severe symptoms of neonatal abstinence.
Persistent Signs of Neonatal Opioid Abstinence
(Duration may be as long as 6 months and more)

- Hyperphagia with increased oral drive
- Sweating
- Hyperacusis
- Irregular sleep patterns
- Loose stools
- Poor tolerance to holding or to abrupt changes of position in space
Maternal Medication Therapy with Methadone or Buprenorphine and Neonatal Abstinence
COULD METHADONE DOSE AND DOSE REGIMEN HAVE AN EFFECT ON NEONATAL ABSTINENCE SYNDROME?

SUMMARY AND HYPOTHESES BY JACK MCCARTHY, M.D., UCD, 2014
A POPULAR BELIEF: “DOSE OF METHADONE INFLUENCES THE INCIDENCE AND SEVERITY OF NEONATAL ABSTINENCE”

BUT WHAT DOES THE DATA SHOW?
Methadone and Neonatal Abstinence Severity

Evidence-based studies show no association between NAS severity and:

- Maternal methadone dose
- Trimester of methadone initiation
- Duration and amount of methadone exposure
- Duration of maternal drug use prior to pregnancy
- No apparent relationship between maternal methadone dose (10-100 mg/day) and frequency or severity of abstinence associated seizures

(Numerous authors: CLEARY, McCarthy, Berghella, Newman, Kandall, Kaltenbach, Herzlinger)
What is the Goal of Methadone Dosing in Pregnancy vis a vis the Fetus?

Is it to protect the fetus from methadone? i.e., use low doses or reduced doses and have the mother endure withdrawal, even at the risk of relapse, in order to reduce risks of NAS.

Or is it to protect the fetus from withdrawal? i.e., treat maternal withdrawal with dose increases to protect the fetus from Intrauterine Abstinence Syndrome (IAS).

McCarthy, JJ, Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone taper: can we assure the safety of the fetus? The Journal of Maternal-Fetal and Neonatal Medicine, Volume 25, Number 2, February 2012, pp. 109-112(4)
Methadone Dosing in Pregnancy is “Idiosyncratic”, i.e. Lacks Standardization (Hayes 2012)

Meta-analysis of 67 studies of methadone dosing in pregnancy reported 4 different approaches to dosing. (Cleary et al, 2010)

1. attempted withdrawal
2. maintenance on low doses
3. maintenance and then reduced doses later in pregnancy
4. dose increases as needed to treat maternal withdrawal (the correct approach)

Meta-analysis found no relationship between dose and severity of NAS

All but one of 67 studies used single methadone doses;

High doses, given as a single dose, may expose the fetus to problematic peak/trough changes. (McCarthy)
The Challenge of Methadone Dosing in Pregnancy

- There is significant genetic diversity for the enzymes that metabolize methadone (3A4, 2D6) resulting in different individual metabolic rates (Eap 1999).
- Pregnancy accelerates methadone metabolism. CYP3A is consistently and significantly increased in all stages of pregnancy. (Tracy et al, 2005)
- Absolute clearance of methadone is greater during pregnancy than post-partum (Pond 1985)
- Methadone elimination is significantly more rapid for pregnant compared to non-pregnant patients (half-life 19 vs. 36 hrs). (Jarvis et al, 1999)
- Serum methadone dilution and perhaps decreased absorption as pregnancy progresses decreases effective serum levels. (Jarvis, 1999)
Do Different Methadone Dosing Practices Affect NAS Severity?

The fetus is exposed to the **serum level, not the oral dose**. If methadone is cleared rapidly then the dose can be quite high and yet fetal exposure quite low.

• Different dosing practices may effect NAS and partially explain the extreme variability of NAS severity. Rates of RX for NAS in different studies range between 13-93%. (Cleary 2010)
• If maternal withdrawal equates with fetal withdrawal (Kenner and Lott 2007), can maternal withdrawal, or under-dosing, or even single dosing during treatment sensitize the fetus to withdrawal (Rothwell 2010) or otherwise compromise fetal health, i.e. stress the fetus during development?
Could Single Doses of Methadone be Problematic for the Fetus? Evidence?

- Significant behavioral abnormalities were found on ultrasound with single doses, i.e., increased activity before and significant depression after the AM dose. Ultrasounds normalized on a BID regimen. *Are these daily episodes of fetal ‘withdrawal’ causing significant fetal stress?* (Whitman and Segal 1991)

- Fetal cardiac rhythm parameters were found to be abnormal on single doses but to improve on a BID regimen. (Jansen et al 2011)
The Rationale for Methadone Split Dosing

• More sustained plasma levels are achieved with BID dosing than by increasing single doses; This produces 90% higher plasma trough levels and fewer withdrawal symptoms in mother and infant (Swift 1989).

• Increased doses and dose intervals are recommended to compensate for the pharmacodynamic and pharmacokinetic changes in pregnancy. Jarvis (1999) and Pond (1985)

Can more sustained fetal serum levels with multiple daily dosing protect fetal health by preventing problems at both peak and trough serum levels and consequently reduce risks for NAS?
The MOTHER Study

- **MOTHER** is an important contribution to the literature on opioid addiction treatment in pregnancy.
- The research was a multi-site, international, randomized trial.
- The study was carefully done with rigid standards and monitoring.
- The investigators were well qualified and experienced in addiction, pregnancy or both.

- **Primary outcomes relevant to the newborn:** Treated for NAS; NAS peak score; total amount of morphine; Infant hospital stay in days; Head circumference;
- **MOTHER** had stringent eligibility criteria not always practical for clinical situations;
Methods
MOTHER Study I

• All pregnant women in the study initially received rapid-release-morphine sulfate to prevent withdrawal.

• Participants completed a comprehensive screening assessment battery characterizing their obstetrical, medical, and psychiatric health.

• Randomized to methadone or buprenorphine and transitioned to double-blind, double-dummy study medication administered daily, under supervision, with sublingual tablets (buprenorphine or placebo) followed by oral liquid (methadone or placebo).
Methods
MOTHER Study II

- Flexible dose range of 2 to 32 mg of buprenorphine (Subutex) and 20 to 140 mg of methadone was used
- To reduce concomitant drug use: monetary vouchers for providing urine samples thrice weekly that tested negative for opioids and other illicit drugs
Methods
MOTHER Study III

Using a modified Finnegan Scale, all neonates were repeatedly evaluated for NAS for a minimum of 10 days by trained staff – fixed morphine dose depended on the score. *(Heterogenous across sites with regard to scoring & treatment intervals)*
The MOTHER Study
Maternal Results

• No significant differences with regard to safety and efficacy of MM or BUP in the treatment of opioid dependence in pregnancy.
• No significant difference in the rates of opioid use during treatment with either medication.
• Low levels of concomitant use of alcohol and illicit drugs, in the presence of comprehensive care, showed that both medications improved maternal outcomes.
• Differing rates of attrition between the medications largely due to dissatisfaction with BUP in which attrition was greater than that with MM.
The MOTHER Study
Neonatal Results

• No significant differences in: Overall rates of NAS needing treatment, peak NAS score, and head circumference –RX: 57% (M) vs. 47% (B)**

• Reduction of severity of NAS in buprenorphine exposed neonates defined as: Total amount of morphine needed in mg, length of hospital stay and number of days for treatment. **These parameters are inter-related;

• Differences in the outcomes for NAS treatment (METH  --BUP  ) and severity (METH  -- BUP  ) were found in urban, rural and European sites

Neonatal Abstention Syndrome-MOTHER Study Site differences

Baewert et al.; Eur Addict Res 2012;18:130-139

All Sites (n = 68; 52%)

Urban (n = 28; 51%)

Europe (n = 28; 76%)

Rural (n = 12; 31%)

Treatment NAS Meth (x10) Treatment NAS Bup (x10)

NAS: p=0.001, Treatment: p=0.001

NAS: p=0.189, Treatment: p=0.073

NAS: p=0.234, Treatment: p=0.126

NAS: p=0.006, Treatment: p=0.005
Why is there so much variability in the expression of abstinence in different neonates?
Onset and Severity of NAS Symptoms Vary in Infants of Different Gestational Ages
(TM Doberczak and S Kandall, J. Peds., 1991)

In TERM babies more severe, more treatment needed, peak severity earlier, less seizures;
Decreased NAS in PRE-TERM babies may be due to decreased total exposure or developmental immaturity of the CNS (immaturity of either dendritic ramifications, specific opiate receptors or neurotransmitter function)
Plasma methadone level and severity of withdrawal

Rate of decline of neonatal plasma methadone level from day 1 to day 4 of life influenced the severity of withdrawal.

(Rosen & Pippenger, J.Pediatrics, 1976; Doberczak et al, Obs & Gyn, 1993)
INFANTS BORN TO METHADONE MAINTAINED MOTHERS WHO SMOKED 20 OR MORE CIGARETTES PER DAY HAD SIGNIFICANTLY HIGHER NAS PEAK SCORES AND TOOK LONGER TO PEAK THAN LIGHT SMOKERS OF 10 OR FEWER CIGARETTES PER DAY.

Maternal Autonomic Regulation and Neonatal Opioid Abstinence

- Characteristics of maternal autonomic regulation may predispose infants to increased NAS expression
- Increased maternal vagal lability in response to methadone produced infants more likely to have severe NAS

Jansson, 2007
Postnatal *Environment* and NAS Severity

- The opioid exposed baby is usually separated from the mother, admitted for observation in a quiet, dimly lit environment, or more likely to a NICU and treated for abstinence, if necessary.
- Separation from the mother and sensory deprivation have not been studied as independent predictors of improvement in NAS.
- Separation might contribute to increased NAS symptoms, decreased maternal attachment and neonatal abandonment.
Rooming-in of the Opioid Exposed Baby with Mother: Advantage in NAS?

- Newborns who roomed in with their methadone or heroin using mothers versus those who received traditional care in the NICU were compared in Vancouver, BC.

- Incidence of treatment and hospital stay: Rx: RI=11%; NICU=45%; Hospital stay: RI=7 days; NICU=13 days;


Can breast feeding influence neonatal opioid abstinence expression?
Breastfeeding and pharmacological treatment for NAS
Well-Strand et al., Acta Paedtrica, 2013

- Norwegian National cohort of 124 women treated with methadone or buprenorphine. (1999-2009)
- 77% of women on opioid maintenance treatment initiated breastfeeding
- Breastfed infants exposed to methadone prenatally had a lower incidence of NAS requiring treatment (53% vs. 80%)
- Breastfed infants exposed to Methadone or Buprenorphine needed shorter pharmacological treatment of NAS than neonates who were not breastfed.
Link between Genetics and NAS Expression


Certain genes in their common form without variations are associated with a higher risk of opioid addiction in adults. Genes may provide future answers for infants with NAS.
Maine, Mass., Texas & New York; 86 mother-child pairs exposed to methadone or buprenorphine were studied. DNA analyzed.

Infants with variation of the OPRM1 gene were in hospital 8.5 days less than those without the variation with a higher chance of not needing treatment. With COMT gene, babies were in hospital 10.8 fewer days and had less treatment.

Summarizing the issues influencing variability in the expression of NAS

- Gestational age—pre-term vs. full term
- Methadone vs. buprenorphine
- Maternal nicotine smoking
- Rate of decline of neonatal plasma level of methadone
- Lack of standardization regarding methadone dosing during pregnancy
- Knowledge gaps concerning methadone pharmacodynamics and pharmacokinetics during pregnancy
- Maternal autonomic regulation
- Breastfeeding
- Rooming-In with mother post-partum
- Genetic predisposition
With the burgeoning numbers of mothers dependent on opioids and babies with NAS, a major challenge for the United States is to be able to provide adequate treatment facilities for pregnant opioid using women and their babies.
Through appropriate recognition, assessment and treatment for neonatal opioid abstinence coupled with good orientation of the future caretaker, we can better assure a nurturing, healthy environment for the child and hopefully prevent the potential of the intergenerational transmission of drug dependence…
Although progress has been made over the last 40 years, we still have more research to accomplish in order to fully delineate the variables contributing to expression of NAS and its’ ramifications.
The drug exposed baby deserves as much as any baby born in this world…
Abrahams, RR et al., Rooming-in compared with standard care for newborns of mothers using methadone or heroin. Canadian Family Physician 53:1722-1730, 2007


References


McCarthy, JJ, Intrauterine abstinence syndrome (IAS) during buprenorphine inductions and methadone taper: can we assure the safety of the fetus? The Journal of Maternal-Fetal and Neonatal Medicine, Volume 25, Number 2, February 2012, pp. 109-112(4)


THE END

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PCSS-MAT Mentoring Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS-MAT Mentors comprise a national network of trained providers with expertise in medication-assisted treatment, addictions and clinical education.

- Our 3-tiered mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.

- The mentoring program is available, at no cost to providers.

For more information on requesting or becoming a mentor visit: pcssmat.org/mentoring
PCSSMAT is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society of Addiction Medicine (ASAM) and Association for Medical Education and Research in Substance Abuse (AMERSA).

For More Information: www.pcssmat.org

Twitter: @PCSSProjects

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