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

Loretta P. Finnegan, M.D., LLD, (Hon.), ScD(Hon.) President, Finnegan Consulting, LLC
Professor of Pediatrics, Psychiatry and Human Behavior, Thomas Jefferson University (Retired)
Founder and Former Director of Family Center, Comprehensive Services for Pregnant Drug Dependent Women, Philadelphia, Pennsylvania, USA
Former Medical Advisor to the Director, Office of Research on Women's Health, National Institutes of Health, US Department of Health and Human Services (Retired)
Loretta P. Finnegan, M.D.,
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 it is their responsibility to disclose this information.
<table>
<thead>
<tr>
<th>Name</th>
<th>Nature of Relevant Financial Relationship</th>
<th>Commercial Interest</th>
<th>What was received?</th>
<th>For what role?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yngvild Olsen, MD, MPH, FASAM</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adam J. Gordon, MD, MPH, FACP, FASAM, CMRO, Chair, Activity Reviewer</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwin A. Salsitz, MD, FASAM, Acting Vice Chair</td>
<td>Reckitt-Benckiser</td>
<td>Honorarium</td>
<td>Speaker</td>
<td></td>
</tr>
<tr>
<td>James L. Ferguson, DO, FASAM</td>
<td>First Lab</td>
<td>Salary</td>
<td>Medical Director</td>
<td></td>
</tr>
<tr>
<td>Dawn Howell, ASAM Staff</td>
<td></td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Nature of Relevant Financial Relationship</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Commercial Interest</td>
<td>What was received?</td>
<td>For what role?</td>
<td></td>
</tr>
<tr>
<td>Noel Ilogu, MD, MRCP</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hebert L. Malinoff, MD, FACP, FASAM, Activity Reviewer</td>
<td>Orexo Pharmaceuticals</td>
<td>Honorarium</td>
<td>Speaker</td>
<td></td>
</tr>
<tr>
<td>Mark P. Schwartz, MD, FASAM, FAAFP</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>John C. Tanner, DO, FASAM</td>
<td>Reckitt-Benckiser</td>
<td>Honorarium</td>
<td>Speaker and consultant</td>
<td></td>
</tr>
<tr>
<td>Jeanette Tetrault, MD, FACP</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.
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: May 25, 2016
- Date of Expiration: July 31, 2018
System Requirements

- In order to complete this online module you will need Adobe Reader. To install for free click the link below:
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
- Describe the issues that can lead to death in the baby with unrecognized/untreated NAS
- Know conditions that could affect the onset and persistence of symptoms of NAS
- Discuss issues related to methadone
  - The effect of methadone dose on expression of NAS
  - The challenges of methadone dosing in pregnant women
- Know the causes of variability in NAS expression
Baby Tommy

- 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. The entire pregnancy treatment plan was dedicated to assure a healthy pregnancy with the outcome of 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 addiction even though a medication called buprenorphine can be efficacious.
Baby Tommy (con’t)

- The pregnancy went smoothly and Janet delivered at term a healthy 3500 gram little boy 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 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”
Are Babies Addicted?

- 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 2016
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

Images by Yngvild Olsen, MD
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 et al., 2010; McCarthy, 2012; Berghella et al., 2003; Newman et al., 2011; Jones et al., 2010; Herzlinger, et al. 1977)
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, 2012
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, 2012)
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 et al., 1998)
- 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 et al., 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 et al., 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 NAS requiring treatment 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?* (Whittman and Segal, 1991)

- Fetal cardiac rhythm parameters were found to be abnormal on single doses but to improve on a BID regimen. (Jansson et al., 2009)
The Rationale for Methadone Split Dosing

The Question
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?

• 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 et al., 1989)

• Increased doses and dose intervals are recommended to compensate for the pharmacodynamic and pharmacokinetic changes in pregnancy. (Jarvis, 1999 and Pond, 1985)
The MOTHER Study (Jones et al., 2010)

- 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 who administered a fixed morphine dose depending on the score. *(Issue: Heterogeneity 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 (M □--B ▪) and severity (M ▥-- B ▫) were found in urban, rural and European sites
Neonatal Abstinence Syndrome: MOTHER Study Site differences
Baewert et al., 2012

All Sites (n = 68; 52%)
- NAS outcome M
- NAS severity M
- NAS outcome B
- NAS severity B

Urban (n = 28; 51%)
- NAS outcome M
- NAS severity M
- NAS outcome B
- NAS severity B

Europe (n = 28; 76%)
- NAS outcome M
- NAS severity M
- NAS outcome B
- NAS severity B

Rural (n = 12; 31%)
- NAS outcome M
- NAS severity M
- NAS outcome B
- NAS severity B

NAS: p = 0.189, Treatment: p = 0.073
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

(Doberczak et al., 1991)

In TERM babies NAS more severe, more treatment is 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 and Pippenger, 1976; Doberczak et al., 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.

Choo RE, et al., 2004

Image provided by Vermont Department of Health
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 et al., 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 (RI) 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;

Abrahams et al., 2007; Hodgson and Abrahams, 2012
Can breast feeding influence neonatal opioid abstinence expression?
Breastfeeding and pharmacological treatment for NAS
Welle-Strand et al., 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.
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.
Multi-center cohort study: 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.

Wachman et al., 2013
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…
Please Click the Link Below to Access the Post Test for the Online Module

Click HERE for Post Test

Upon completion of the Post Test:

• You will receive an email detailing correct answers, explanations and references for each question.

• You will be directed to an online module evaluation, upon completion of which you will be emailed your Certificate of Completion or CME.
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) and American Society of Addiction Medicine (ASAM).

For More Information: [www.pcssmat.org](http://www.pcssmat.org)

Twitter: [@PCSSProjects](https://twitter.com/PCSSProjects)
References


Baby photos provided by Paige Morley, Jennifer Butchart and Yngvild Olsen, MD. Stock images purchased from BigStockPhoto.com


References


• High interindividual variability of methadone enantiomer blood levels to dose ratios. Arch. Gen. Psychiatry, 55: 89–90


References


References


THE END

EMAIL FOR QUESTIONS: FINNEGAL337@AOL.COM