Neonatal Abstinence Syndrome:  
Focus on Prevention and Role of Collaboratives  

Brevard County Health Department  
Melbourne, FL  
April 7, 2017  

Mark L. Hudak, MD  
Professor and Chairman of Pediatrics  
University of Florida College of Medicine - Jacksonville
I am a consultant to the Maryland Patient Safety Center.

I have no financial arrangements or affiliations with a commercial entity to disclose.

Any drug therapy I discuss related to NAS is “off label” usage.
CLINICAL REPORT

Neonatal Drug Withdrawal

abstract

Maternal use of certain drugs during pregnancy can result in transient neonatal signs consistent with withdrawal or acute toxicity or cause sustained signs consistent with a lasting drug effect. In addition, hospitalized infants who are treated with opioids or benzodiazepines to provide analgesia or sedation may be at risk for manifesting signs of withdrawal. This statement updates information about the clinical presentation of infants exposed to intrauterine drugs and the therapeutic options for treatment of withdrawal and is expanded to include evidence-based approaches to the management of the hospitalized infant who requires weaning from analgesics or sedatives. Pediatrics 2012;129:e540–e560

Mark L. Hudak, MD, Rosamarie C. Tan, MD, PhD, THE COMMITTEE ON DRUGS, and THE COMMITTEE ON FETUS AND NEWBORN

KEY WORDS
opioid, methadone, heroin, fentanyl, benzodiazepine, cocaine, methamphetamine, SSRI, drug withdrawal, newborn, abstinence syndrome

ABBREVIATIONS
CNS—central nervous system
DTD—diluted tincture of opium
ECMO—extracorporeal membrane oxygenation
FDA—Food and Drug Administration
5-HIAA—5-hydroxyindoleacetic acid
ICD-9—International Classification of Diseases, Ninth Revision
NAS—neonatal abstinence syndrome
SSRI—selective serotonin reuptake inhibitor
Highlights From the AAP Clinical Report

1. Consensus protocol for maternal screening for substance abuse and evaluation/management of infants at risk for or with signs of withdrawal.

2. Emphasis on non-pharmacologic support.


5. Optimal threshold score for initiating treatment is unknown.

6. Encouragement of breastfeeding when indicated.

7. Pharmacologic treatment with opioids. Absolute indications include seizures, feeding intolerance, dehydration/poor weight gain.

8. Duration of in-hospital observation; outpatient follow-up.
What can be done to reduce the burden of NAS in your community?

Primary
Secondary
Tertiary
Prevention Model

OVERVIEW OF NAS PREVENTION
# OVERVIEW: LEVELS OF PREVENTION OF NAS

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Reduce number of fetuses exposed to opioids</td>
</tr>
<tr>
<td>Secondary</td>
<td>Mitigate risk factors that increase likelihood or severity of NAS in mother/fetus dyads exposed to opioids</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Improve treatment of neonates with or at risk for NAS to reduce length of stay, need for drug treatment, and duration of drug treatment; or to improve parent-infant bonding or outcomes after discharge</td>
</tr>
</tbody>
</table>
EXPANDING BURDEN OF NAS

- Increasing population of fertile women on maintenance opioid therapy
- Marked increase in use/abuse of prescription opioids
- Resurgence of street opioids (heroin) as access to prescription opioids is tightened
- Over 14% of pregnant women with an opioid prescription; over 1% used prescription opioids or heroin illicitly
- High rate of “unintended pregnancy” in women on opioids
FACTORS FOR RISE IN PRESCRIPTION RX

- Development of extended-release opioids
- Pharmaceutical company promotion
- Higher social acceptability
- Perception of less harm
### National Survey on Drug Use and Health 2014

#### DEPENDENCY OR ABUSE BY U.S. POPULATION

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARIJUANA</td>
<td>4,200,000</td>
</tr>
<tr>
<td>PAIN RELIEVERS</td>
<td>1,900,000</td>
</tr>
<tr>
<td>COCAINE</td>
<td>913,000</td>
</tr>
</tbody>
</table>

#### Sources for non-medical use (2013)

- **FRIEND/RELATIVE (free)**: 53% (5/6 from single MD)
- **PRESCRIBED BY 1 MD**: 21%
- **FRIEND/RELATIVE (bought)**: 15%
- **OTHER**: 4%
- **DRUG DEALER**: 4%
- **PRESCRIBED BY > 1 MD**: 3%
- **INTERNET PURCHASE**: 0.1%
Overall rate of heroin initiation increased for women from 0.06% in 2002-2004 to 0.10% in 2009-2011

Increase in estimated people dependent on heroin from 180,000 in 2007 to 586,000 in 2014

Strong association between nonmedical use of opioids and subsequent past year initiation of heroin

Heroin incidence rates are 19x higher among people who reported prior nonmedical use of pain relievers
Dozens of heroin overdoses reported in Ohio as state battles epidemic

By Faith Karimi, CNN
Updated 1117 GMT (1917 HKT) September 11, 2016

Story highlights

Heroin laced with fentanyl and carfentanil is suspected

So far, 112 people have died as a result of overdoses in Akron

(CNN) — Ohio authorities reported at least 24 heroin overdoses in Akron as the state battles a drug epidemic.

The overdoses Friday night occurred in separate incidents, and heroin laced with fentanyl and carfentanil is suspected, CNN affiliate WEWS reported.

The conditions of those who overdosed Friday are unclear. The incidents come a day after four people died from overdoses Thursday in Akron, bringing the total number of overdose deaths in the city this year to 112, authorities told the affiliate.
OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary
• Prevent non-medically indicated population opioid use

Secondary

Tertiary
NEW CDC ADVICE ON OPIOIDS AND CHRONIC PAIN

Determining when to initiate or continue opioids for chronic pain (3 points)

Opioid selection, dosage, duration, follow-up and discontinuation (4 points)
• Prescribe immediate release opioids rather than ER/LA options
• Start with lowest effective dose
• Prescribe for expected duration of severe pain (often ≤ 3 days)

Assess risk and address harm of opioid use (5 points)
• No concurrent opioids and benzodiazepines

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary
• Prevent non-medically indicated population opioid use
• Prevent pregnancy in women on opioids (e.g., LARCs)

Secondary

Tertiary
In the Weeds with Medicaid LARC Policy

**Effective for dates of service April 15, 2016 and forward, the Department of Social Services (DSS) will reimburse enrolled hospitals for long-acting reversible contraception (LARC) devices including intrauterine devices (IUD) and subdermal implants when placed immediately postpartum in the inpatient hospital setting.**

**CMCS Informational Bulletin**

**DATE:** April 08, 2016  
**FROM:** Vikki Wachino, Director  
Center for Medicaid and CHIP Services  
**SUBJECT:** State Medicaid Payment Approaches to Improve Access to Long-Acting Reversible Contraception

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Contraceptive Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7300</td>
<td>Intrauterine copper contraceptive (Paragard)</td>
</tr>
<tr>
<td>J7301</td>
<td>Levonorgestrel-releasing intrauterine contraceptive system, (Skylark), 13.5 mg</td>
</tr>
<tr>
<td>J7302</td>
<td>Levonorgestrel-releasing intrauterine contraceptive system, 52 mg (Mirena)</td>
</tr>
<tr>
<td>J7307</td>
<td>Etonogestrel (contraceptive) implant system, including implant and supplies (Implanon, Nexplanon)</td>
</tr>
</tbody>
</table>
Postpartum LARC Medicaid Payments
OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary
- Prevent non-medically indicated population opioid use
- Prevent pregnancy in women on opioids (e.g., LARCs)
- ? Supervised medication withdrawal of selected pregnant women

Secondary

Tertiary
## NOVEL APPROACHES TO MOTHERS ON OPIOIDS

### Narcotic tapering in pregnancy using long–acting morphine

An 18-month prospective cohort study in northwestern Ontario

<table>
<thead>
<tr>
<th>Year</th>
<th>% opioid-exposed pregnancies</th>
<th>% NAS among opioid-exposed mothers</th>
<th>% total population treated with opioids for NAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>17</td>
<td>29.5</td>
<td>2.5</td>
</tr>
<tr>
<td>2013</td>
<td>28</td>
<td>18.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

### Detoxification from opiate drugs during pregnancy

Jennifer Bell, MD; Craig V. Towers, MD; Mark D. Hennessy, MD; Callie Heitzman, RN; Barbara Smith; Katie Chattin

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>108</td>
<td>23</td>
<td>77</td>
<td>93</td>
<td>301</td>
</tr>
<tr>
<td>Gestational age at detoxification and NICU admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detoxification first trimester, 5–13 wks gestation</td>
<td>10 (9%)</td>
<td>4 (17%)</td>
<td>12 (15%)</td>
<td>2 (2%)</td>
<td>28 (9%)</td>
</tr>
<tr>
<td>Detoxification second trimester, 14–27 wks gestation</td>
<td>65 (60%)</td>
<td>10 (43%)</td>
<td>36 (47%)</td>
<td>37 (40%)</td>
<td>148 (49%)</td>
</tr>
<tr>
<td>Detoxification third trimester, ≥28 wks gestation</td>
<td>33 (31%)</td>
<td>9 (39%)</td>
<td>29 (38%)</td>
<td>54 (58%)</td>
<td>125 (42%)</td>
</tr>
<tr>
<td>Preterm deliveries prior to 37 wks gestation</td>
<td>21 (19%)</td>
<td>3 (13%)</td>
<td>13 (17%)</td>
<td>16 (17%)</td>
<td>53 (17.6%)</td>
</tr>
<tr>
<td>Neonatal intensive care unit admission</td>
<td>32 (30%)</td>
<td>5 (22%)</td>
<td>60 (78%)</td>
<td>22 (24%)</td>
<td>119 (40%)</td>
</tr>
<tr>
<td>Pregnancy outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of NAS</td>
<td>20 (18.5%)</td>
<td>4 (17.4%)</td>
<td>54 (70.1%)</td>
<td>16 (17.2%)</td>
<td>94 (31%)</td>
</tr>
<tr>
<td>Rate of relapse</td>
<td>25 (23.1%)</td>
<td>4 (17.4%)</td>
<td>57 (74.0%)</td>
<td>21 (22.5%)</td>
<td>107 (36%)</td>
</tr>
</tbody>
</table>
The Perinatal Outcome of Children Born to Women With Substance Dependence Detoxified in Residential Treatment During Pregnancy

Kristin Johanne Haabrekke PhD Candidate\textsuperscript{ab}, Kari Slinning PhD\textsuperscript{a}, Kristine Beate Walhovd PhD\textsuperscript{b}, Tore Wentzel-Larsen MSc\textsuperscript{ac} & Vibeke Moe PhD\textsuperscript{ab}

\textsuperscript{a} National Network for Infant Mental Health, the Center for Child and Adolescent Mental Health, Oslo, Norway
\textsuperscript{b} Department of Psychology, University of Oslo, Norway
\textsuperscript{c} Norwegian Center for Violence and Traumatic Stress Studies, Oslo, Norway

Accepted author version posted online: 09 Apr 2014. Published online: 24 Jun 2014.

<table>
<thead>
<tr>
<th>Substance abuse</th>
<th>Cohort 1: Mothers out-patients (n = 78), no. (%)</th>
<th>Cohort 2: Mothers in-patients (n = 21), no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st Trimester</td>
<td>2nd Trimester</td>
</tr>
<tr>
<td>Opiates</td>
<td>46 (59.0)</td>
<td>45 (57.7)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>35 (44.9)</td>
<td>37 (47.4)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>24 (30.8)</td>
<td>23 (29.5)</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>13 (16.7)</td>
<td>15 (19.2)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>29 (37.7)</td>
<td>26 (33.3)</td>
</tr>
<tr>
<td>Nicotine daily</td>
<td>78 (100)</td>
<td>—</td>
</tr>
<tr>
<td>Other substances*</td>
<td>13 (16.7)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Barbiturates, cocaine, ecstasy.
## Norway Study: Outcomes

### TABLE 2. Birth Parameters in Cohorts 1 and 2

<table>
<thead>
<tr>
<th>Birth Parameters</th>
<th>Cohort 1</th>
<th></th>
<th>Cohort 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mothers out-patients, n = 78 (45 boys)</td>
<td>Comparison group, n = 58 (35 boys)</td>
<td>Mothers in treatment, n = 22 (12 boys)</td>
<td>Comparison group, n = 30 (18 boys)</td>
</tr>
<tr>
<td>Gestational age, mean (SD)</td>
<td>38.3 (2.4)</td>
<td>40.4 (1.4)</td>
<td>39.4 (1.2)</td>
<td>40.0 (1.2)</td>
</tr>
<tr>
<td>Birthweight, mean (SD)</td>
<td>3022 (715)</td>
<td>3707 (455)</td>
<td>3293 (428)</td>
<td>3720 (433)</td>
</tr>
<tr>
<td>Head circumference, mean (SD)</td>
<td>33.9 (1.9)</td>
<td>35.6 (1.2)</td>
<td>34.8 (1.5)</td>
<td>35.4 (1.2)</td>
</tr>
<tr>
<td>Maternal age at delivery, mean (SD)</td>
<td>28.5 (5.4)</td>
<td>29 (3.7)</td>
<td>27.3 (6.0)</td>
<td>33.3 (5.0)</td>
</tr>
<tr>
<td>Apgar 1 min, mean (SD)</td>
<td>8.4 (1.3)</td>
<td>—</td>
<td>9.1 (0.4)</td>
<td>—</td>
</tr>
<tr>
<td>Apgar 5 min, mean (SD)</td>
<td>9.0 (0.6)</td>
<td>—</td>
<td>9.6 (0.5)</td>
<td>—</td>
</tr>
<tr>
<td>Gestational age &lt;37 weeks, no. (%)</td>
<td>20 (25.6)</td>
<td>1 (1.72)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NAS, no. (%)</td>
<td>60 (76.92)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*a* Birthweight is given in grams, gestational age in weeks, and head circumference in cm.

*b* Apgar score was obtained for 62 and 14 infants from the study groups in cohorts 1 and 2, respectively.

NAS = neonatal abstinence syndrome; SD = standard deviation.
OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary
• Prevent non-medically indicated population opioid use
• Prevent pregnancy in women on opioids (e.g., LARCs)
• ? Supervised medication withdrawal of selected pregnant women

Secondary
• Screen/? test pregnant women for substance use
• Incorporate treatment of substance use disorders into prenatal care
• Optimize maternal OMT (e.g., methadone vs. buprenorphine)

Tertiary
Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study*

2002: FDA approval of buprenorphine (partial μ-opioid receptor agonist, partial κ-opioid receptor antagonist) for males and non-pregnant females

MOTHER: RCT of efficacy of methadone vs. buprenorphine (Subutex): 6 US centers, 1 European center

175 mothers randomized, 131 infants followed to birth (73 methadone, 58 buprenorphine)

Attrition 33% in buprenorphine, 18% in methadone groups

Both drugs are Pregnancy Category C: animal reproductive studies show adverse effect on fetus; no adequate and well-controlled studies in humans; potential benefits may warrant use despite potential risks

METHADONE VS. BUPRENORPHINE

Different panel of presenting signs for NAS
- Higher tremor and hyperactive Moro in M-exposed
- Higher nasal stuffiness, sneezing, loose stools in B-exposed

Severity scores higher in M than B-exposed infants

Peak NAS scores occurred later in B-exposed infants

Mean onset of initiation of treatment:
- 36 hours M-exposed
- 59 hours B-exposed
METHADONE VS. BUPRENORPHINE

Mothers' Buprenorphine Treatment During Pregnancy Benefits Infants

- Hospital Stay
- Duration of Withdrawal (Neonatal Abstinence Syndrome) Treatment
- Total Dose of Morphine

Medication Mother Received During Pregnancy

- Methadone (n=73)
- Buprenorphine (n=58)

OVERVIEW: LEVELS OF PREVENTION OF NOWS

Primary
- Prevent non-medically indicated population opioid use
- Prevent pregnancy in women on opioids (e.g., LARCs)
- ? Supervised medication withdrawal of selected pregnant women

Secondary
- Screen/? test pregnant women for substance use
- Incorporate treatment of substance use disorders into prenatal care
- Optimize maternal OMT (e.g., methadone vs. buprenorphine)
- Smoking cessation programs

Tertiary
### POTENTIATING FACTORS: SMOKING and SSRIs

#### TABLE 3 Probability of NAS According to Varying Exposures of Short-Acting Opioids and Maintenance Opioids, Tobacco, and SSRI Use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Short-Acting (e.g., Oxycodone Hydrochloride 10 mg q6h)</th>
<th>Maintenance (e.g., Buprenorphine Hydrochloride Tablet 24 mg q24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Probability (95% CI)</td>
<td>Probability (95% CI)</td>
</tr>
<tr>
<td>5-wk duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cigarette use, SSRI use</td>
<td>0.011 (0.008–0.016)</td>
<td>0.132 (0.085–0.199)</td>
</tr>
<tr>
<td>5 cigarettes/d, no SSRI</td>
<td>0.023 (0.016–0.034)</td>
<td>0.241 (0.157–0.351)</td>
</tr>
<tr>
<td>5 cigarettes/d, SSRI</td>
<td>0.026 (0.020–0.033)</td>
<td>0.165 (0.123–0.219)</td>
</tr>
<tr>
<td>20 cigarettes/d, no SSRI</td>
<td>0.037 (0.029–0.047)</td>
<td>0.179 (0.137–0.231)</td>
</tr>
<tr>
<td>20 cigarettes/d and SSRI use</td>
<td>0.074 (0.056–0.098)</td>
<td>0.314 (0.239–0.399)</td>
</tr>
<tr>
<td>25-wk duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cigarette use, SSRI use</td>
<td>0.048 (0.028–0.081)</td>
<td>0.153 (0.103–0.247)</td>
</tr>
<tr>
<td>5 cigarettes/d, no SSRI</td>
<td>0.095 (0.055–0.158)</td>
<td>0.289 (0.188–0.416)</td>
</tr>
<tr>
<td>5 cigarettes/d, SSRI</td>
<td>0.073 (0.045–0.115)</td>
<td>0.172 (0.123–0.236)</td>
</tr>
<tr>
<td>20 cigarettes/d, no SSRI</td>
<td>0.141 (0.088–0.220)</td>
<td>0.303 (0.218–0.404)</td>
</tr>
<tr>
<td>20 cigarettes/d and SSRI use</td>
<td>0.196 (0.129–0.285)</td>
<td>0.366 (0.270–0.474)</td>
</tr>
</tbody>
</table>

OVERVIEW: LEVELS OF PREVENTION OF NOWS

Primary
- Prevent non-medically indicated population opioid use
- Prevent pregnancy in women on opioids (e.g., LARCs)
- ? Supervised medication withdrawal of selected pregnant women

Secondary
- Screen/? test pregnant women for substance use
- Incorporate treatment of substance use disorders into prenatal care
- Optimize maternal OMT (e.g., methadone vs. buprenorphine)
- Smoking cessation programs
- Prenatal risk assessment

Tertiary
# NAS AND MATERNAL OPIOID USE

<table>
<thead>
<tr>
<th>OPIOID:</th>
<th>PRESCRIPTION OPIOIDS (SA)</th>
<th>HEROIN</th>
<th>BUPRENOR-PHINE</th>
<th>METHADONE/ PRESCRIPTION OPIOIDS (LA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life in neonates</td>
<td>Short (2-6 hours)</td>
<td>Short (2-6 hours)</td>
<td>Long (24+ hours)</td>
<td>Long (24 hours)</td>
</tr>
<tr>
<td>Onset of signs</td>
<td>Not well described, likely &lt; 24-48 hours</td>
<td>Usually &lt; 24 hours</td>
<td>Usually 24-72 hours</td>
<td>Usually 24-48 hours but may be 3-7 days</td>
</tr>
<tr>
<td>Severity of signs</td>
<td>Variable</td>
<td>Mild-moderate</td>
<td>Mild-moderate</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Likelihood of NOWS</td>
<td>1-20%, duration and cofactor dependent</td>
<td>50-70%</td>
<td>Intermediate</td>
<td>High (up to 94%)</td>
</tr>
</tbody>
</table>
KEY DETERMINANTS OF INCIDENCE AND SEVERITY OF NOWS

Maternal opioid exposure close to delivery

Potentiating factors
• Smoking
• Benzodiazepines
• Selective serotonin reuptake inhibitors
• Marijuana
• ? Alcohol, cocaine, stress

Placental metabolism

Gestational age, infant co-morbidities

Environment of care (physical; caregiver(s))

Efficacy of pharmacologic treatment

Genetics and epigenetics
OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

Tertiary

• Novel drug treatments of pregnant women during labor and babies after birth
• Optimization of non-pharmacologic support of babies
• Care of families
OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

Tertiary
- Novel drug treatments of pregnant women during labor and babies after birth
- Optimization of non-pharmacologic support of babies
- Care of families
- Pharmacologic treatment of babies
WITHIN OUR WALLS: WHAT WE DO NOT KNOW

- Optimal first-line medication
- Threshold for starting pharmacologic treatment
- Best escalation practice
- Etiology(ies) responsible for “outlier” lengths of stay
- Criteria for adjunctive drug treatment
NAS: TREATMENT ISSUES

Goals of treatment
Non-pharmacologic treatment
Role of breast feeding
Drug therapy: When to start; what drugs to use; how to dose
Care of families
GOALS OF TREATMENT

Support vital infant functions and development
- Hydration, feeding, growth
- Sleep
- Reasonable comfort, not sedation
- Socialization

Achieve family bonding (integrated care, breastfeeding when possible)

Avoid complications
- Seizures
- Skin breakdown
- Nutritional and sleep disturbances
- Marginalization of social supports

Educate family and marshall post-discharge medical/social support
First line drug treatment (U.S. and U.K.): opioid (oral morphine > methadone), but significant use of phenobarbital

Initial dose is usually titrated to Finnegan scores

If signs of NAS are not relieved by maximum dose of single drug, a second drug is added (phenobarbital > clonidine > benzodiazepine)

Dose is weaned by 10-20% every 1-2 days so long as Finnegan scores are generally < 8
ASSESSMENTS AND TREATMENTS

Any assessment instrument that is used to dichotomize treatment vs. non-treatment generates a risk of overtreatment.

NAS scores above threshold, although accurate, may have been inflated by environmental stimuli, hunger, and suboptimal caretaker-infant interactions.

Accurate scores above treatment threshold may result from factors other than opioid withdrawal.

Once initiated, the minimum duration of pharmacologic therapy under most protocols will be 10 days.
Pharmacological Treatment

- Morphine: 83%
- Methadone: 15%
- Buprenorphine: 0%
- Clonidine: 7%
- Phenobarbital: 26%
- Paregoric: 0.1%
- DTO: 4%
MORPHINE TREATMENT OF NAS

NAS scores > 8

Single NAS score
< 8
> 8

Dose q4
-
0.07 mg/kg

Weight Based

NAS scores > 8

Single NAS score
9-12
13-16
17-20
21-24
> 25

Dose q4
0.04 mg
0.08 mg
0.12 mg
0.16 mg
0.20 mg

Symptom Based
DOSING CONSIDERATIONS

Steady State
- Attained after approximately four half-times
- Time to steady state independent of dosage

Steady State Concentrations
Absorption and distribution
• Incomplete oral absorption and first pass hepatic metabolism
• Bioavailability is about 40%
• Morphine and metabolites are hydrophilic, enter brain slowly
• Peak effect about 60 minutes

Metabolism
• 90% metabolism: undergoes glucuronidation in liver to morphine-6G (analgesic) and morphine-3G (nonanalgesic, neuroexcitatory); also N-methylation to normorphine
• Morphine-6G is excreted by kidneys

Excretion
• Plasma half life is 2-3 hours
• Duration of effect is slightly longer
• 90% renal: 10% biliary excretion
• Complete elimination by 24 hours
DOSING CONSIDERATIONS

- Maintenance doses

- Loading dose and Maintenance doses
ORAL MORPHINE VS. METHADONE

Evidence from observational studies

Hall ES et al. Pediatrics 2014;134:e527-534. No difference in LOS or LOT.


Randomized controlled trials


Davis JM. Double-blind multicenter NIDA-funded RCT morphine vs. methadone in progress. Enrollment passed halfway mark.
DRUG TREATMENTS

Primary
• Oral morphine
• Oral methadone
• Sublingual buprenorphine
• Clonidine

Secondary
• Clonidine
• Phenobarbital
CURRENT STATE OF EVIDENCE

Most existing trials do not clearly identify the most effective drug class or the most effective drug within a class; many older studies have methodological weaknesses.

No trial has critically compared different criteria for initiation of drug therapy.

BUT: adherence to a standard protocol reduces the length of hospital stay.
OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

Tertiary
• Novel drug treatments of pregnant women during labor and babies after birth
• Optimization of non-pharmacologic support of babies
• Care of families
• Pharmacologic treatment of babies
• Outpatient management and outcomes
OUTPATIENT MANAGEMENT

Outpatient management

- Occurs in some areas of the country by necessity
- Literature (Europe and U.S.) documents excessive lengths of outpatient treatment and prolonged use of drugs such as phenobarbital that may have additional long-term morbidity
- Does benefit:risk equation justify potential long-term exposure to drugs as an outpatient over few-several additional days in the hospital
- Requires excellent family selection and close follow-up: it only takes one serious morbidity to dismantle a program
CLONIDINE vs. PHENOBARB AS ADJUNCT

Unblinded study of morphine plus clonidine vs. morphine plus phenobarbital (34 infants in each group)

Primary outcome: days of morphine therapy

Protocol: Clonidine weaned in hospital but infants could be discharged home on phenobarbital

Results: Phenobarbital continued for mean of 3.8 (range, 1-8) months

<table>
<thead>
<tr>
<th></th>
<th>CLONIDINE</th>
<th>PHENOBARBITAL</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of morphine</td>
<td>18.2</td>
<td>13.6</td>
<td>0.037</td>
</tr>
<tr>
<td>Morphine (mg)</td>
<td>5.7</td>
<td>4.6</td>
<td>0.069</td>
</tr>
</tbody>
</table>

OUTCOMES AFTER DISCHARGE

What is known about these babies post discharge?

Experience from New South Wales, Australia, 2000-11

- Higher risk of rehospitalization (OR 1.6)
- Higher risk of death during hospitalization (OR 3.3)
- Higher risk of hospitalization due to assaults (OR 15.2), maltreatment (OR 21.0), poisoning (OR 3.6), mental/behavioral disorders (OR 2.6)
- NAS most important predictor of admissions for maltreatment (OR 4.5) and mental/behavioral disorders (OR 2.3) even after correcting for prematurity, maternal age, and indigenous status

ACTIVITIES OF OTHER COLLABORATIVES
OHIO Perinatal Quality Collaborative
NAS Project

In 2011, Ohio witnessed 19,000 NAS patient days at a cost of over $70 M.
Pilot work by the Ohio Children’s Hospital Association estimated up to 50% of
NAS babies might have benefitted from better care in accord with existing
standards.

Initial aims of the OPQC NAS Project were modest:
• Increase identification and compassionate treatment of babies with NAS
• Reduce the length of stay by 1 day across collaborating sites by June 30, 2016
Level 1 Key Driver Diagram

Project Name: OPQC Neonatal NAS  
Leader: Michelle Walsh, MD

GLOBAL AIM
To reduce the number of moms and babies with narcotic exposure, and reduce the need for treatment of NAS.

SMART AIM
By increasing identification of and compassionate withdrawal treatment for full-term infants born with Neonatal Abstinence Syndrome (NAS), we will reduce length of stay by 20% across participating sites by June 30, 2015.

KEY DRIVERS
- Prenatal Identification of Mom  
  Implement Optimal Med Rx Program
- Improve recognition and non-judgmental support for Narcotic addicted women and infants
- Utilize Lipsitz scoring tool to standardize identification
- Optimize Non-Pharmacologic Rx Bundle
- Standardize referral those needing treatment
- Partner with Families to Establish Safety Plan for Infant

INTERVENTIONS
- All MD and RN staff to view “Nurture the Mother, Nurture the Child”
- Monthly education on addiction care
- All staff view webinar on scoring with Lipsitz tool.
- Swaddling, low stimulation.
- Encourage kangaroo care
- Feed on demand- MBM if appropriate or lactose free, 22 cal formula
- Collaborate with DHS/ CPS to ensure infant safety.
- Engage families in Safety Planning.
Impact of Ohio Weaning Protocol
STANDARDIZATION IMPROVES NAS OUTCOMES

- Adoption of a consensus “better” protocol within a unit should achieve better than “mean” results by eliminating practices that have produced outlier results:

- Adoption of a consensus “better” protocol reduces the likelihood of unit operational uncertainties and of individual variability in responses to clinical situations, both of which tend to worsen outcomes (e.g., LOS)
Protocol-based weaning achieved shorter durations of treatment (17.7 vs 32.1 days) and shorter LOS (22.7 vs 32.1 days)

No differences in treatment duration or LOS between morphine or methadone

Differences in use of secondary drug may also have been due to differences in protocol specificity
AIM 1.

Engage centers in a multi-center QI collaborative focused on improving the quality, safety and value of care for substance exposed infants and families.

AIM 2.

Promote the rapid cycle adoption of the AAP NAS guidelines into clinical practice by standardizing NAS-relevant policies and practices.
VON’s iniq Intervention’s components

NAS QI Toolkit

8 Potentially Better Practices

Structured educational curriculum
  • Expert-led Webinar Series
  • List-Serve coaching

Case studies / data-driven improvement stories

Virtual Video Visit to Center of Excellence
  • Trauma-informed, family-centered care

Audit and feedback of data
VON’S Potentially Better Practices

**PBP 1:** Develop and implement a standardized process for the Identification; Evaluation, Treatment; Discharge management for infants with NAS.

**PBP 2:** Develop and implement a standardized process for measuring and reporting rates of NAS and drug exposure.

**PBP 3:** Create a culture of compassion, understanding and healing for the mother-infant dyad.

**PBP 4:** Provide care for infants and families in sites that promote parental engagement in care and avoid separation of mothers and infants.
VON’S Potentially Better Practices

**PBP 5:** Engage mothers / family members in providing non-pharmacologic interventions as “first-line” therapy for all substance-exposed infants.

**PBP 6:** Develop clear eligibility criteria for breastfeeding and actively promote and support breastfeeding by eligible mothers.

**PBP 7:** Develop a standardized process to ensure safe discharge into the community.

**PBP 8:** Provide Interdisciplinary Universal Education / Training to All Caregivers Who May Encounter Substance-Exposed Infants and Families.
Virtual Video Visit – Nurture the Mother - Nurture the Child

Highlighting an integrated model of care that addresses the social determinants of health
• BC Women’s Fir Square inpatient unit
• Vancouver’s Sheway community care center

Put a human face on addiction . . . Empowering women to teach us how to best partner with them
• Mother-baby contact
• Rooming-in model of care
Tools to Impact Attitudes

A trauma-informed, family-centered approach to supporting women with substance use issues who are pregnant and newly parenting.
Created NAS Toolkit to assist units to address 3 areas of “potentially better practices” (PBPs)

- Develop and implement standardized process to identify, evaluate, treat, and discharge infants with NAS
- Develop and implement standardized process to measure and report rates of NAS and drug exposure
- Improve the environmental culture of care for the family of an infant with NAS

Instituted four multicenter audits that assessed evolution of adoption of PBPs and key outcomes across participating centers

Disseminated information and encouraged continuing improvement by hosting regular iNICQ webinars

Facilitated statewide collaboratives (AK, MA, MI, NH, VT, WI)
VON Day NAS Audit Guidelines and Policies

All Participating Centers

- Maternal Screening
  - Audit 1: 78%
  - Audit 2: 79%
  - Audit 3: 80%
  - Audit 4: 90%

- Evaluation and Treatment
  - Audit 1: 76%
  - Audit 2: 83%
  - Audit 3: 88%
  - Audit 4: 95%

- Standardization of Scoring
  - Audit 1: 45%
  - Audit 2: 59%
  - Audit 3: 67%
  - Audit 4: 76%

VON NAS COLLABORATIVE
VON NAS COLLABORATIVE

VON Day Quality Audits / NAS

NICU and Hospital Length of Stay
for centers in both audits 1 and 4!

IQR
3rd Quartile

1st Quartile

AUDIT 1 NICU LOS
AUDIT 4 NICU LOS

AUDIT 1 Hospital LOS
AUDIT 4 Hospital LOS

Audit 1
Audit 4
## VON Day Quality Audits / NAS

### Pharmacologic Agents Administered for Treatment of NAS

<table>
<thead>
<tr>
<th>PHARMACOLOGIC AGENT</th>
<th>AUDIT 1</th>
<th>AUDIT 2</th>
<th>AUDIT 3</th>
<th>AUDIT 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>82%</td>
<td>82%</td>
<td>82%</td>
<td>89%</td>
</tr>
<tr>
<td>Methadone</td>
<td>16%</td>
<td>15%</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>7%</td>
<td>10%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>27%</td>
<td>24%</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>Paregoric</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>DTO</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>
# Presence of Hospital NAS Policies

<table>
<thead>
<tr>
<th></th>
<th>February 2013</th>
<th>August 2013</th>
<th>February 2014</th>
<th>August 2014</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal substance use screen</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Evaluation and treatment</td>
<td>75</td>
<td>78</td>
<td>81</td>
<td>90</td>
<td>0.002</td>
</tr>
<tr>
<td>Standardization scoring</td>
<td>45</td>
<td>59</td>
<td>67</td>
<td>77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-pharmacologic treatment</td>
<td>59</td>
<td>66</td>
<td>69</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pharmacologic treatment</td>
<td>68</td>
<td>81</td>
<td>84</td>
<td>92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>49</td>
<td>55</td>
<td>57</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Infant Outcomes N=3458

<table>
<thead>
<tr>
<th></th>
<th>February 2013</th>
<th>August 2013</th>
<th>February 2014</th>
<th>August 2014</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length of treatment (days)</strong></td>
<td>16 (10, 27)</td>
<td>15 (10, 23)</td>
<td>15 (10, 24)</td>
<td>15 (10, 24)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Length of hospital stay (days)</strong></td>
<td>21 (14, 33)</td>
<td>20 (14, 28)</td>
<td>20 (14, 29)</td>
<td>19 (15, 28)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

VON Tools for Improvement

VON Launches Two New Resources—Now Endorsed by NANN!

Improving Outcomes for infants and families affected by the opioid epidemic.

- 18 Micro-lessons relevant to every care team member, with CME/CNE.
- A VON NAS Quality Improvement Toolkit.
- Sample policies, procedures, guidelines and family educational tools centered for NAS Care.
- Over 100 NAS-related quality improvement stories, and data—showing real-world examples of measurable improvement in length of stay, length of treatment and cost.

"Our paper, published in Pediatrics in 2016, reported that participating VON NICU centers reduced hospital length of stay by 2 days. If scaled nationally we estimate potential savings in hospital charges of $710 million dollars."

NAS Universal Training Program

Providing high-reliability neonatal care requires developing standardized clinical processes and universal training programs. VON’s Universal Training Programs is presented by 25 world-class NAS experts and is available online 24/7. These resources include:

NAS Statewide Implementation Package

The NAS Universal Training Program is now available to States/Perinatal Quality Improvement Collaboratives, health systems, and health centers, enabling these organizations to dramatically improve their patient outcomes on a system-wide basis while reducing both the length of stay and the number of infants who are discharged on medication for NAS.

States and/or health systems may also elect to employ VON Day Quality Audits to measure ongoing improvement.

Featured Faculty

Lisa Haedt, GHF Mother's Hospital, Stephen S. Patrick, Vanderbilt University, Robert Schniederjans, University of Michigan

Levels of Subscription

- **Basic** 3-Week de-Risked Quality Improvement Collaboratives Subscription
  - Significant discounts available upon request. Call for price quote.
  - Unlimited access, CME/CNEs for your entire team.
  - VON Member: $3000
  - NANN Member: $3500
  - Non-Member: $5000

- **Basic** Individual Subscription
  - Access and CME/CNE certificates for 1 provider.
  - VON Member: $450
  - NANN Member: $500
  - Non-Member: $950

- **Health System Subscription**
  - Provides universal training, unlimited access, CME/CNE for your entire health system.
  - VON Member: $10,000
  - NANN Member: $12,000
  - Non-Member: $15,000

Health System subscription extended to NANN members acknowledging the ongoing collaboration of VON and NANN in support of high-quality education and care.

Register at www.vtonline.org
For more information call Pam Ford, pford@vttonline.org 802-865-4914 x4204
• Rural children’s hospital within an academic tertiary care center in Lebanon, NH
  • 2012: 1.8% infants with NAS, ~2x this at risk
    • 47% at-risk infants treated
    • Ave LOS = 16.9 days
  • 2014: 5% infants at risk
  • 2015: 10% infants at risk
CHaD’s QI Work

1. RN scoring training/reliability
2. Family interviews
3. Baby-centered scoring & care
4. Prenatal education
5. Parent symptom diary
6. Standardize score interpretation
7. Rooming-in pilot
8. “Cuddlers”
9. Full rooming-in
10. Addiction training
11. Transfers

Jan 2013: Formed Multi-D VON NAS QI team
April 2013 - Oct 2014: 11 PDSA cycles

October 2014

April 2013
Post-QI NAS Care

Parent & provider education
Rooming-in through entire stay
Family involvement in scoring
Standardized scoring
Pre-scoring: STS and BF
Scoring: STS and in mom’s arms
Score on baby’s schedule
Evaluate at bedside for 3 scores of ≥ 8 or 2 of ≥ 12
  ◦ Assess & interpret score
  ◦ Determine Rx criteria
Decreased Need for Pharm Rx

% Opioid-exposed Newborns Receiving Morphine

- Baseline: 46%
- Intervention Year 1: 51%
- Intervention Year 2: 27%

% Opioid-exposed Newborns Receiving Adjunctive Agents

- Baseline: 13%
- Intervention Year 1: 7%
- Intervention Year 2: 2%

N = opioid-exposed infants per year

Decreased Length of Stay

Mean = 16.9 days

Mean = 12.3 days

Change in physician score interpretation

RN Scoring Training
Baby-Centered Scoring
Rooming-In Pilot
Full Rooming-In

MASSACHUSETTS NeoQIC
Neonatal Quality Improvement Collaborative

Neonatal Quality Improvement Collaborative of Massachusetts
Incidence of Neonatal Abstinence Syndrome, 2012-2013
30 Massachusetts Hospitals
Infants Identified by ICD-9 code 779.5

2012: 16.7
2013: 17.8
NeoQIC Project Components

Webinar series (VON)

Partnerships
• Department of Public Health
• Department of Children and Families
• Bureau of Substance Abuse Services
• Early Intervention

Hospital-based improvement teams

Twice-yearly state meetings

Twice-yearly data audits
# NeoQIC NAS Improvements

**Areas of Improvement:**
- Standardization of practices
- Increased focus on non-pharmacologic care
- Increased involvement of families as partners
- Improved coordination with community partners
- Changing attitudes

<table>
<thead>
<tr>
<th>Risk identification</th>
<th>NAS symptoms</th>
<th>Supportive care</th>
<th>Pharmacologic management</th>
<th>Family support</th>
</tr>
</thead>
</table>
| • Screening  
  • Testing | • Standardized scoring scales | • Environment  
  • Rooming-in  
  • Breast-feeding  
  • Nutrition | • Morphine  
  • Phenobarbital  
  • Clonidine | • Partnership  
  • Social work  
  • DCF  
  • Follow-up |
Duration of Pharmacologic Therapy
Audits 1 to 6 (2012 to 2015)

<table>
<thead>
<tr>
<th>Audit</th>
<th>Median (Days)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audit 1</td>
<td>19</td>
<td>214</td>
</tr>
<tr>
<td>Audit 2</td>
<td>17</td>
<td>173</td>
</tr>
<tr>
<td>Audit 3</td>
<td>16</td>
<td>202</td>
</tr>
<tr>
<td>Audit 4</td>
<td>16</td>
<td>177</td>
</tr>
<tr>
<td>Audit 5</td>
<td>17</td>
<td>194</td>
</tr>
<tr>
<td>Audit 6</td>
<td>14</td>
<td>137</td>
</tr>
</tbody>
</table>
NeoQIC NAS Project – Next Steps

Further education: VON Universal Curriculum
Better improvement – DATABASE!
More coordination with other statewide efforts
Fall summit in coordination with MPQC
Engage and educate providers, community members
Rapid and easy access to treatment for women
Adequate resources for DCF
Early Intervention for all infants with NAS

**Change public dialogue**

Develop MEASURABLE statewide improvement goals

Coordinate incredible efforts by so many people!
NAS: Public Health / Population Metrics?

- Percent of infants with NAS whose mothers are in treatment programs
- Average waiting time for women age 15 to 40 seeking treatment for opiate abuse
- Percent of DCF caseworkers with caseload 15 or less
- Percent of infants with NAS enrolled in EI at 1 year of age
- Percent of infants with NAS in custody of biologic family at 1 year of age