Moving Care Forward: New Research and Ongoing Clinical Trials

Michele Walsh and Heather Kaplan
New Research

• Genetic determinants
• Treatment of the Opiate Addicted Mother
• Infant Outcomes
• Alternatives to Opioid treatment
Genetic Determinants of Fetal Opiate Exposure and Risk of Neonatal Abstinence Syndrome: Knowledge Deficits and Prospects for Future Research

T Lewis, J Dinh, JS Leeder.
Clinical Pharmacology & Therapeutics
September 2015
Highly Variable NAS Phenotype

• Authors investigate genetic variants in opiate metabolism, placental transfer and fetal response.

• 17 genetic variants known- all alter how the opiate is processed, and what fetus is exposed to

• May explain why infants exposed to same dose have different symptoms.

• In the future, could identify high risk and low risk infants.
Narcotic tapering in pregnancy using long-acting morphine. An 18-month prospective cohort study in northwestern Ontario

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Canadian Family Physician; 2015: 61; e88-95
Summary

• Traditional management avoids narcotic taper during pregnancy to avoid relapse.
• In response to epidemic (28% of pregnancies opiate addicted), study of taper.
• 600 women enrolled.
• Taper guided by patient comfort and degree of dependence.
Results

• By delivery, 91.9% of tapered patients had quit (9.3%) or decreased (82.6%) narcotic substitutes.

• Tapering using long-acting morphine decreased neonatal withdrawal significantly— from 29.5% to 18.1%.

• All mother-infant dyads roomed in together post-partum. All discharged to the First Nations Hotel and housed for 7-10 days before discharge home.

• Very low rates of pharmacologic treatment to begin with 2.5% decreased to 1.5%.

• Can we translate to our population? Is this the taper or the whole approach to non-pharm management.
Prescription Opioid Epidemic and Infant Outcomes

Cooper Warren, Katherine E. Hartmann, E. Wesley Ely, Carlos G. Grijalva and William O. Stephen W. Patrick, Judith Dudley, Peter R. Martin, Frank E. Harrell, Michael D. P

Pediatrics 2015;135;842; originally published online April 2015
Methods

• Studied administrative data in Tennessee, 2009-2011; 112,029 pregnant women.

• Analyzed opiate and SSRI prescriptions, diagnoses, and tobacco exposure
Results

• **27%** of women filled **one or more** opiate prescriptions during pregnancy.

• Women taking opiod pain relievers were:
  – more often white (72% vs 66%)
  - Diagnosed with depression (5% vs 3%)
  - Diagnosed with anxiety disorder (4% vs 2%)
  - Headache/migraine (8% vs 2%)
  - Musculoskeletal disease (24% vs 6%)
  - Used tobacco (42% vs 26%)
  - Use SSRI (4% vs 2%)
Likelihood of NAS Varied

- Short term opiate vs Maintenance Rx
- Tobacco
- SSRI exposure
Probability of NAS. A, Opioid type and cumulative morphine milligram equivalents (MMEs).
Conclusions:

• Some low risk infants can be safely discharged from the hospital earlier, while higher risk infants may be monitored longer.

• Also has implications for the optimal site of care.
LONG-ACTING OPIOIDS FOR TREATING NEONATAL ABSTINENCE SYNDROME A HIGH PRICE FOR A SHORT STAY?

Gary Peltz, Kanwaljeet Anand; JAMA Viewpoint Nov 2015

- Authors are conducting a randomized trial of Ondasteron (Zofran) to prevent NAS in narcotic exposed pregnant women.

- Argue that this approach could prevent NAS completely.
Laser Acupuncture for NAS

- Small RCT (n=28)
- Laser at acupuncture sites Plus morphine/phenobarb vs morphine/phenobarb alone
- It worked!
- Rx 28 vs 39 days.

Raith WF et al; Pediatrics Nov 2015
CLINICAL TRIALS. GOV

Heather Kaplan, MD
“Neonatal Abstinence Syndrome” and Child (0-17 years), n=22 studies
  – Drug (n=14)
  – Supplement/Diet (n=2)
  – Procedure/Acupuncture (n=2)
  – Behavior Modification (n=3)
  – Epidemiology (n=1)
## Dietary Supplements & Alternative Therapies

<table>
<thead>
<tr>
<th>Status</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruiting</td>
<td>Donor Human Milk in NAS</td>
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<tr>
<td>Recruiting</td>
<td>Acupuncture in NAS Babies</td>
</tr>
<tr>
<td>Recruiting</td>
<td>RESPECT PLUS Services for Infants with Prenatal Opiate Exposure</td>
</tr>
<tr>
<td>Completed</td>
<td>High vs. Standard Calorie Formula for Methadone-Exposed Infants</td>
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</table>
Donor Human Milk in NAS (06/2016?)

University of Louisville and Medolac Laboratories

- **Objective**: Determine acceptability and benefit of DHM in infants undergoing pharmacologic treatment for NAS
- **Rationale**: To determine if reduction in symptoms/Finnegan scores seen with MHM (possibly related to transmission of opiates in MHM) can be replicated with DHM
- **Design**: Comparison with historical controls fed formula (n=15)
- **Intervention**: 2-weeks of DHM initiated after symptoms stabilized with oral Morphine
- **Outcomes**: Change in GI subscore and total Finnegan Scoring tool from baseline to 2 weeks; growth (weight and OFC)

*Study currently recruiting but having difficulty enrolling*
Objective: Determine if an evidence-based behavioral intervention will strengthen family protective factors for opiate exposed infants in the first year of life

Rationale: Children born to parents with substance abuse disorders are 3-4X more likely to suffer abuse or neglect; RESPECT PLUS may prevent child maltreatment

Design: RCT of standard of care vs. RESPECT PLUS for mothers of infants with NAS in a treatment program

Intervention: Family specialist teaches mothers about (1) child maltreatment (Project DULCE) and (2) infant soothing using Harvey Karp’s “5 S’s” and All Babies Cry; Specialist joins routine WCC visits and has optional home visits (over 1 year)

Outcomes: Time to change in custody; change in parental resilience, self-care, community engagement, social support and parenting skills (composite)

*Almost complete 6 month follow up, 12 month follow up ongoing
Acupuncture in NAS Babies (7/2015?)

University of South Florida

- **Objective**: Determine if auricular acupuncture as an adjunctive treatment in NAS infants receiving pharmacologic therapy is feasible
- **Rationale**: determine feasibility and test/generate hypotheses in preparation for RCT
- **Design**: pilot feasibility study (n=40)
- **Intervention**: auricular acupuncture
- **Outcomes**: patient/staff acceptability, infant tolerance, Finnegan score items associated with sympathetic nervous system, time to return to birth weight
Objective: To evaluate if high-calorie formula results in more normal patterns of weight loss/gain, less severe NAS symptoms, and shorter hospital stays

Rationale: Inadequate caloric intake among methadone exposed infants may result in excessive weight loss, slow weight regain and exacerbation of NAS leading to higher needs for treatment doses and longer LOS.

Design: Pilot RCT (n=49 infants, mothers on methadone)

Intervention: 24 kcal/oz vs. standard formula from 72 hours to 21 days (double blind)

Outcomes: days to return to BW, days to weight nadir, max % weight loss, LOS, Length of treatment, mean Finnegan scores (day 3-10), max concentration morphine
High Calorie vs. Standard Formula in NAS (completed)

*University of Pittsburgh*

<table>
<thead>
<tr>
<th></th>
<th>Standard Cal (N=22)</th>
<th>High Calorie (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>%</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-36 weeks</td>
<td>3 14%</td>
<td>1 4%</td>
</tr>
<tr>
<td>37-38 weeks</td>
<td>6 27%</td>
<td>10 37%</td>
</tr>
<tr>
<td>≥39 weeks</td>
<td>13 59%</td>
<td>16 59%</td>
</tr>
<tr>
<td><strong>Ever treated for NAS</strong></td>
<td>16 73%</td>
<td>18 67%</td>
</tr>
<tr>
<td><strong>Ever fed any breastmilk</strong></td>
<td>8 36%</td>
<td>13 48%</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>Median</strong></td>
<td><strong>Mean</strong></td>
</tr>
<tr>
<td>Days treated for NAS (if required tx)</td>
<td>14.4 13</td>
<td>17.1 15</td>
</tr>
<tr>
<td>LOS (for infants requiring tx)</td>
<td>18.5 18.5</td>
<td>18.5</td>
</tr>
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High Calorie vs. Standard Formula in NAS (completed)

University of Pittsburgh

<table>
<thead>
<tr>
<th></th>
<th>Standard Cal (N=22)</th>
<th>High Calorie (N=27)</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>Days to weight nadir</td>
<td>5</td>
<td>5</td>
<td>4.4</td>
</tr>
<tr>
<td>Days to return to BW</td>
<td>14.7</td>
<td>15</td>
<td>13.8</td>
</tr>
<tr>
<td>Max % weight loss</td>
<td>-9.4%</td>
<td>-9.7%</td>
<td>-8.6%</td>
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Higher percent weight gain per day in 24-kal group (p=0.003)
High Calorie vs. Standard Formula in NAS (completed)

University of Pittsburgh

• Safety:
  – Formula changes
    • 1 infant in high calorie (4%) and 6 in standard calorie (27%) were switched to open-label high calorie feeds due to slow weight gain
  – No difference in mean number of stools
  – No difference in hyperphagia (>190 mL/kg/day)

Courtesy of Debra Bogen, MD- Do NOT share
# Drugs

<table>
<thead>
<tr>
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<th>Status</th>
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<tbody>
<tr>
<td>Ondansetron</td>
<td>Recruiting</td>
<td>Can Ondansetron Prevent NAS?</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Active (not recruiting)</td>
<td>NAS Treatment Opiate (Morphine) vs. Non-Opiate (Clonidine)</td>
</tr>
<tr>
<td></td>
<td>Completed</td>
<td>Clonidine as an adjunct Therapy for NAS</td>
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<tr>
<td></td>
<td>Terminated (results)</td>
<td>Clonidine for NAS</td>
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<tr>
<td>Buprenorphine</td>
<td>Recruiting</td>
<td>Blinded Trial of Buprenorphine vs. Methadone in NAS treatment</td>
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<tr>
<td></td>
<td>Recruiting</td>
<td>Sublingual buprenorphine for Treatment of NAS</td>
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<tr>
<td></td>
<td>Completed</td>
<td>Buprenorphine for NAS treatment (safety and tolerability)</td>
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<tr>
<td>Standard Opiates</td>
<td>Recruiting</td>
<td>Improving Outcomes in NAS (Morphine vs. Methadone)</td>
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<tr>
<td></td>
<td>Completed (results)</td>
<td>Treatment of NAS (Methadone vs. DTO)</td>
</tr>
<tr>
<td></td>
<td>Completed</td>
<td>Comparison between Methadone and Morphine</td>
</tr>
</tbody>
</table>
Objective: To determine if ondansetron given to mothers prior to delivery and babies after delivery prevents or lessens the symptoms of NAS

Rationale: Administration of a 5-HT3 antagonist (ondansetron) prevented the symptoms of narcotic drug withdrawal in experimental studies in mice and in humans

Design: RCT of mother-baby pairs (n=90)

Intervention: mothers receive IV drug/placebo x 1-2 doses prior to delivery and neonates receive same drug every 24 hours for up to 5 days

Outcomes: need for pharmacologic treatment for NAS, LOS, total dose of narcotic needed to treat symptoms, need to include barbiturates in treatment
Blinded Trial of Buprenorphine or Morphine (05/2016)
Thomas Jefferson University

- **Objective**: To determine if buprenorphine results in shorter LOS/LOT compared to standard of care morphine
- **Rationale**: In an open label trial, buprenorphine was associated with a ~30% reduction in LOT. Due to the subjective nature of the scoring instrument, efficacy in a blinded trial is needed
- **Design**: *Double blind, double-dummy RCT* (n=80)
- **Intervention**: sublingual buprenorphine vs. oral morphine
- **Outcomes**: LOT, LOS, need for secondary medication, adverse events, feeding patterns, weight gain, pharmacokinetic data
**Objective**: To compare treatment options for NAS

**Rationale/Hypothesis**: Morphine treated infants may do better, requiring fewer days in the hospital and have better neurodevelopmental outcome

**Design**: multi-center RCT (n=184 infants)

**Intervention**: Morphine vs. Methadone

**Outcomes**: LOS, total opioid days, max opioid dose, mean Finnegan score, need for second NAS medication, developmental testing at 18-months (NICU Network Neurobehavioral Scale at discharge), Bayley III