Trends in Opioid Abuse: Prescription Opioid Abuse & The Recent Transition to Heroin

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The ASAM State of the Art Course
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Disclosure Information

Dr. Theodore Cicero
NIDA-Grant-Research Support
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Pfizer Pharmaceuticals-Consultant Fee- Consultant
Scientific Advisory Board for the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System-Consultant Fee-Member
RADARS® System

- Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System.
- The RADARS® System is supported by subscriptions from pharmaceutical manufacturers for surveillance, research and reporting services.
- Subscribers do NOT participate in data collection or analysis, nor do they have access to the raw data.
Methodology: The SKIP Program

- Survey of Key Informants’ Patients (SKIP) Program
  - 150 Substance Abuse Treatment Centers.
  - Coverage in all 50 states.
  - Opioid abusing patients complete an anonymous survey.
  - $20 Wal-Mart Gift Card.
  - Over 20,000 respondents since 2008.
Methodology: The RAPID Program

- Researchers and Participants Interacting Directly (RAPID) Program
  - 700 former SKIP Participants.
  - Quarterly web-surveys.
  - Adds context to SKIP data.
  - Qualitative information.
  - Establish two-way communication.
The Prescription Opioid Epidemic

- Two major developments of the late 1990s/early 2000s.
  - Joint Commission on Accreditation of Healthcare Organizations.
    - Pain as the fifth vital sign.
    - Recommended increase use of opioids to relieve pain.
  - Release of extended-release oxycodone.
    - Initially thought to have little abuse potential.
    - Snorting/IV injection became common.
    - Became the most widely abused prescription opioid.
The Epidemic Emerges

Why Are Prescription Opioids so Attractive

- Euphorogenic.
- They are legal, approved by FDA and prescribed by doctors.
- Seen as safer than other drugs.
- Trustworthy and predictable.
  - Dosage clearly specified on tablet/pill.
- No stigma of a “junkie”.
“The pain killers... I don’t really know much about, but I know they’re just pain killers and that my dad’s taken 'em before, my grandma’s been prescribed OxyContin before, and so I’m not afraid of those ones just 'cause they’ve been prescribed.”

“I mean... a doctor prescribes them to you... can’t be that bad....”

Confronting the Epidemic: Focus on Supply-Side Efforts

- Prescription Monitoring Programs (PMPs).
- Crackdown on ‘pill mills’.
- Physician education.
- Abuse-deterrent formulations (ADFs).
Impact of Abuse-Deterrent Formulations

- Primary focus of both NIDA and Pharmaceutical companies.
- Goal is to create safer opioids and reduce abuse.
- Chemical reformulations of prescription opioids.
  - Extraction-resistant/crush-resistant
- Lots of regulatory issues with labeling, effectiveness and prescribing outcomes.
Effect on Abuse

How Did the ADF Impact Oxycontin Abusers?

“I was immediately familiar how to get high from both the old and the new versions. I learned this by searching the Internet for information. I did research on how other drug addicts used the new formulation... It was time consuming, but it worked.”
Transition To Heroin: Drugs Selected To “Replace” Oxycontin

“Became easier to find heroin than good oxys. Also heroin was cheaper.”

“Because of the change in the OxyContin formulation I tried heroin for the first time. I did that in part because you couldn’t smoke or snort the OxyContin pills anymore so I resorted to something you could do that with”

“I heard heroin would get me higher and was cheaper and when the Oxys changed so did my choice of drug.”
Increases in Heroin Abuse

- Are ADFs solely responsible for the increase in the use of heroin?
  - Of course not.
- Shined a light on an emerging epidemic.
- Went unnoticed for a long-time.
  - Backseat to prescription opioids.
Prescription Opioids as a “Gateway” to Heroin

Heroin + Prescription Opioids

Heroin + Prescription Opioids

Heroin + Prescription Opioids

Heroin + Prescription Opioids

![Graph showing percentage of respondents over years in the West region for 2008 to 2014. The graph compares the percentage of respondents using prescription opioids only, heroin and prescription opioids, and heroin only. The line for heroin only shows a steady increase, while the other lines show a decrease.]

Heroin + Prescription Opioids

Why?: Practical Factors

“Heroin is cheaper and stronger than prescription drugs, & the supply is typically pretty consistent. It is also much easier to use intravenously than pills and other prescriptions, which often take more complex methods to break down.”

“...it was cheaper & easier to get heroine [sic], which was much stronger & would get you higher than Oxycodone.”
Evidence of Reduced Stigma

♦ “.....EVERY single person I know now that used pills, now uses heroin.....Also EVERY person I know that now uses heroin uses it intravenously. More people than I can count who I never thought would ever even try heroin are now shooting it up.”

♦ “....The 2 dealers and the people around them are middle class white kids, not even kids we were all in the age range of 25-41. It just became easy, and we weren’t really looked at as being addicts because everyone thinks heroin addicts are all homeless, shady looking, dirty junkies.”

♦ “I knew I liked it above all else, and once I had a drug dealer it became almost too easy to get. I had access to money because I’m an upper middle class family and I also became close to my dealers, driving them around so I could get paid in drugs and just becoming super close, even if it meant sexually, so I could get the drug......”
The Demand Side

What makes opioids -prescription or heroin- so attractive?
RAPID Sample

- 75% self-report they used opioids to self-medicate psychiatric related issues.
- 85% self-report the use of opioids to “escape from life”.
- No difference between those who started using from a doctor’s prescription and those who experimented.
How Do Opioids Make You Feel?

Source: Cicero TJ, Ellis MS, Kasper ZA. Understanding the demand side of the prescription opioid epidemic: does the initial source of opioids matter? Drug and Alcohol Dependence. Accepted. In Press.
“I did not have any tools for coping with uncomfortable situations. Which made using drugs my go to coping skill for anything from handling emotional abuse to taking a shower.”

“They made me feel like I could talk to people & not be scared or embarrassed to walk around & just talk & be part of society.”

“Mask inside emotions/traumas, feelings of fear, self-esteem, self-pity, anger & avoiding the growing stress & responsibility of life”

“It made me feel happy & gave me the energy & want to do daily activities such as working that otherwise wouldn’t have been possible due to the debilitating depression at that time in my life.”
Progresses to a Tipping Point

“Right before I entered my first treatment program, I was not “getting high” any more, I was purely seeking the drug to stay well.

I was tired of being addicted but could not stop using on my own, I would get into the withdraw symptoms and need to use because I would get too sick.

I would beg borrow or steal just to be able to get money to get opioids mainly heroin, or oxycontin. Because detoxing on my own was too hard, and no one knew I used so I had to be able to function everyday.”
Supply side efforts cannot exist alone.
Understanding the demand for these drugs is essential to developing effective treatment & prevention strategies.

Conclusion: Where are we headed?
First Opioid of Abuse

Percentage of Opioid Initiators

Year Beginning Regular Abuse

Hydrocodone
Oxycodone
Heroin
Other Prescription Opioids
CDC GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

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Disclosure Information

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78 Americans die every day from opioid overdose – prescription and illegal opioids

Since 1999, sales of prescription opioids in the U.S. have quadrupled.
Purpose of the Guideline

- Be a first step toward more cautious prescribing of opioids
- Reduce the number of patients exposed to opioids
- Support primary care providers with chronic pain patients
- Improve patient provider conversations about the risks and benefits of opioids
Overview of Guideline Development

♦ Conducted systematic literature review using the Grading Recommendations, Assessment, Development and Evaluation method (GRADE)

♦ Rated recommendations as Category A or B
  • Category A: Most patients should receive the recommended course of action
  • Category B: Different choices will be appropriate for different patients; providers and patients discuss values, preferences, and clinical situation

♦ Consulted core group of experts on the initial recommendations
Overview of Guideline Development continued

- Drafted a full Guideline
- Gathered feedback from experts, stakeholders, federal partners, and peer reviewers
- Shared the topline recommendations with constituents
- Revised the Guideline
- Posted for public comment
- Reviewed by the National Center for Injury Prevention and Control Board of Scientific Counselors
- Published on March 15, 2016 in the Morbidity and Mortality Weekly Report
DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

Guideline Recommendations 1-3
Guideline Recommendation 1

Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
Guideline Recommendation 3

Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
Guideline Recommendations 4-7

OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION
Guideline Recommendation 4

When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to $\geq 50$ morphine milligram equivalents (MME)/day, and should avoid increasing dosage to $\geq 90$ MME/day or carefully justify a decision to titrate dosage to $\geq 90$ MME/day.
Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.
Guideline Recommendations 8-12

ASSESSING RISK AND ADDRESSING HARMs OF OPIOID USE
Guideline Recommendation 8

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use are present.
Clinicians should review the patient’s history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
Guideline Recommendation 12

Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.
Clinical Tools
THANK YOU

For more information, please contact:
Centers for Disease Control and Prevention
1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
www.cdc.gov/info
Visit: www.cdc.gov/drugoverdose/prescribing/guideline
Treating Women for Opioid Use Disorders During Pregnancy: The Latest Research

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No potential conflicts of interest to disclose.
Overview

- Discussing methadone and buprenorphine, labeled by the US Food and Drug Administration (FDA) as Category C for use in pregnancy for the treatment of maternal opioid dependence: “Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.”

- Pregnant women with opioid use disorders can be effectively treated with methadone or buprenorphine. Both these medications should not be considered “off-label” use in the treatment of pregnant patients with opioid use disorder (Jones et al., Am J Obstet Gynecol, 2014).
Educational Objectives:

At the conclusion of this session, participants should be able to:

1. Summarize main findings and research gaps regarding medication-assisted withdrawal during pregnancy

2. Articulate the differences and similarities in maternal and neonatal outcomes following prenatal exposure to methadone, buprenorphine alone and buprenorphine + naloxone given in the context of comprehensive care to treat opioid use disorders in pregnant women
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  ♦ R01 DAs: 015764, 015738, 017513, 015778, 018410, 018417, 015741, 15832

♦ Maternal Opioid Treatment: Human Experimental Research (MOTHER) Site PIs and investigative teams

♦ Investigative teams in Chapel Hill and Michigan
Early Methadone and Pregnancy Literature

- 1973 FDA said all pregnant women on methadone must undergo 21 day detox
- The Zuspan et 1973 data showing adverse effects and fetal death helped to reverse the FDA decision
- Reduces maternal craving and fetal exposure to illicit drugs
- Produces drug abstinence, that in turn allows other behavior changes which decrease health risks to both mother and fetus
- Reduces the likelihood of complications with fetal development, labor, and delivery

NAS: Signs and Symptoms

♦ Signs of withdrawal typically start after 24-96 hours after birth depending upon the specific opioid exposure
♦ Central nervous system signs
  ♦ Tremors
  ♦ Irritability, high-pitched crying
  ♦ Sleep disturbances
  ♦ Tight muscles tone, hyperactive reflexes
  ♦ Myoclonic jerks (sometimes misinterpreted as seizures), seizures – rare
♦ Autonomic signs
  ♦ Sweating, fever, yawning and sneezing
  ♦ Rapid breathing, nasal congestion
♦ Gastrointestinal signs
  ♦ Poor feeding, vomiting and loose stools or diarrhea
WHO 2014 Guidelines: “Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification. Opioid maintenance treatment in this context refers to either methadone maintenance treatment or buprenorphine maintenance treatment.”

Guidance regarding medication treatment versus medication-assisted withdrawal has traditionally been based largely on good clinical judgment.

Medication followed by no medication treatment has frequently been found to be unsuccessful, with relatively high attrition and a rapid return to illicit opioid use.

Medication treatment facilitates retention of patients and reduces substance use compared to no medication.

Biggest concern with opioid agonist medication during pregnancy is the potential for occurrence of neonatal abstinence syndrome (NAS) – a treatable condition.
Consistent with past literatures in the ability to withdraw without obstetric complication.

Lack of fetal or maternal monitoring during withdrawal.

Lower relapse rates than most other studies.

No mention of women lost to follow-up.

### TABLE 1

Demographics, gestational age at the time of detoxification, neonatal intensive care unit admission, and pregnancy outcome of the opiate detox study population

<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>Mean maternal age, y</td>
<td>26.9 ± 3.7</td>
<td>26.4 ± 3.5</td>
<td>26.6 ± 3.6</td>
<td>27.2 ± 3.9</td>
<td>26.8 ± 3.7</td>
</tr>
<tr>
<td>Maternal age range, y</td>
<td>18–43</td>
<td>17–38</td>
<td>18–39</td>
<td>17–39</td>
<td>17–43</td>
</tr>
<tr>
<td>Maternal age &lt;30 y</td>
<td>82 (76%)</td>
<td>18 (78%)</td>
<td>55 (71%)</td>
<td>67 (72%)</td>
<td>222 (74%)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>94 (37%)</td>
<td>14 (61%)</td>
<td>54 (70%)</td>
<td>73 (78%)</td>
<td>235 (78%)</td>
</tr>
<tr>
<td>White</td>
<td>85 (79%)</td>
<td>22 (78%)</td>
<td>31 (74%)</td>
<td>27 (78%)</td>
<td>265 (88%)</td>
</tr>
<tr>
<td>African-American</td>
<td>22 (20%)</td>
<td>1 (4%)</td>
<td>3 (4%)</td>
<td>8 (9%)</td>
<td>34 (11%)</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, &gt;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 relapse²</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>

Group 1 consisted of acute detoxification (incarcerated patient). Group 2 consisted of inpatient detoxification with intense behavioral health follow-up. Group 3 consisted of inpatient detoxification without intense behavioral health follow-up. Group 4 consisted of inpatient inpatient buprenorphine detoxification.

NAS: neonatal abstinence syndrome; NICU: neonatal intensive care unit.

² One Hispanic in group 1 and one Asian in group 4. Relapse rate is defined as a positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a positive neonatal meconium test (and includes all of the patients who had neonates treated for neonatal abstinence syndrome).

Summary: Medication-assisted Withdrawal Literature

- Medication-assisted withdrawal can be completed without adverse fetal events in select women

- Less NAS and improved birthweights following successful withdrawal

- When given a choice, approximately 50% of women receiving medication assisted withdrawal choose medication treatment

- Rates of opioid relapse are almost 50%

Conclusions: Medication-assisted Withdrawal Literature

- No evidence that withdrawal is beneficial to mother, fetus or baby performed on an intent to treat basis

- Medication-assisted withdrawal has been mostly compared with methadone treatment; limited data suggest that maintenance with buprenorphine could achieve outcomes close to that of detoxification.

- Lack of evidence that direct fetal opioid withdrawal (as opposed to impaired uteroplacental blood flow) explains the fetal response to maternal opioid withdrawal
Gaps in Knowledge: Medication-assisted Withdrawal Literature

- What are the effects of medication-assisted withdrawal on maternal and fetal physiology?

- What is the relative efficacy and effectiveness of medication-assisted withdrawal compared to medication treatment for the mother, fetus and child using prospective and intent to treat designs? (any differences between women with opioid use dependence vs. chronic pain?)

- Who are the best candidates and what are the best protocols to support women who want medication-assisted withdrawal?

- To what extent are such withdrawal protocols optimal fetal monitoring at different gestational ages during detoxification?
Medication for Opioid Use Disorders

- Prevents erratic maternal opioid levels that occurs with use of illicit opioids, and so lessens fetal exposure to repeated withdrawal episodes

- Reduces maternal craving and fetal exposure to illicit drugs

- Produces drug abstinence, that in turn allows other behavior changes which decrease health risks to both mother and fetus (for example: HIV, hepatitis, and sexually transmitted infections)

- Reduces the likelihood of complications with fetal development, labor, and delivery
Medication Options

- Methadone
- Buprenorphine alone
- Buprenorphine + Naloxone
Compared with methadone-exposed neonates, buprenorphine-exposed neonates:
- Required 89% less morphine to treat NAS
- Spent 43% less time in the hospital
- Spent 58% less time in the hospital being medicated for NAS

Both medications in the context of comprehensive care produced similar maternal treatment and delivery outcomes.

Notes: Significant results are encircled. Site was a blocking factor in all analyses. The O'Brien-Fleming α spending function resulted in α = .0091 for the inferential tests of the Medication Condition effect for the 5 primary outcome measures at the conclusion of the trial.

Jones et al., N Engl J Med. 2010
OLS and Poisson regression analyses were used to test average daily number of cigarettes smoked in the past 30 days at \( \alpha = .05 \), adjusting for both Medication Condition and Site. Below-average cigarette smoking was defined as 6 cigarettes/day (-1 SD), average cigarette smoking as 14 cigarettes/day (Mean), and above-average cigarette smoking as 21 cigarettes/day (+1 SD).

Jones et al., *DAD*, 2013.
MOTHER Child Outcomes up to 36 months

N=97 children

- No pattern of differences in physical or behavioral development to support medication superiority

- No pattern of differences for infants treated for NAS v. infants who did not receive treatment for NAS

- Results indicate children born in the MOTHER study are following a path of normal development in terms of growth, cognitive and psychological development

  (Unpublished data, manuscript under review)
## Methadone v. Buprenorphine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>38.6 ± 1.5</td>
<td>39.5 ± 2.0</td>
<td>.06</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2941 ± 483</td>
<td>3250 ± 528</td>
<td>.008</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>47.6 ± 2.2</td>
<td>48.4 ± 2.5</td>
<td>.12</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>33.8 ± 1.5</td>
<td>34.0 ± 1.4</td>
<td>ns</td>
</tr>
<tr>
<td>Infants with birth weight &lt; 2500 g</td>
<td>9 (25)</td>
<td>3 (6.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Infants with birth weight ≤ −2 SD</td>
<td>11 (30.6%)</td>
<td>6 (12.8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Infants with birth height/head circ.</td>
<td>1 (2.8%)</td>
<td>1 (2.1%)</td>
<td>ns</td>
</tr>
</tbody>
</table>


Results are given as absolute numbers followed by percentages, or as means ± SD.

Buprenorphine vs. Methadone:

- Gestational age: p = .06
- Birth weight: p = .008
- Birth length: p = .12
- Head circumference: ns
- Infants with birth weight < 2500 g: p = .03
- Infants with birth weight ≤ −2 SD: ns
- Infants with birth height/head circumference ratio ≤ −2SD: ns
## Methadone v. Buprenorphine

### Neonatal Abstinence Symptoms and Treatment for the entire study period, 1982–2006

<table>
<thead>
<tr>
<th>Category</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants with any NAS</td>
<td>28 (77.8%)</td>
<td>19 (40.4%)</td>
<td>.0008</td>
</tr>
<tr>
<td>Infants treated for NAS</td>
<td>19 (52.8%)</td>
<td>7 (14.9%)</td>
<td>.0004</td>
</tr>
<tr>
<td>Total hospital stay (days)</td>
<td>19.7 ± 18.8</td>
<td>9.4 ± 8.4</td>
<td>.0009</td>
</tr>
</tbody>
</table>

# Methadone v. Buprenorphine: Newborn Outcomes

<table>
<thead>
<tr>
<th>Infant Characteristics</th>
<th>Methadone (n = 248)</th>
<th>Buprenorphine (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
</tr>
<tr>
<td>Male</td>
<td>248</td>
<td>111 (45%)</td>
</tr>
<tr>
<td>EGA at Delivery (weeks)</td>
<td>248</td>
<td>38.2 (2.5)</td>
</tr>
<tr>
<td>Preterm (EGA &lt; 37 weeks)</td>
<td>248</td>
<td>43 (17%)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>248</td>
<td>2899.7 (583.1)</td>
</tr>
<tr>
<td>Standardized, z score</td>
<td>248</td>
<td>-0.59 (.93)</td>
</tr>
<tr>
<td>&lt; 5th percentile</td>
<td>248</td>
<td>32 (13%)</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>209</td>
<td>33.0 (2.0)</td>
</tr>
<tr>
<td>Standardized, z score</td>
<td>209</td>
<td>-.50 (.80)</td>
</tr>
<tr>
<td>Treated for NAS</td>
<td>245</td>
<td>106 (42%)</td>
</tr>
<tr>
<td>Days of NAS treatment</td>
<td>106</td>
<td>133 ± 83</td>
</tr>
<tr>
<td>Length of Stay (EGA ≥ 37 weeks)</td>
<td>205</td>
<td>5.6 (2.8)</td>
</tr>
<tr>
<td>Breast Milk at Discharge</td>
<td>247</td>
<td>156 (63%)</td>
</tr>
<tr>
<td>Discharged to Mother/Family</td>
<td>248</td>
<td>237 (96%)</td>
</tr>
</tbody>
</table>

Meyer et al., *J Addict Med*, 2015
## Buprenorphine+Naloxone: Outcomes

### Maternal

<table>
<thead>
<tr>
<th></th>
<th>f (%)</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal weight gain (kg)</td>
<td></td>
<td>7.8 (3.9)</td>
</tr>
<tr>
<td>Cesarean section [yes]</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Analgesia during delivery [yes] †</td>
<td>6 (67%)</td>
<td></td>
</tr>
<tr>
<td>Urine drug screening at delivery [positive] ‡</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Days of maternal hospital stay</td>
<td></td>
<td>4.1 (4.5)</td>
</tr>
<tr>
<td>Began breastfeeding after delivery [yes]</td>
<td>3 (30%)</td>
<td></td>
</tr>
</tbody>
</table>

### Neonatal

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery (in weeks)</td>
<td>37.5 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Preterm (&lt; 37 weeks)</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td>Apgar score at 1 min / 5 min</td>
<td>8.0 (2.5) / 8.6 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>32.8 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Birthweight (gm)</td>
<td>2816.1 (368.3)</td>
<td></td>
</tr>
<tr>
<td>Infant length (cm)</td>
<td>46.3 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Treated for NAS [yes]</td>
<td>4 (40%)</td>
<td></td>
</tr>
<tr>
<td>Total amount of morphine for NAS (mg)</td>
<td>3.5 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Days treated for neonatal abstinence syndrome</td>
<td>6.9 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Days of infant hospital stay</td>
<td>10.1 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>
Buprenorphine+Naloxone v. Buprenorphine v. Methadone

Neonatal outcomes in 7 published studies: Comparing Buprenorphine+naloxone (B+N) to Buprenorphine (B), Methadone (M), and Methadone-assisted withdrawal (MAW)

- Mean head circumference was significantly higher in B+N neonates than in the MAW neonates
- Birth length for B+N neonates was shorter on average compared to B neonates, although both groups were within the normal range according to the World Health Organization (WHO) international standards of child growth
- Mean Apgar scores at 5 minutes was significantly lower in the B+N group than in the B group – with scores in the 7-10 range being considered normal.
## Buprenorphine+Naloxone v. Methadone

<table>
<thead>
<tr>
<th>Neonatal Outcomes</th>
<th>Buprenorphine + Naloxone (n=31)</th>
<th>Methadone (n=31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Treated for NAS</td>
<td>8 (25.1%)</td>
<td>16 (51.6%)</td>
<td>.01</td>
</tr>
<tr>
<td>Amount of Morphine (mg)</td>
<td>3.4 (1.2)</td>
<td>5/0 (3.3)</td>
<td>.18</td>
</tr>
<tr>
<td>Duration of NAS treatment (days)</td>
<td>10.6 (3.1)</td>
<td>11.4 (3.4)</td>
<td>.88</td>
</tr>
<tr>
<td>Peak NAS Score (range 1-25)</td>
<td>9.0 (4.4)</td>
<td>10.7 (3.7)</td>
<td>.02</td>
</tr>
</tbody>
</table>
# Buprenorphine+Naloxone v. Methadone

<table>
<thead>
<tr>
<th>Neonatal Outcomes</th>
<th>Buprenorphine + Naloxone (n=31)</th>
<th>Methadone (n=31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Preterm</td>
<td>1 (3.2%)</td>
<td>5 (16.1%)</td>
<td>.20</td>
</tr>
<tr>
<td>Apgar 5 minute</td>
<td>8 (range: 3-9)</td>
<td>8 (range: 3-9)</td>
<td>.71</td>
</tr>
<tr>
<td>Birthweight (gm)</td>
<td>3,175 (533)</td>
<td>2,886 (691)</td>
<td>.92</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>50.1 (2.5)</td>
<td>47.9 (4.0)</td>
<td>.57</td>
</tr>
<tr>
<td>Head Circumference (cm)</td>
<td>34.4 (1.4)</td>
<td>32.9 (2.5)</td>
<td>.21</td>
</tr>
<tr>
<td>Number admitted to NICU</td>
<td>6 (19.4%)</td>
<td>11 (35.5%)</td>
<td>.74</td>
</tr>
<tr>
<td>Length of hospitalization (days)</td>
<td>5.6 (5.0)</td>
<td>9.8 (7.4)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Buprenorphine+Naloxone v. Methadone

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine/ naloxone</th>
<th>Methadone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>58</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Required NAS treatment, n (%)</td>
<td>37 (64)</td>
<td>74 (80)</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to NAS onset, (days) median (range)</td>
<td>2 (1–6)</td>
<td>2 (1–9)</td>
<td>NS</td>
</tr>
<tr>
<td>Cumulative methadone dose (mg)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 ± 3</td>
<td>7 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Oral morphine equivalent (mg)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21 ± 14</td>
<td>28 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>Total NAS treatment duration (days)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32 ± 21</td>
<td>38 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>Required adjunctive phenobarbital, n (%)</td>
<td>4 (7)</td>
<td>5 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>NAS-related hospital readmission, n (%)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NAS: neonatal abstinence syndrome; SD: standard deviation.

<sup>a</sup>Mean ± SD.

<sup>b</sup>1 mg methadone = 4 mg morphine sulfate.
Encourage understanding of diversion and misuse while in treatment as indicators of medication non-adherence and evaluate and treat therapeutically.

Need careful public policy understanding that cutting off treatment access or greatly reducing it will not eliminate or guarantee less diversion and misuse.

Restricting treatment may adversely affect mortality rates.

Credit: Michelle Lofwall, MD
Summary

- Medication-assisted withdrawal may be beneficial for some select women - *many research questions need answers*.

- Current data are reassuring in that prenatal exposure to buprenorphine+naloxone outcomes do not differ from those of buprenorphine alone or methadone.
OPIOID THERAPY FOR CHRONIC PAIN IN THE UNITED STATES: PROMISES AND PERILS

Mark Sullivan, MD, PhD
University of Washington
Psychiatry and Behavioral Sciences
Anesthesiology and Pain Medicine
Bioethics and Humanities
Opioid Therapy for Chronic Pain in the United States:
Promises and Perils
October 6, 2016
Disclosure Information

Mark D. Sullivan, MD, PhD
Chrono Therapeutics- Consulting Fee- Consultant
Outline

- Promises
  - Ethical
  - Scientific
- Perils
  - Trends
  - Long-term effectiveness
  - Risks
  - Roots of opioid epidemic
- Answers and questions
Promises:

“Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.”

--Thomas Sydenham (1692)
Ethical argument for pain treatment

- Dying in pain is established as ethically unacceptable
- Ethical mandate for pain relief extended from end of life to all cancer pain
- Mandate extended to chronic non-cancer pain
  - Produces equal suffering and disability, with higher prevalence and longer duration (Sullivan and Farrell, 2005)
  - IASP Declaration of Montreal (2010) “access to pain management without discrimination”
  - US Institute of Medicine (2012): prevalent pain is undertreated pain
Ethical argument for opioid treatment

- **1986 Portenoy and Foley**: “opioid maintenance therapy can be a safe, salutary and more humane alternative... in those patients with intractable non-malignant pain and no history of drug abuse.”

- **2011 Foley et al**: “We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect.”
Responsibility to Relieve Pain and Suffering: The Opioid Interpretation

- The proper dose of pain medication is the dose that is sufficient to relieve pain and suffering. To allow a patient to experience unbearable pain or suffering is unethical medical practice.

Scientific argument for opioid treatment: efficacy

- RCTs of opioids for chronic pain show efficacy over placebo with pain intensity reduced ~30% during the usual 12 week duration of trials, with variable effects on function.

- NIH Pathways to Prevention Workshop (9/2014)
  “Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms.”
  - Chou R et al Annals Intern Med 2015; 162:276-86
Scientific argument for opioid treatment: safety

- Addiction risks for opioid therapy were initially estimated using in-patient samples and out-patient RCT samples.
- These excluded patients with MH and SA disorders, now known to be the patients most likely to receive and continue opioids in clinical practice.
  - Initial estimates: Opioid addiction 0.05%, abuse 0.4% (Porter and Jick, 1980)
  - Presence of pain thought to protect from addiction (Hagen et al 1995)
- Recent consensus addiction estimates are much higher
  - Degenhardt (2015): DSM-V mod-severe OUD 9%
Perils:

- “I was so healthy before Edmund was born. But bearing Edmund was the last straw. I was so sick afterwards... All (that doctor) knew was I was in pain. It was easy for him to stop the pain.”
- “(The medicine) kills the pain. You go back until at last you are beyond its reach. Only the past when you were happy is real.”

--Mary Tyrone,

   A Long Day’s Journey Into Night, by Eugene O’Neill
CDC: Parallel increases in opioid sales, deaths and substance abuse

From 2000-2014, 500,000 deaths from drug overdose
78 Americans die per day from opioid overdose
Still increasing...

US Rx opioid sales and deaths quadrupled since 1999

Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)

Long-term Opioid Therapy (LtOT) Trends in TROUP and CONSORT Studies

- Treatment guidelines recommended LtOT for patients with intractable pain and no history of substance abuse, with caution urged for those with a history of mental health disorder (Chou 2009)
- Studies of actual clinical practice reveal that these patients are MORE likely to receive LtOT: 
  - “Adverse selection”
    - 3-4x more likely: history of depression or other MH disorder (Braden 2009, Edlund 2010)
    - 4-5x more likely: history of alcohol or non-opioid drug abuse (Weisner 2009, Edlund 2010)
    - 5-10x more likely: opioid abuse or dependence (Weisner 2009, Edlund 2010)
- Patients with SA and MH disorders are also more likely to receive:
  - Higher opioid daily doses, higher potency DEA Schedule II opioids
  - Concurrent sedative-hypnotic medications (Saunders 2012)
Long-term Opioid Therapy (LtOT) for CNCP -- Characteristics

- COT rates similar for CNCP conditions, but COT rates double with each additional CNCP diagnosis (Braden, 2008).
- 30-40% of COT recipients use sedative-hypnotics most days. 13% drink alcohol within 2 hours of opioid use (Saunders, 2012)
- Opioid use uniquely highly concentrated (Edlund 2010):
  - In commercially insured, 5% of CNCP pts use 70% of opioids
  - In publicly insured, 5% of CNCP pts use 48% of opioids
  - MH and SA disorders concentrated in high dose users (Morasco 2010, Seal 2012, Kobus under review, Merrill under review)
Who Discontinues LtOT?

- The vast majority of opioid therapy for chronic pain is short-term.
- Even among “ideal” candidates for opioid therapy of CNCP, most discontinue therapy before reaching 90 days of therapy, either due to side-effects or lack of efficacy. (Noble 2010, Furlan 2006, Roth 2000)
- However, once LtOT (>90d) is achieved, it persists
- TROUP study of ‘daily’ LtOT recipients (Martin 2011)
  - Sample: used at least 90 days Outcome: 6 months without any opioid Rx
  - In commercially insured and Medicaid, 2/3 of patients remain on opioids years later
  - COT continuation predicted by: high daily dose (>120mg MED) and opioid misuse
- Nationwide VA study: >70% continue opioids (Vanderlip, 2014)
  - LtOT continuation predicted by: high opioid dose, multiple opioids, multiple pain problems, tobacco use, but NOT other SA, MH disorders
Long-term Effectiveness of COT

- No RCT data concerning effectiveness over years of use
- Prospective observational data
  - Opioid therapy associated with lack of pain improvement and worse physical functioning in middle-aged women (Braden 2012)
- Opioid discontinuation data
  - Opioid discontinuation during pain rehabilitation programs, associated with pain decrease, not increase (Hooten 2012)
  - Recently completed pilot RCT of outpatient opioid taper support also found pain decrease with supported opioid taper (Sullivan 2016)
Risks of COT: Medical

- Mortality and overdose
  - 47,055 lethal drug overdoses in 2014. 18,893 Rx opioid overdose deaths; 10,574 heroin overdose deaths
  - Highest rates: men, middle-aged, rural, poor, whites, (MMWR 2011)
  - Overdoses initially attributed to drug diversion and doctor-shopping: bad patient behavior (Hall 2008), but multiple studies have shown prescribed dose-dependent risk for accidental overdose and death (Dunn 2010, Gomes 2011, Bohnert 2011, Paulozzi 2012)
Risks of COT: Medical (cont’d)

- Emergency Department visits
  - CDC: 366,000 ED visits in 2011 due to misuse of opioids
  - Among patients prescribed COT, 20-30% make an ED visit per year
  - Associated with:
    - Substance abuse
    - Mental health disorder
    - Short-acting Schedule II opioid (Braden 2009)
Risks of COT: Medical (cont’d.)

- Falls and fractures
  - For patients over 60, opioids > 50mg MED doubled the risk of fractures (Saunders 2009, Miller 2011)

- Neonatal abstinence syndrome
  - Increased 2.8x from 2000-2009, with increased low birth weight, respiratory complication, and costs, especially in Medicaid (Patrick 2012)
Risks of COT: Behavioral
Indirect- US General Population Surveys

• In 2014:
  • 467,000 adolescents were nonmedical users of Rx pain relievers
  • 168,000 had an addiction to prescription pain relievers.
  • 28,000 adolescents had used heroin in the past year
  • 16,000 were current heroin users.
• Most adolescents who misuse prescription pain relievers are given them for free by a friend or relative.
• But prescribing rates for prescription opioids among adolescents and young adults nearly doubled from 1994 to 2007.
Promises and Perils of COT: Results from the US Experiment

- Promises of general safety and effectiveness of COT are unfulfilled
  - COT regimens and target populations where COT is safe and effective remain to be defined: lower dose, intermittent use?, older?
- Perils of COT beyond addiction to broader iatrogenesis
  - Clinical iatrogenesis: overdose, abuse, adverse effects in patients
  - Social iatrogenesis: escalating opioid diversion, abuse, overdose in adolescents and poor rural middle-aged adults
  - Cultural iatrogenesis: erosion of ability to manage pain in non-medical ways, and unrealistic expectations of relief. (Illich, 1976)
- The US has conducted an experiment of population-wide treatment of chronic pain with long-term opioid therapy. The benefits have been hard to demonstrate, but the harms are well demonstrated.
Interpreting Opioid Clinical Practice: Endogenous Opioid System Functions

- This system serves many other functions besides stress-induced analgesia:
  - Maternal-infant bonding
  - Reward associated with alcohol (naltrexone)
  - Sexual reward and sex drive (hypogonadism)
  - Mood regulation (Major Depression opioid dysfunction)
  - Social status and stress
  - Eating, drinking, other appetitive behaviors...
Shared Neural Substrates for Physical & Social Pain

- Physical pain and social pain use shared neural substrates.
- In primates, social attachment system borrowed the pain system, to prevent social separation (Eisenberger 2012)
  - Social pain (rejection, exclusion, loss) activates physical pain-related neural regions (anterior cingulate, anterior insula) (Eisenberger 2003)
  - Sensitivity to social or physical pain increase and decrease in parallel (Eisenberger 2006)
- Opioids decrease both physical and social pain
  - Opiates reduce distress of social separation (Panskepp 1978)
  - Opioid deficient mice show impaired maternal-infant bonding (Moles 2004)
Roots of the Opioid Epidemic

- **Adverse selection**: high risk patients paired with high-risk regimens
- False belief that guidelines and regulations can focus LtOT on physical pain
- Focus on pain intensity (0-10 NRS) as measure of treatment need:
  - Wrong goal
  - Wrong patients
  - Wrong understanding

  (Ballantyne and Sullivan, NEJM, 2015; Sullivan and Ballantyne, Pain, 2016)
Answers to Opioid Epidemic:
Opioid Risk vs Opioid Dose Reduction Strategies

- Opioid risk reduction: “universal precautions”
  - ORT, UDT, PDMP, opioid contracts, no early refills
- Opioid dose reduction: limit high daily dose opioid use
  - 2007: WA state opioid dosing guidelines (>120mg MED needs consultation)
  - 2016: CDC opioid guidelines
    - 1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain.
    - 5. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day
Parting Provocative Comments

- Framing policy as a “balanced approach” is invalid
  - Balancing: access to pain relief vs addiction/overdose risk
  - Assumes that long-term opioid therapy does provide lasting pain relief
  - And that this is the right goal in chronic pain treatment
Parting Provocative Comments (cont’d.)

- Impossible to restrict long-term opioid therapy to treatment of “physical pain” through treatment guidelines or regulations
  - Endogenous opioid system regulates both ‘physical’ and ‘mental’ pain
  - No purely biological or purely peripheral component of human pain and suffering can be identified and isolated