


**Methadone and Buprenorphine during Pregnancy**  
The Importance of Science and Clinical Care Informing Each Other



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**Objectives**

- Compare and contrast the benefits and risks of providing methadone, buprenorphine or medication assisted-withdrawal during pregnancy for the mother, fetus and neonate.
- Identify the benefits of measuring and treating neonatal opioid withdrawal using different assessment tools and medication strategies.
- Examine the different approaches for dealing with problem behaviors related to opioid addiction during pregnancy and the postpartum period.

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**Disclosures**

- Discussing 2 medications, methadone and buprenorphine, currently 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 opioid-dependent pregnant patients.
- Reckitt-Benckiser Pharmaceuticals for donated active placebo tablets and reimbursement for time and travel in 2011.

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### Acknowledgements

- Study patients and infants
- National Institute on Drug Abuse
  - 101 DAs: 015764, 015735, 017513, 015778, 018410, 018417, 015741, 15832
- Maternal Opioid Treatment: Human Experimental Research (MOHER) Site PI's and investigative teams




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### Outline



- Contexts of Opioid Use during Pregnancy
  - Historical
  - Current
- Pharmacotherapy for the opioid-dependent pregnant patient
  - Methadone
  - Buprenorphine
- NAS Measures and treatments
- Strategies for addressing challenging patients

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### Historical Context of Opioid Use during Pregnancy

- > Morphine was marketed by Merck beginning in 1827 for pain relief, treatment of opium addiction and 'alcoholism' treatment.
- > It became popular as a recreational substance with the development of the hypodermic needle.
- > Women in the US were twice as likely as men to use morphine, many of whom were middle- or upper-middle class women who had first used the drug to treat any of a variety of illnesses.
- > Diacetylmorphine was discovered in 1874 in England, and subsequently synthesized and brought to market in 1898 by the Bayer pharmaceutical company in Germany under the trade name Heroin.
- > The marketing campaign stressed that Heroin was a "safe, non-addictive" substitute for morphine. Indeed, the American Medical Association approved Heroin for general use in 1906, and recommended that it be used in place of morphine.




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### Historical Context of Opioid Use during Pregnancy

Substance use during pregnancy in the USA has been a long-standing important health issue. In the 1800s:

- 88-76% of individuals with opium use disorders were women
- Women's most common opium source was medical prescriptions to treat pain
- Physicians recognized neonatal opioid withdrawal and the need to treat in utero opium exposure with morphine in order to prevent morbidity and mortality
- Following the 1914 Harrison Narcotics Act, the treatment of substance use disorders was segregated from mainstream medical practice



Kovak, Substance and Abuse, 1994, Paris, Medical Students, 1993

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### Current Context of Opioid Use during Pregnancy

#### Neonatal abstinence syndrome (NAS)

#### Signs and Symptoms

- > **Neurologic excitability**  
hyperactivity, irritability, sleep disturbance
- > **Gastrointestinal dysfunction**  
uncoordinated sucking, swallowing, vomiting
- > **Autonomic signs**  
fever, sweating, nasal stuffiness

#### History

- 1985 Goodfriend et al., and associates report neonatal withdrawal signs
- 1971 Zelson et al., reported frequency of signs of neonatal withdrawal in 250 of 384 infants born to drug-abusing mothers
- 1975 Diamond and Wilson publish Neonatal abstinence syndrome: Recognition and diagnosis.
- 1975 Finnegan et al., publish neonatal abstinence syndrome tool

Finnegan and Kulkarni, J. R., Washburn, R.K., Pridmore, S.B., Wilson and K.D. Rubin, Pediatrics, 1972

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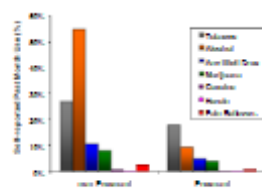
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### Current Context of Opioid Use during Pregnancy

National Survey on Drug Use and Health 2011/12  
Past Month Use



- The two most common drugs used by non-pregnant women have been alcohol and tobacco
- This same statement is true for pregnant women
- Among pregnant women in the United States, approximately 18% smoked cigarettes, 9.4% drank alcohol, and 5% used illicit drugs in the past month
- Among pregnant women, approximately .2% used heroin, and .9% used pain relievers non-medically in the past month

NSDUHS Office of Applied Publications, 2011 2012

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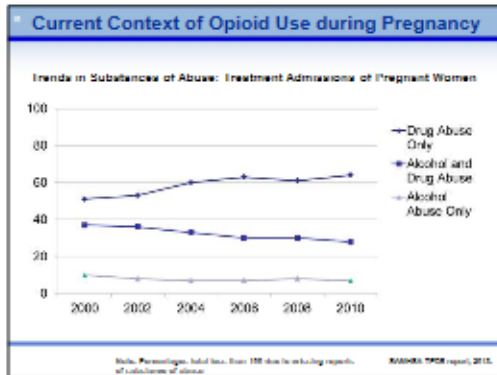
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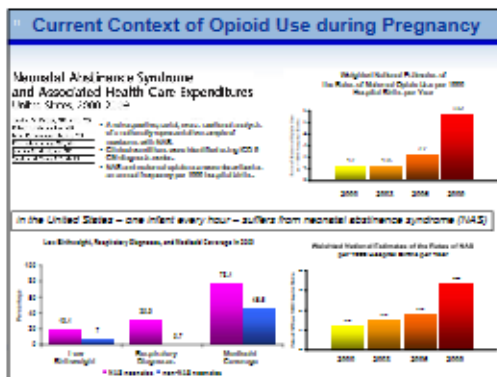
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### Current Context of Opioid Use during Pregnancy

**In the US, it is estimated that:**

- 100 million people have chronic pain
- 22 million are living with addiction, and of those individuals
  - ↳ 7 million misuse prescription medications

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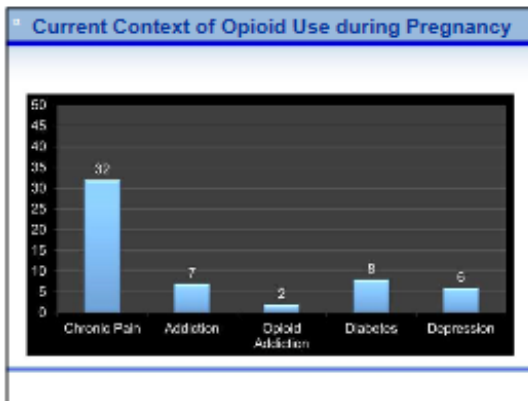
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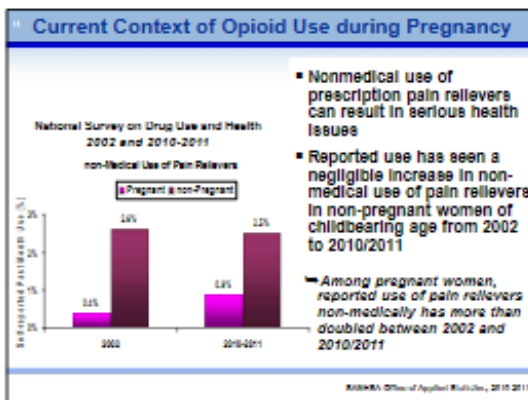
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**Current Context of Opioid Use during Pregnancy**

**MEDIA AND POLITICAL ATTENTION**

July, 2012. New York Senator Charles Schumer called on the FDA to provide clear labels so women and health care professionals know the potential dangers of the medication they are taking. He said that SAMHSA must educate physicians to better identify symptoms of prescription drug abuse, and NIH and CDC need to conduct more research that will help mothers avoid addiction.

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**Current Context of Opioid Use during Pregnancy**

Why are more individuals, including pregnant women, using opioids?

- There has been an increase in the access to these medications
- It has become the 5<sup>th</sup> vital sign in the early 21<sup>st</sup> century
- Federal prosecutors allege in documents filed in U.S. District Court that Chris and Jeff George from Florida dramatically increased the numbers of pain clinics in Florida and routed opioid pain medications to Kentucky, Ohio and South Carolina




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**Current Context of Opioid Use during Pregnancy**

Examined whether maternal opioid treatment between 1 month before pregnancy and the first trimester was associated with birth with at least 200 case infants or at least 4 exposed case infants using data from National Birth Defects Prevention Study for the period 1997 through 2005.

Therapeutic opioid use was reported by 2.8% of 17,440 case mothers and 2.0% of 8,701 control mothers

- Opioid treatment was statistically significantly associated with
  - conotruncular septal defects
  - atrioventricular septal defects
  - hypoplastic left heart syndrome
  - spina bifida gastrochisis
- Moderate absolute increase in risk above the baseline birth defects risk. For example, the estimated birth prevalence of hypoplastic left heart syndrome in the United States is 2,470,000 live births
- Findings suggest a potentially 2.4-fold increased risk for a hypoplastic left heart syndrome-affected pregnancy in a woman taking opioid analgesics periconceptionally
- Would suggest up to a 5.8 in 10,000 (0.058%) chance of that woman having an infant with hypoplastic left heart syndrome

Rosenfeld et al., Am J Obstet Gynecol 2011

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**Current Context of Opioid Use during Pregnancy**

Three concerns severely limit its future research and clinical usefulness:

- Drug use data are collected retrospectively "between 6 weeks and 2 years" post delivery
- Measuring tobacco use as "periconceptional smoking status (no-smoking from 1 month before to 1 month postconception, smoking at least once in the same period)" ignores mothers smoking 1 cigarette once to mothers smoking 2 packs daily

These 2 measurement issues seriously threaten the study's statistical conclusion validity.

- Respondents (60%) reported common prescription opioid use reasons were "surgical procedures (41%), infections (24%), chronic diseases (20%), and injuries (10%)."  
The extent to which these issues are independently related to the birth defects described is unknown.
  - Also unknown is whether or not the cases and controls differed in their respective prevalence of these events. These are stressful events, and stress can influence fetal and neonatal outcomes
  - Limiting the measurement and statistical control of stressful events potentially biases the results
  - The potential relationship between birth defects and other medications (e.g., acetaminophen) that are present in opioid analgesic medications was not addressed

James et al., Am J Obstet Gynecol 2011

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**Definition of Addiction**

**American Society of Addiction Medicine:**

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

Addiction is characterized by inability to:

- > consistently abstain
- > engage in behavioral control
- > craving
- > diminished recognition of significant problems with one's behaviors and interpersonal relationships
- > dysfunctional emotional response

Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

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**What Does Addiction Look Like In Women?**



- Initiation of drug use
- How she obtains her drugs
- Where she uses her drugs
- How she recovers from drug use

→ Untreated addiction places a woman and her fetus at risk for multiple adverse consequences

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**Current Context of Opioid Use during Pregnancy**

**Issues facing drug-using pregnant women and their children**



- Exposure to violence and trauma
- Generational drug use
- Lack of formal education
- Lack of job acquisition and maintenance skills
- Gender inequality/male-focused society
- Legal involvement
- Multiple drug exposure
- Limited parenting skills and resources
- History of child abuse and neglect
- Multiple psychiatric issues
- Unstable housing
- Lack of positive and supportive relationships
- Food insecurity and lack of nutrition

→ These factors with or without drug use can influence mother and child outcomes

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**Current Context of Opioid Use during Pregnancy**

**Factors Influencing Mother and Child Outcomes**



- Exposure to emotional, physical and sexual violence
- History of childhood abuse and neglect
- Multiple drug exposure (e.g., alcohol and tobacco)
- Poor maternal/child attachment
- Child abuse
- Psychiatric status of caregiver
- Stable caregiver and environment
- Nutrition

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**Summary of Historical and Current Context**

- ◆ Although less frequent than alcohol and tobacco use, opioid misuse during pregnancy is nonetheless a serious and growing issue
- ◆ This increase in use of opioids by pregnant women appears to be driving an increase in the incidence of neonatal opioid withdrawal
- ◆ Opioid use by pregnant women is often complicated by polydrug use, and often occurs intertwined with complex personal, interpersonal, family, social, and environmental factors that can contribute to adverse consequences
- ◆ Women have unique needs for addiction treatment and multi-faceted interventions are needed to help prevent and treat opioid-dependence among women during pregnancy and their infants

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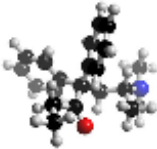
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**Pharmacotherapy for Opioid Dependence**



- Prevention of erratic maternal opioid levels lessens fetal exposure to repeated withdrawal episodes
- Reduces maternal craving and fetal exposure to illicit drugs
- With drug abstinence, other behavior changes can follow which decrease risks to mother/fetus of infection from HIV, hepatitis and sexually transmitted infections
- Reduces the incidence of obstetrical and fetal complications and improves outcomes

Revised by K. B. Smith et al., *Current Opinion in Obstetrics and Gynecology*, 2012.

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### 26 Methadone



- Schedule II opioid
- Synthetically derived
- $\mu$ -opioid receptor agonist
- also uniquely a  $\delta$ -opioid receptor agonist
- Antagonist at NMDA receptors
- Half-life estimated to fall in the range of 24-36 hours
- It is one part of a complete treatment approach

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### 27 Methadone: Induction and Dosing



- Can be provided in inpatient or outpatient settings
- Patients typically begun on methadone when they are in mild withdrawal
- Benzodiazepines and alcohol should be ruled out before induction to minimize the likelihood of overmeditation
- Patients are typically given in observed doses; 1<sup>st</sup> dose is small; observe for possible adverse effects
- Assuming no adverse effects, dose is titrated until it prevents withdrawal, cravings, and possible continued use of illicit opioids

- Optimal dose varies greatly between patients
- Blood concentrations of patients on an equivalent dose, adjusted for body weight, have been estimated to vary between 17- and 41-fold
- Dosing does not have to be more complicated for pregnant patients

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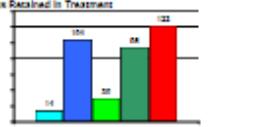
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### 28 Methadone v. Tapering

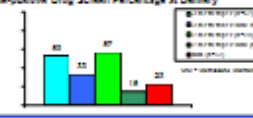
**Days Retained in Treatment**



Group	Days Retained
1 (Tapering)	14
2 (Methadone)	106
3 (Methadone)	37
4 (Methadone)	88
5 (Methadone)	122

- Guidance regarding tapering v. maintenance was based largely on good clinical judgment
- Methadone taper followed by drug-free treatment is frequently unsuccessful
- Methadone maintenance facilitates retention of patients and reduces drug use

**Urine-positive Drug Screen Percentage at Delivery**



Group	Percentage
1 (Tapering)	43
2 (Methadone)	22
3 (Methadone)	67
4 (Methadone)	18
5 (Methadone)	25

Jensen et al., *Am J Obstet Gynecol*, 2005.

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### Methadone: Dosing during Pregnancy

- In the 1970s, a positive relationship between maternal methadone dose and NAS severity was reported
- Recommendations to maintain pregnant women on methadone doses between 20 to 40 mg
- 3 decades of research shows an inconsistent relationship between maternal methadone dose and NAS severity
- The latest systematic review and meta-analysis concluded that the "severity of the neonatal abstinence syndrome does not appear to differ according to whether mothers are on high- or low-dose methadone maintenance therapy."

Review by Chang et al., Pediatrics, 2010.

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### Methadone: Dosing during Pregnancy


#### Split Dosing

- **Maternal Results**
  - increase drug negative urine during treatment
  - increased adherence with treatment
  - decrease withdrawal symptoms in mother
  - No change in maternal heart rate, vagal tone or skin conductance
- **Fetal Results**
  - Minimize the reduction in breathing
  - Minimize the reduction in movement
  - fetal movement-fetal heart rate coupling less suppressed

AM



12 hrs



PM

DuPont et al., 1998; Kroll et al., 1999; Williams et al., 1997; Jansson et al., 2009

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### Methadone: NAS

Methadone-associated NAS	
NAS signs	55-80%
Requiring medication	~ 80%
NAS appears	45 to 72 hrs
NAS peaks	40 to 120 hrs

- Most common medication for treatment is morphine
- Most common assessment tool is a "modified" Finnegan scale
- No current standard uniform protocol for treatment

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**Methadone: Pain Management**

**Pain and Opioid Dependence  
Common Misconceptions**

- + Maintenance agonist doses provide analgesia
- + Prescription of opioids will be additive and cause respiratory depression and overdose
- + Prescription of short-acting opioids even in a controlled setting to an addicted person will cause a relapse
- + Request for pain management with opioids is part of "addictive behavior" by the patient



(Schnoll, et al., 2010)

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**Methadone: Pain Management**

- Savage and Schotterman noted that patients who use opioids may have a "syndrome of pain facilitation"
- Their pain is worsened by their experience of their addiction, including:
  - subtle withdrawal signs and symptoms
  - miscalculation
  - withdrawal-related sympathetic nervous system arousal
  - sleep disturbances
  - affective changes
- Patients who are dependent on opioids are known to be less tolerant of pain than formerly opioid-dependent individuals
- Long-term exposure to opioids produces both tolerance and hyperalgesia, reducing the analgesic effectiveness of opioids themselves
- Treatment of post-partum acute pain likely best attempted with PCA and/or acetaminophen and/or NSAIDS in addition to methadone dosing

*Pregnant women in methadone maintenance treatment should not receive opioid agonist/antagonist pain medications (such as pentazocine or butorphanol) for acute pain because these medications may cause an acute opioid withdrawal syndrome*

Rouge & Robinson, In: Wilton & M. B. Fildes, Editors, 1998, Jones, et al., Am J Drug Abuse, 2005, Meyer et al., Death & Space, 2007.

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**Methadone: Pain Management**

**General Recommendations**

- > Uninterrupted agonist therapy
- > Aggressive pain management with nonpharmacologic and nonopioid analgesic pain-relieving interventions
- > Titrate opioid analgesics to achieve pain relief (generally higher doses of opioid analgesic administered at shorter intervals)
- > Reduce anxiety of patient and treatment team with clear open communication (especially important in those with PTSD as fear of pain is elevated in adults with co-occurring trauma-related stress and social anxiety symptoms)



(Schnoll, et al., 2010, Alexander et al., 2008)

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**Methadone: Breastfeeding**

**Breastfeeding in Methadone-Stabilized Mothers**

- Methadone detected in breast milk in very low levels
- Methadone concentrations in breast milk are unrelated to maternal methadone dose
- The amount of methadone ingested by the infant is low (i.e., an average 0.2 mg/day by 30 days post-delivery)
- The amount of methadone ingested by the infant remains low even 6 months later
- Several studies show relationships between breastfeeding and reduced NAS severity and duration
- Hepatitis C is not a contraindication for breastfeeding
- Contraindications: HIV+, unstable recovery



Chenillo, Clin Obstet Gynecol 2010; AAP Pediatrics 2012; Wallace et al., 2011; Jansen et al., 2007; Jansen et al., 2010.

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**Methadone: Breastfeeding**

**Barriers to Breast Feeding**

- Infant experiencing NAS may have significant difficulties with breastfeeding
  - Excessive irritability
  - Crying
  - Disorganized suck
  - Mother's feelings of guilt about causing the NAS- may prefer not to further upset the infant
- Pediatric providers that are unaware of current recommendations
- Stigma resulting in discouraging or undermining of women's effort to breast feed



eg, Jansen et al., J Fam Pract 2011

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**Methadone: Child Development**

Research focusing on the effects of prenatal exposure to methadone has been inconsistent

- Long-term effects on physical growth have not been demonstrated
- Although some research has shown that methadone-exposed school-age children to be less interactive, more aggressive, and showing poorer achievement than children not so exposed, other research has failed to show any differences in either cognitive or social development
- The issue is confounded by the fact that children exposed to methadone in utero may experience a nutritional, family, and parenting history quite different than children not so exposed.

Kelso et al., Pediatrics 2010; Kral et al., Can J Neurology 2010.

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**Methadone: Summary**

*40 years of documented benefits of methadone during pregnancy*



- Induction is relatively simple
- Adequate doses are needed to prevent withdrawal and other opioid use
- Indicators of fetal well-being are less compromised with split-dosing
- NAS is worse with heavier smoking
- Breastfeeding is compatible with methadone

Reference: Kolobashov et al., *Current Opinion in Obstetrics and Gynecology*, 2008.

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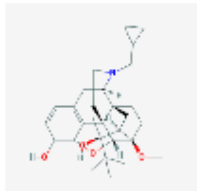
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**Buprenorphine**

- A derivative of the opioid alkaloid thebaine
- Schedule III opioid
- $\mu$ -opioid receptor partial agonist
- primarily antagonistic actions on  $\kappa$ -opioid and  $\delta$ -opioid receptors
- Half-life estimated to fall in the range of 24-60 hours



Reference: In Jones et al., *Diagn, 2012, and Self-Help, In press.*

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**Buprenorphine: Formulations**

- Buprenorphine mono product (e.g., Subutex)
- Buprenorphine + naloxone (e.g., Suboxone)
  - 4:1 ratio to prevent misuse by injection
- 2 mg and 8 mg sublingual tablets
- 2 mg/0.5 mg and 8 mg/2 mg sublingual film strips



Reference: In Jones et al., *Diagn, 2012, and Self-Help, In press.*

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**Buprenorphine: Induction and Dosing**

- Patient must already be in withdrawal or buprenorphine may precipitate withdrawal
- Patients dependent on short-acting opioids (e.g., heroin, most prescription narcotics) will not take as long to enter withdrawal as patients dependent on long-acting opioids (e.g., methadone)
- Induction typically then takes places over a 3-day period, beginning with either 2 mg or 4 mg, with a maximum dose of:
  - 8 mg – 12 mg on Day 1
  - 12 mg – 16 mg on Day 2
  - 16 mg up to 32 mg on Day 3

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**Buprenorphine: Induction and Dosing**

→ The best induction protocol for opioid-dependent pregnant women is not known

Meyer has developed an outpatient protocol:

- Similar to established protocols for non-pregnant patients
- Ask patient to abstain from opioid use 1-2 days prior
- Expect a CINA score in 10-12 range to initiate treatment
- Adjust dose every 1-3 days
- Titrate to symptom control as for non-pregnant patients
- Takes place in the context of considerable program staff support

→ As with methadone, there is the potential need to increase dosage during the course of pregnancy

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**Buprenorphine and Pregnancy**

- Since 1995, over 40 published reports of prenatal exposure to buprenorphine maintenance
- Approximately 750 babies prenatally exposed to buprenorphine (number of cases per report ranged from 1 to 159; Median=14)
- Dose range 0.4 to 32 mg
- 88% reported concomitant drug use



Reardon, et al. Journal of Drug Abuse, 2012, and Jaffe et al., 2012.

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### Buprenorphine: Maternal Outcomes

- Research with buprenorphine not as extensive as with methadone
- Well-tolerated and generally safe
- In contrast to the research with methadone, little research has compared buprenorphine to an untreated control group
- Rather, buprenorphine has been compared in both retrospective and prospective studies to methadone
- Majority of research would suggest that maternal outcomes are not in any way different than for methadone



Marlow, In Jones, et al., Drugs, 2012, and Walker, 2012.

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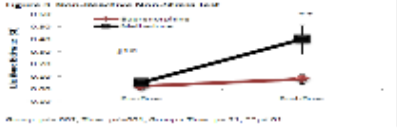
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### Buprenorphine: Fetal Outcomes

**Figure 9. Neurobehavioral Assessment Scale**



Time Point	Buprenorphine (Mean ± SD)	Methadone (Mean ± SD)
24 hours	~10.5 (1.5)	~10.5 (1.5)
48 hours	~10.5 (1.5)	~11.5 (1.5)

**Figure 10. Apgar 1 and 5 Scores**



Time Point	Parameter	Buprenorphine (Mean ± SD)	Methadone (Mean ± SD)
24 hours	Apgar 1	~8.5 (0.5)	~8.5 (0.5)
	Apgar 5	~9.5 (0.5)	~9.5 (0.5)
48 hours	Apgar 1	~8.5 (0.5)	~8.5 (0.5)
	Apgar 5	~9.5 (0.5)	~9.5 (0.5)

Ball, et al., Walker, 2012.

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### Buprenorphine: NAS

- Incidence rate for NAS is estimated to be 60% – about the same as for methadone
- NAS onset approximately 48 hours
- Peaking within approximately 72-88 hours
- Exceptions to this onset history have been the few neonates with NAS onset of 3-10 days postnatal age
  - such a protracted withdrawal syndrome may be due to withdrawal from concomitant drug exposure (e.g., benzodiazepines) rather than a direct effect of buprenorphine withdrawal
- Correlation between buprenorphine dose and NAS severity has been inconsistent

Marlow, In Jones, et al., Drugs, 2012, and Walker, 2012.

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### Buprenorphine: Pain Management



- Full agonist opioids can effectively treat pain in patients stabilized on either methadone or buprenorphine
- These results are consistent with data from non-pregnant surgery patients
- The importance of uninterrupted methadone or buprenorphine treatment in these patients is critical
- Each patient needs a pain management plan before delivery

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### Buprenorphine: Breastfeeding



- Buprenorphine is found in breast milk 2 hours post-maternal dosing
- Concentration of buprenorphine in breast milk is low
- Amount of buprenorphine or norbuprenorphine the infant receives via breast milk is only 1%
- Most recent guidelines: "the amounts of buprenorphine in human milk are small and unlikely to have negative effects on the developing infant"
- "The advantages of breastfeeding prevail despite the risks of an infant opiate intoxication caused by methadone or buprenorphine."

Alkawas et al., 1999; Wang et al., 1997; Johnson et al., 2011; Borek et al., 2008; Schneider et al., 2009; Johnson et al., 2009; Wilson et al., 2011.

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### Buprenorphine: Child Development



- Research on the neonatal consequences of prenatal exposure to buprenorphine is quite limited
- Not enough births have been followed for a sufficient period of time to collect convincing data regarding factors such as cognitive and social development
- Same issue of confounding parental and family factors in teasing apart developmental effect

Reardon, in Jones et al., Drugs, 2012, and Johnson, 2012.

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### MOTHER: Sites

**Lead Site:** Johns Hopkins U. PI: H. Jones  
**Co-Lead Site:** U. Pitt. PI: D. Lester  
**Other Sites:** Thomas Jefferson U. PI: K. Kabanbach  
 U. Vermont PI: S. Hill  
 U. Miami PI: G. Fischer  
 U. Toronto PI: P. Galby  
 Vanderbilt U. PI: P. Martin  
 Wayne State U. PI: S. Saha  
 Coordinating Center: PI: A. Arora

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### MOTHER: Buprenorphine v. Methadone

- Compared with methadone-exposed neonates, buprenorphine-exposed neonates
  - Required 32% less morphine to treat NAC
  - Spent 42% less time in the hospital
  - Spent 55% less time in the hospital being medicated for NAC
- Both medications in the context of comprehensive care produced similar maternal treatment and delivery outcomes

Note: All p-values are unadjusted. NAC = naloxone. Data are from a trial analysis. The Opioid Challenge Study was registered on ClinicalTrials.gov (NCT00740001) in 2005. For the full text of the study, please refer to the Supplementary Appendices of the manuscript at [www.jco.org](http://www.jco.org).

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### MOTHER: Buprenorphine v. Methadone

- Clinically meaningful attrition rate in buprenorphine condition
- Low rates of illicit drug use during pregnancy and at delivery
- Maternal outcomes similar in the 2 study conditions

Note: All p-values are unadjusted. Data are from a trial analysis. The Opioid Challenge Study was registered on ClinicalTrials.gov (NCT00740001) in 2005. For the full text of the study, please refer to the Supplementary Appendices of the manuscript at [www.jco.org](http://www.jco.org).

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**Summary: Buprenorphine**

- MOTHER provided the first RCT data to support the safety and efficacy of methadone
- Maternal outcomes are similar between medications
- Pain management and breastfeeding recommendations are similar between medications
- In terms of NAS severity, buprenorphine should be a front-line medication option for managing opioid-dependence for pregnant women who are new to treatment or maintained on buprenorphine pre-pregnancy
- NAS, its treatment and elucidating factors that exacerbate and minimize it, remains a significant clinical concern for prenatally opioid-exposed neonates
- Currently there is great variation in terms of medications and use of tools.

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**NAS: Factors**

Other factors that contribute to severity of NAS in neonates exposed to opioid agonists in utero:

- > Genetics
- > Other Substances
  - Cigarette smoking
  - Benzodiazepines
  - SSRI's
- > Hospital Protocols
  - The NAS assessment and medication titration and weaning protocols
  - Not breastfeeding
  - Rooming in or separating mother and baby



Jensen and Wiley, Curr Opin Pediatrics, 2012

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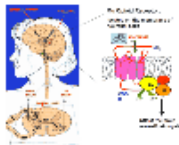
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**NAS: Factors**

A study of newborns with NAS found a relationship between allelic variants of OPRM1 (opioid receptor  $\mu_1$ ), COMT (catechol-o-methyltransferase) which affect autonomic instability during withdrawal, and ABCB1 (multidrug resistance):



- > Variants in the OPRM1 and COMT genes were associated with a shorter length of hospital stay and less need for treatment.
- > Associations with the ABCB1 were not significant

Chen et al., PLoS One, 2012

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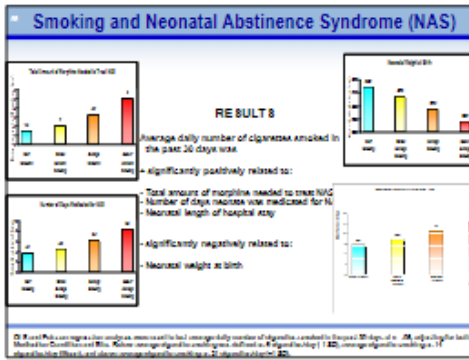
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**Smoking and Neonatal Abstinence Syndrome (NAS)**

**Practical Viewpoint on the Results**

Among pregnant women in opioid agonist treatment, compared to those women who do not smoke, smoking an average of a pack of cigarettes per day would likely be related to the following:

- More than 3% decrease in neonatal birth weight
- More than triple the total amount of morphine needed to treat NAS
- More than double the number of days required to treat NAS
- Almost double the length of the neonatal hospital stay

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**NAS: Assessment and Treatment Background**

- It is essential that infection, hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyperthyroidism, CN 8 hemorrhage, and anoxia be ruled out as the cause of the signs.
- Each nursery should adopt an abstinence scoring method to measure the severity of withdrawal.
- If pharmacologic management is chosen, relatively specific therapy, that is, a drug from the same class as that causing withdrawal, is preferable.



Canadian Paediatric Society, Committee on Drugs. Neonatal drug withdrawal. Paediatrics, 2012, 125:e817-85.

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**NAS: Assessment and Treatment Background**

- The decision to use drug therapy must be individualized, based on the severity of withdrawal signs and an assessment of the risks and benefits of therapy.
- Infants with confirmed drug exposure who do not have signs of withdrawal do not require therapy.
- Indications for drug therapy are seizures, poor feeding, diarrhea, and vomiting resulting in excessive weight loss and dehydration, inability to sleep, and fever unrelated to infection.



American Academy of Pediatrics. Committee on Drugs. Neonatal drug withdrawal. Pediatrics. 2012; 129:e107-15.

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**NAS: Assessment and Treatment Background**

- Improvement in abstinence scores should assist in assessing the appropriate timing for decreasing the dose of the drug chosen.
- Guides to adequate therapy include a normal temperature curve, the ability of the infant to sleep between feeding and medications, a decrease in activity and crying, a decrease in motor instability, and weight gain.



American Academy of Pediatrics. Committee on Drugs. Neonatal drug withdrawal. Pediatrics. 2012; 129:e107-15.

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**NAS: Measurement**

- The NUDSS (Lipsett 1 et al) assigns a score of 0-3 for tremors, irritability, reflexes, stools, muscle tone, skin abrasions, and tachypnea. In addition, a score of 0 or 1 is assigned for repetitive sneezing, repetitive yawning, and vomiting or fever. The AAP had previously endorsed the NUDSS as the method of choice for the measurement of NAS in 1998, because it uses a relatively simple numerical scoring method, with a 77% sensitivity as an indication of significant signs of withdrawal, using a cutoff score of 5 or greater.
- The Oatrea system scores only vomiting, diarrhea, weight loss, irritability, tremors or twitching, and tachypnea, and uses a simple ranking of mild, moderate, or severe rather than a numeric scale. This ranking procedure is often seen as a limitation, as it prevents the summation of the severity of multiple signs and symptoms.
- The Finnegan Scale uses a weighted score of 21 items, and requires considerable staff training and time for assessment of the neonate.
- A modified Finnegan scale is the most commonly used NAS assessment method (85% of surveyed hospitals)

Reke, David J. Pediatrics. 2008; Jensen, Vibe; Klemm, J. Child Health. 2008; Jensen, Vibe; Pediatrics. 2011.

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### NAS: Measurement and Response

- All NAS instruments have common features of summing item scores and/or weighting the severity of presenting signs
- NAS evaluation is recommended every 3 to 4 hours during hospitalization; surveillance should last for several days after birth and for entire hospitalization
- Scores above a threshold trigger medication initiation to reduce NAS severity – no or delayed treatment can result in morbidity or mortality
- Stabilization on medication promotes regular eating and sleeping patterns, weight gain, and improved interaction with caregivers
- Medication amount is increased then gradually decreased until the neonate is stable without medication

Reilly, Davis. J Perinatol 2009; January/February; Kwonan. J Spinal Nursing 2009; January/February; Kim 2011.

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### NAS Assessment: MOTHER NAS Scale

The screenshot shows a complex assessment form with multiple columns for recording different signs and symptoms over time. The form includes sections for patient information, a list of signs to be observed, and a grid for recording the presence and severity of these signs. The grid has columns for 'Present', 'Absent', and 'Score' for each sign.

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### NAS Assessment: MOTHER NAS Scale

#### Modified Finnegan Scale

- ▶ Scoring for the Following Signs and Symptoms:
  - Excessive cry (2-3)
  - Sleeping problems (1-3)
  - Tonal problems
    - Exaggerated Moro reflex (1-2), Tremor (1-2), Hypertonicity (1-2)
  - Excoriation (1-2)
  - Seizures (3)
  - Autonomic signs
    - Hyperthermia (1), Yawning (1), Nasal stuffiness (1), Sneezing (1)
  - Tachypnea (2)
  - Feeding concerns
    - Poor feeding (2), Vomiting (2), Loose stools (2)
  - Failure to Thrive (2)
  - Irritability (1-3)

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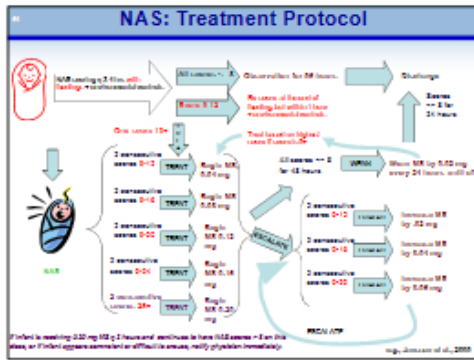
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### NAS Treatment

- + Opiates used for NAS due to opiate withdrawal have included:
  - tincture of opium or morphine (65%)
  - methadone (20%)
  - paregoric (contains anhydrous morphine with antispasmodics, amphetamines, 45% ethanol, and benzoin)
- + Sedatives used for opiate withdrawal have included:
  - chloralhydrate (an alpha2 pre-synaptic blocker)
  - chlorpromazine
  - phenobarbital
  - diazepam
- + Non-pharmacological treatments used have included swaddling, settling, massage, relaxation baths, pacifiers and waterbeds

Chen MK, Davis RB. American Journal of Diseases of Children 155(10):1085-9, 2001. Also: Kelly M, Miller Y, Rosen RM. Pediatrics 106(1):108-11, 2000. Baker, Davis. Management of neonatal abstinence syndrome in neonatal intensive care units with a protocol. Pediatrics 115(2):24-7, 2005.

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### NAS: Recommendations

- NAS occurs in the majority of all prenatally opiate-exposed neonates
- Medication to treat NAS is required in approximately 50% of the cases
- NAS following prenatal exposure to an opiate agonist is best assessed with a standard scoring tool and best treated with an opiate medication
- Patients and the providers who treat them will be best served through having a range of medication options from which to tailor treatment
- As treatment for maternal opiate dependence advances, so must neonatal treatment (i.e., buprenorphine in the infant may be an important medication for treatment of buprenorphine exposure in utero)

Chen MK et al. Opiate treatment for opiate withdrawal in newborn infants. Pediatrics 115(2):24-7, 2005.

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### Strategies to Deal with Challenging Patients

- ▶ Praise good behavior
- ▶ Validate and support
- ▶ Affirm and offer hope
- ▶ Treat with respect
- ▶ Reflect and re-frame her perspective  
(e.g., if she says she can't – see what CAN she do?)
- ▶ Do not take things personally
- ▶ Ask questions rather than making statements
- ▶ Prepare the environment

**About a Nurse**



*"The doctor doesn't need to answer your question. The nurse is most likely from hitting the call button over 50 times in the last hour."*

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### Nurture Yourself


#### Tips to reduce burnout

- Create opportunities to debrief, and use professional counseling when appropriate
- Be kind to yourself and have fun
- Stay healthy through restorative self-care and remember to laugh
- Set healthy boundaries
- Acknowledge your own attitudes, values and preferences
- Create rituals to delineate work time from personal time
- Reflect on powerful or difficult experiences through journaling and the support of peers, spiritual teachers and mentors to recover a sense of meaning, purpose and connection in life.

**About a Nurse**



*"Frank, just go and mediate. I just have to get the blood test."*



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### Take-home Messages



- ▶ Opioid addiction is a treatable illness
- ▶ Having more medications given in the context of comprehensive services to treat opioid-dependent pregnant women will optimize care
- ▶ Resilience or vulnerability following prenatal exposure to either illicit drugs or the medications to treat them are largely a function of the postnatal not the prenatal environment
- ▶ NAS is a treatable condition that deserves more study to find the most optimal medications and treatment protocols
- ▶ Nurturing yourself is critical to caring for others

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**Resources**



Vermont Oxford Network

- ▶ <http://www.youtube.com/watch?v=2Hsmx2b6L28>
- ▶ [DHMC Neonatal Abstinence Syndrome](#)
- ▶ <http://pcmh.uon.ca/LinkClick.aspx?linkid=2119&pgbID=333&tabid=40>
- ▶ <http://www.nesadventure.com/index.html>
- ▶ <http://www.vfoxford.org/home.aspx>
- ▶ [http://www.health.qld.gov.au/qcpj/documents/qj\\_nsa2-0.pdf](http://www.health.qld.gov.au/qcpj/documents/qj_nsa2-0.pdf)
- ▶ <http://www.uvm.edu/medicine/vchp/documents/VCHP%20NEONATAL%20GUIDELINES.pdf>
- ▶ <http://pediatrics.aappublications.org/content/101/8/1079.full>

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Questions & Answers

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