PHARMACOTHERAPY: PERINATAL OPIOID USE DISORDERS

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PERINATAL OPIOID USE DISORDERS

OBJECTIVES

- Approach
- Treatment
  - Pharmacotherapy & Management
    - Medications for Opioid Use Disorders (MOUD) [NOTE: No longer use term Medication Assisted Therapy (MAT)]

GOAL 1: PROVIDER
BUILDING FRONTLINE PROVIDER CAPACITY

GOAL 2: PATIENT
ACCESS TO MH/SUD CARE

843-792-MOMS
(843)-792-6667
Muschealth.org/momsimpactt

- **Mom's IMPACTT has 3 components and provides:**
  - **Real-time psychiatric consultation for providers** to support them in effectively managing maternal mental health and substance use disorders.
  - **Mental health and substance use disorder trainings** tailored to the needs of the hospital and/or outpatient practice's providers and staff.
  - **Brief Phone assessment by Care Coordinator** to provide appropriate referral to treatment and community-based resources.

Treatment of Perinatal Treatment of Opioid Use Disorder

- OUD Treatment Mother-Infant Dyad
  - Pharmacotherapy (MOUD)
  - Psychotherapy (relapse prevention)
  - Mental health & trauma
  - Social Determinants of Health

- Integrated Prenatal and OUD Treatment
  - Retention in treatment
  - Maternal and newborn outcomes
  - Cost-effective

Ecker et al, 2019 Substance Use Disorders in Pregnancy: Clinical, Ethical and Research Imperatives. AJOG

APPROACH TO TREATING PSUDS WITH MEDICATIONS

- Risks/Benefits of Medication Vs. Risk of Untreated Illness
- Shared Decision Making: Informed Treatment Choices
- Treatment Choices Prioritize Women's Health
- Continue Effective Treatments
- Starting Treatment: Use the one the worked the best in the past
- Minimize Polypharmacy
- Optimize therapy, supports and resources

Medications for Opioid Use Disorder (MOUD)

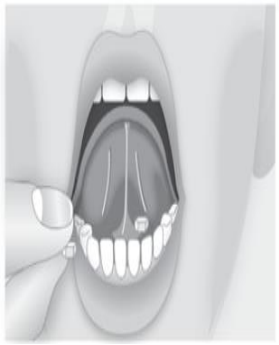
ACOG Committee Opinion No. 524 and 711:

Opioid Abuse, Dependence, and Addiction in Pregnancy (2012)

Opioid Use and Opioid use Disorder in Pregnancy (2017)

Gold Standard of Treatment:

- Methadone
- Buprenorphine



Substance Abuse and Mental Health Services Administration (SAMHSA), American Society for Addiction Medicine (ASAM), World Health Organization (WHO) and United Nations (UN)

Methadone and Buprenorphine

DECREASE:

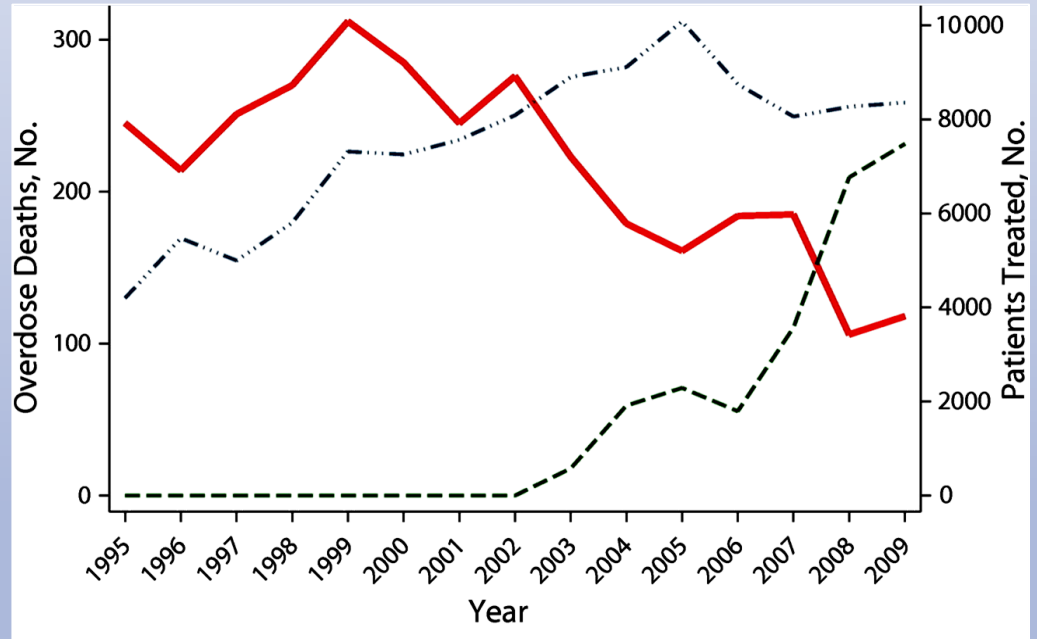
- Opioid use
- Opioid-related overdose
- Opioid mortality
- Criminal activity
- Infectious disease transmission

And INCREASE

- Social functioning
- Employment
- Retention in treatment

Opioid Agonist Treatments Decreased Heroin OD Deaths

Baltimore, Maryland, 1995-2009

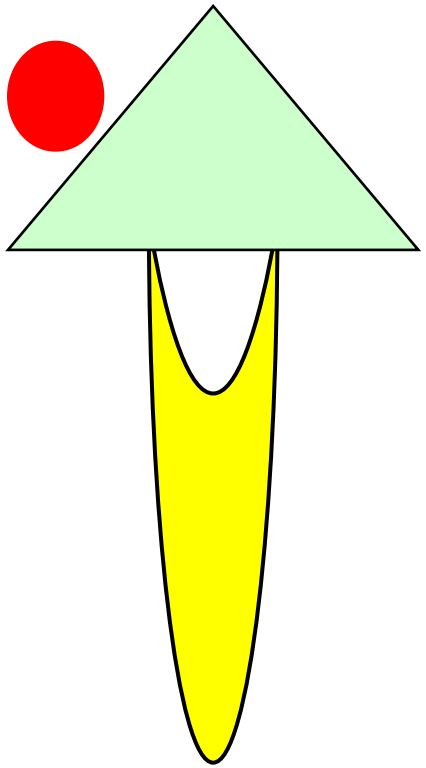


Schwartz RP et al., Am J Public Health 2013.

Medication for Opioid Use Disorder

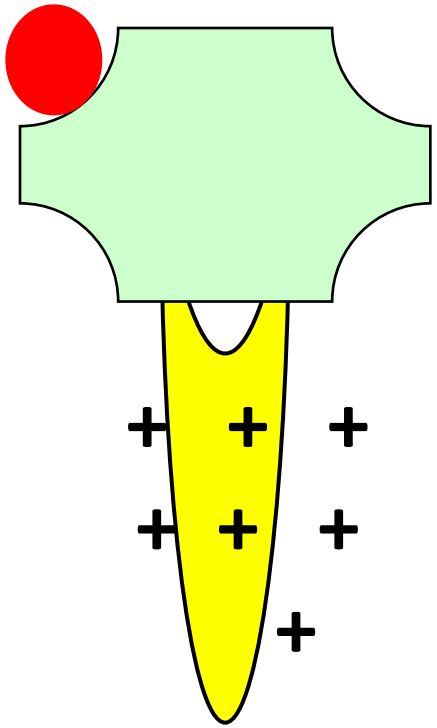
Naltrexone

Antagonist



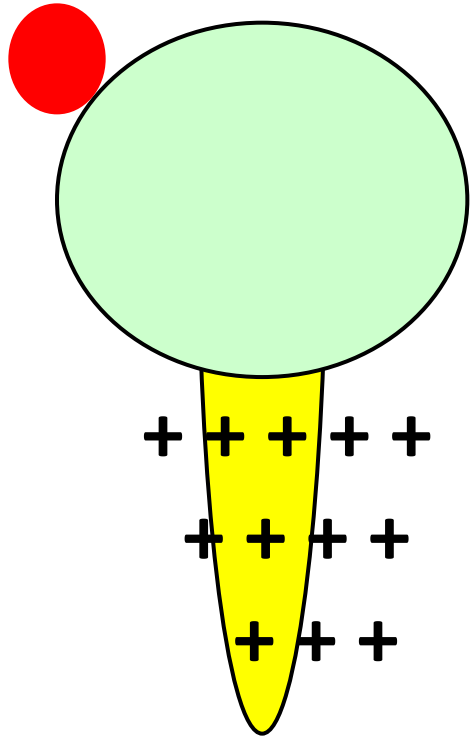
Buprenorphine

Partial Agonist



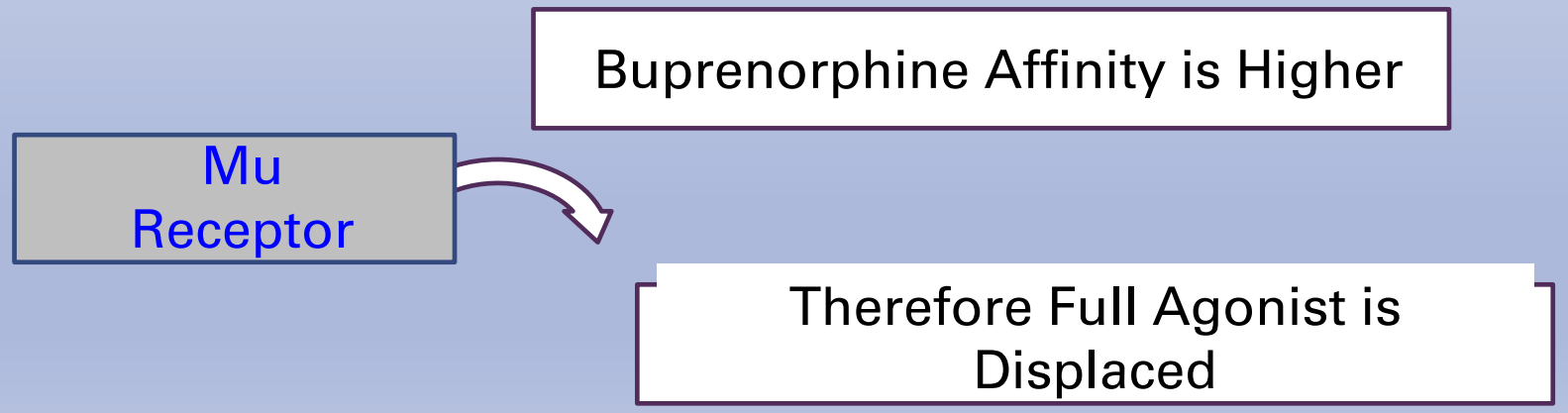
Methadone

Agonist



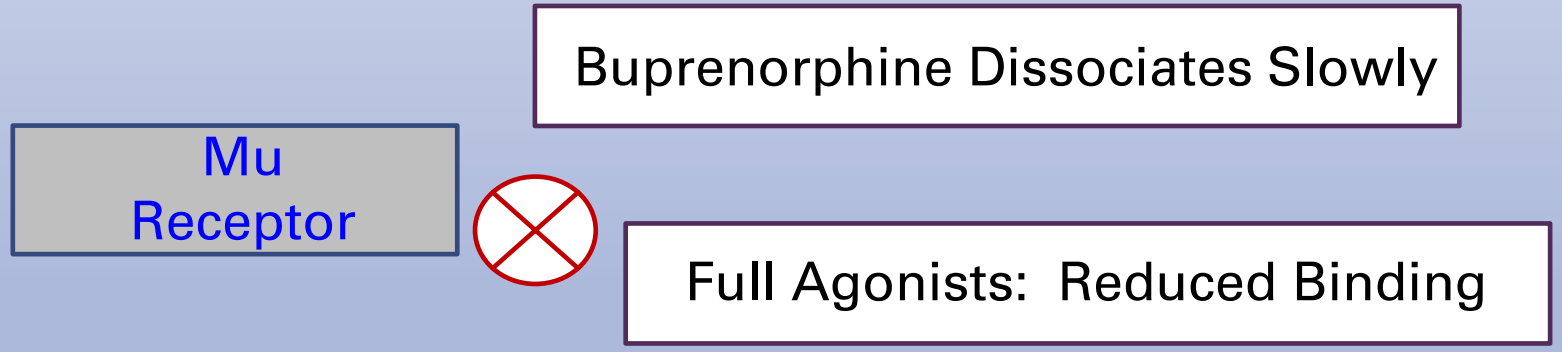
HOW DOES BUPRENORPHINE WORK?

- AFFINITY is the strength with which a drug physically binds to a receptor
  - Buprenorphine has strong affinity; will displace full mu receptor agonists like heroin and methadone
  - Receptor binding strength (strong or weak), is NOT the same as receptor activation



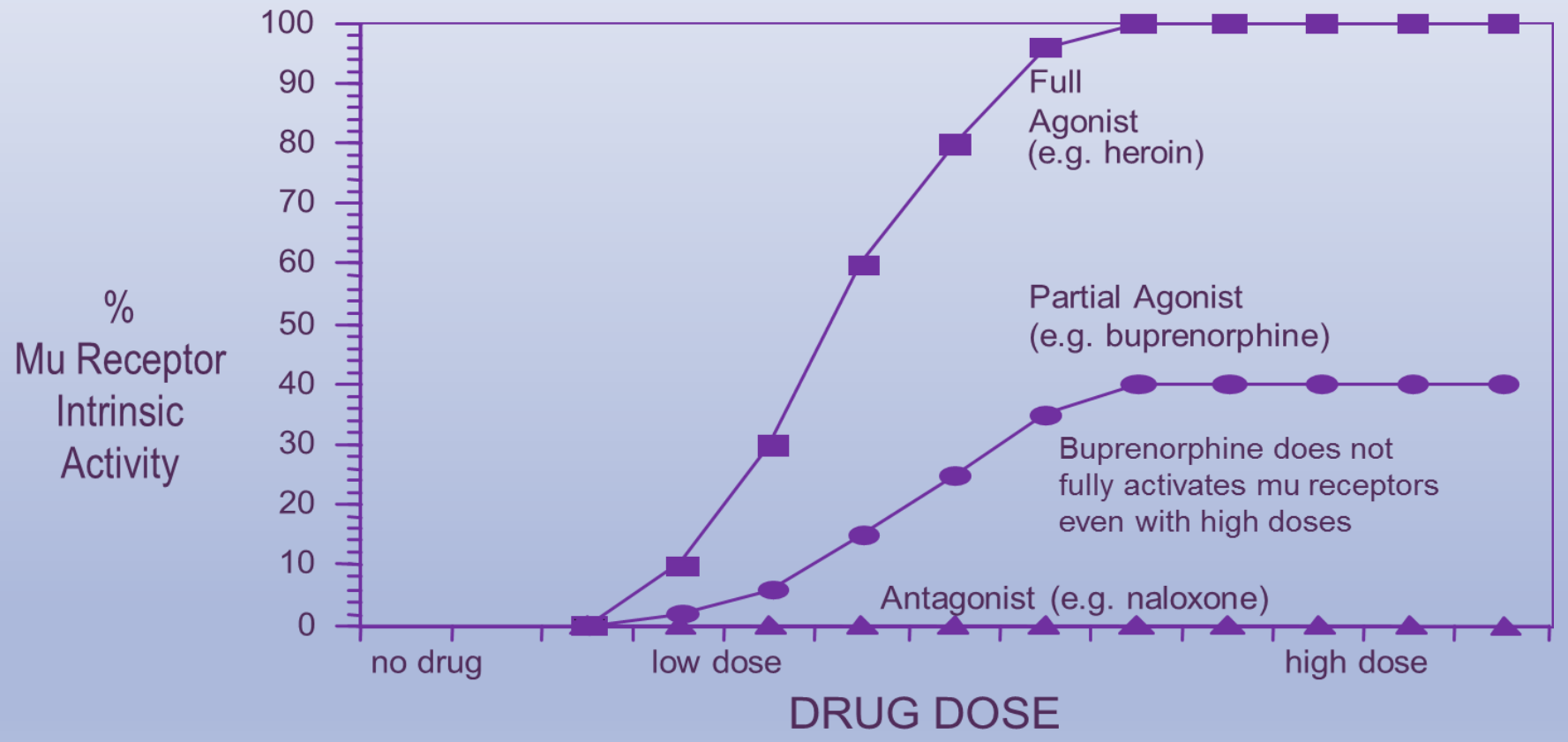
HOW DOES BUPRENORPHINE WORK?

- DISSOCIATION is the speed (slow or fast) of disengagement or uncoupling of a drug from the receptor
  - Buprenorphine dissociates slowly



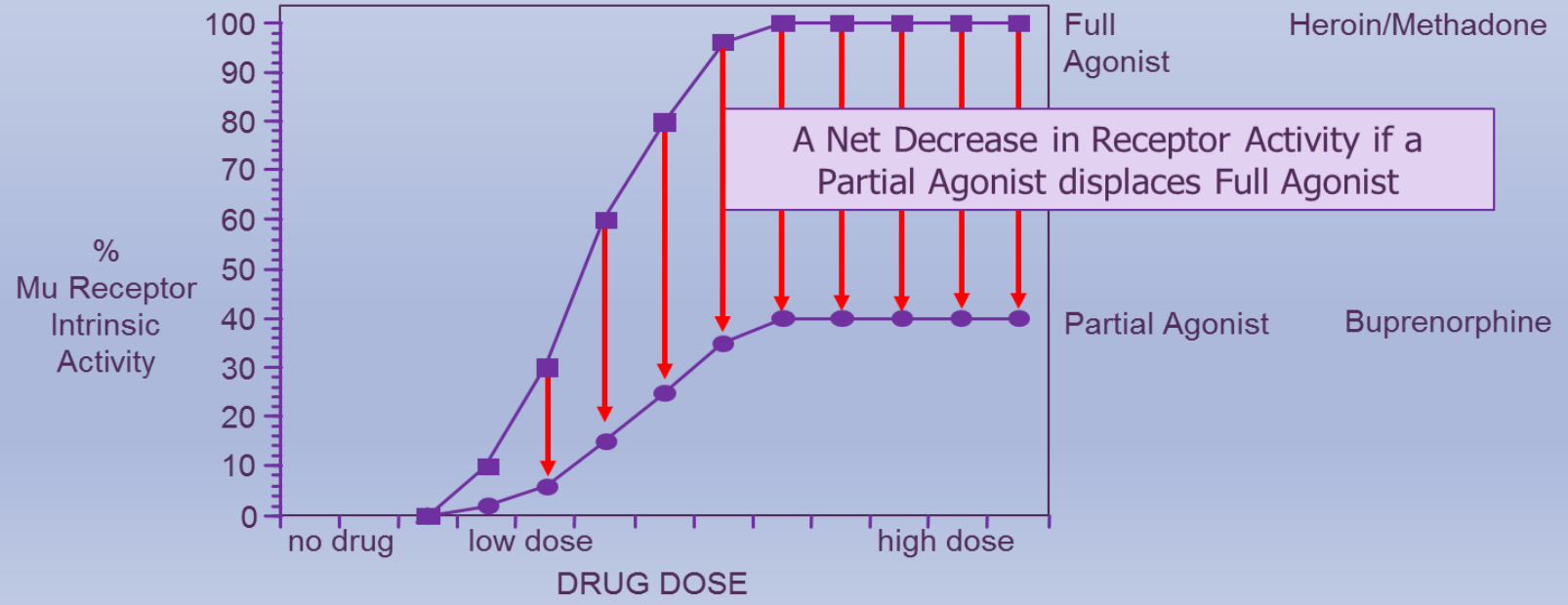
  - Therefore buprenorphine stays on the receptor a long time and blocks heroin, methadone and other opioids from binding to those receptors

BUPRENORPHINE IS A PARTIAL AGONIST



PHARMACOLOGY OF FULL VS. PARTIAL AGONISTS

- Buprenorphine can precipitate withdrawal if it displaces a full agonist from the mu receptors
- Buprenorphine only partially activates the receptors; therefore, a net decrease in activation occurs and withdrawal develops



Risks of Relapse and Drug Use

Risks & Benefits of Medication Vs. Risk of Untreated Illness

Women

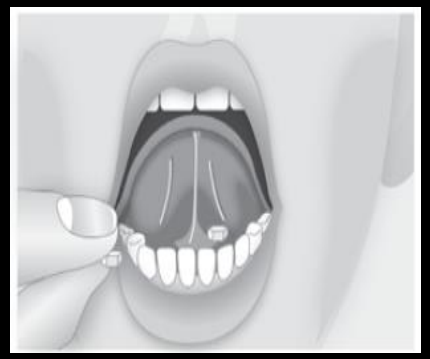
- Cycles Intoxication/Withdrawal
- Risk of Infections
- High risk behaviors
  - Risk of STI
  - Victim of violence
  - Legal ramifications
- Overdose and death

Obstetric/Newborn

- Prematurity
- Low birth weight
- Severe maternal complications
- NAS

Child Development

- Maternal-newborn separation



Risks of Medications for OUD

Risks & Benefits of Medication Vs. Risk of Untreated Illness

Women

- Access (travel and cost)
- Preference to not take medications

Obstetric/Newborn

- Prematurity
- Low birth weight
- NAS
  - Extended hospital stay
  - Cost

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Buprenorphine versus Methadone for Opioid Use Disorder in Pregnancy

E.A. Suarez, K.F. Huybrechts, L. Straub, S. Hernández-Díaz, H.E. Jones, H.S. Connery, J.M. Davis, K.J. Gray, B. Lester, M. Terplan, H. Mogun, and B.T. Bateman

Public Insurance Programs in US 2000-2018

- 2,548,372 pregnancies
  - 11,272 exposed to Buprenorphine
  - 5,056 exposed to Methadone

- **Neonatal Abstinence Syndrome (NAS)**
  - Buprenorphine (52%) vs. Methadone (69.2%) [Adjusted RR, 0.73; 95% CI, 0.71 to 0.75]
- **Preterm Birth**
  - Buprenorphine (14.4%) vs. Methadone (24.9%) [Adjusted RR, 0.58; 95% CI, 0.35 to 0.62]
- **Small for Gestational Age**
  - Buprenorphine (12.1%) vs. Methadone (15.3%) [Adjusted RR, 0.72; 95% CI, 0.66 to 0.80]
- **Low Birth Weight**
  - Buprenorphine (8.3%) vs. Methadone (14.9%) [Adjusted RR, 0.56; 95% CI, 0.5 to 0.63]
- **No differences in rates of Cesarean Section or Severe Maternal Complications**

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- **Clinical Decision: Buprenorphine Vs. Methadone**
  - **Starting Treatment**
    - **Choose medication that is best for the mother!**
      - **Accessible, available and reduces risk of relapse.**
  - **Continuing Effective Treatment**
    - **Do not switch effective treatment!**
    - **Methadone to Buprenorphine Risks**
      - **Destabilization of illness**
      - **Precipitated withdrawal**
      - **Increase exposures to 2 medications**
      - **If not effective, exposure to illness**
      - **Unknown if switch lowers risk of NAS**

Perinatal Opioid Use Disorder

Research

JAMA | Original Investigation

Comparative Safety of In Utero Exposure to Buprenorphine Combined With Naloxone vs Buprenorphine Alone

Loreen Straub, MD, MS; Brian T. Bateman, MD, MS; Sonia Hernández-Díaz, MD, DrPH; Yanmin Zhu, PhD, MS; Elizabeth A. Suarez, PhD, MPH; Seanna M. Vine, MPH; Hendrée E. Jones, PhD; Hilary S. Connery, MD, PhD; Jonathan M. Davis, MD; Kathryn J. Gray, MD, PhD; Barry Lester, PhD; Mishka Terplan, MD, MPH; Heidi Zakoul, BS; Helen Mogun, MS; Krista F. Huybrechts, MS, PhD

Medicaid Insurance Programs in US 2000-2018

- 3,369 exposed to Buprenorphine/Naloxone
- 5,326 exposed to Buprenorphine

- **Neonatal Abstinence Syndrome (NAS)**
  - Bup/Nal (37.4) vs. Bup (55.8%) [Adjusted RR, 0.77 [95% CI, 0.70-0.84]]
- **NICU Admission**
  - Bup/Nal (30.6%) vs. Bup (34.9%) [Adjusted RR, 0.91 [95% CI, 0.85-0.98]]
- **Small for Gestational Age**
  - Bup/Nal (10.0%) vs. Bup (12.4%) [Adjusted RR, 0.86 [95% CI, 0.75-0.98]]
- **No differences in rates of maternal morbidity, congenital malformations, low birth weight, preterm birth, respiratory symptoms or cesarean section**

BUPRENORPHINE & PAIN MANAGEMENT

- Pregnant and Laboring Women on Buprenorphine or Methadone should:
- Stay on same dose of medication during labor and delivery
- Same pain management regime as all other women having a NVD or c-section.
- Split dose of Buprenorphine/ Methadone (BID, TID, QID) can help for pain control.
- Encourage epidural/spinal-epidural, schedule NASAID/Tylenol postpartum
- Avoid nalbuphine [Nubain] or butorphanol [Stadol] – can precipitate withdrawal on buprenorphine
- Can breastfeed while taking Buprenorphine or Methadone (except if active drug use, or HIV+)

BUPRENORPHINE PREGNANCY

- **Types of oral buprenorphine medication:**
- Subutex
  - (buprenorphine tablet)
- Zubsolv
  - (buprenorphine/naloxone sublingual tablet)
- Suboxone
  - (buprenorphine/naloxone sublingual film strip)

BUPRENORPHINE INITIATION DURING PREGNANCY: OUTPATIENT SETTING

Induction:

COWS (Clinical Opioid Withdrawal Scale)

- >8-12 [If not in withdrawal, Bup will cause withdrawal]

Buprenorphine SL 8 mg tablets OR buprenorphine/naloxone SL film 8/2mg

- Day 1: 4 mg SL wait 30 min, 4mg SL
- Day 2: 8 mg SL BID
- Day 3 CONTINUE: 8 mg SL BID

If Bup induction precipitates withdrawal:

- TX w/ Buprenorphine:
  - Given another 4mg

- Tx Symptoms of Withdrawal
  - Add Ancillary medications:

- Tizanidine 2-4 mg Q6h (muscle relaxant)
- Hydroxyzine 50 mg Q6h (anxiety)
- Gabapentin 300 mg Q6h (severity sx)
- Mirtazapine 15 mg QHS (sleep)
- Dicyclomine 20 mg Q6h (GI cramping)

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Anticipate need to increase during pregnancy in response to craving and withdrawal symptoms

OBSTETRICS

An evidence-based recommendation to increase the dosing frequency of buprenorphine during pregnancy

Steve N. Caritis, MD; Jaime R. Bastian, PharmD; Hongfei Zhang, MSc; Hari Kalluri, PharmD; Dennis English, MD; Michael England, MD; Stephanie Bobby, RN; Raman Venkataramanan, PhD

TABLE 2
Time that dose-normalized plasma concentrations are below 1 ng/mL during intensive sampling PK study in subjects during pregnancy and postpartum state

	Hours below 1 ng/mL		
Variables	4 mg dose	8 mg dose	12 mg dose
Second trimester	10	8	8
Third trimester	10	4	0
Pregnancy average (second and third trimesters)	10	6	4
Postpartum	8	0	0

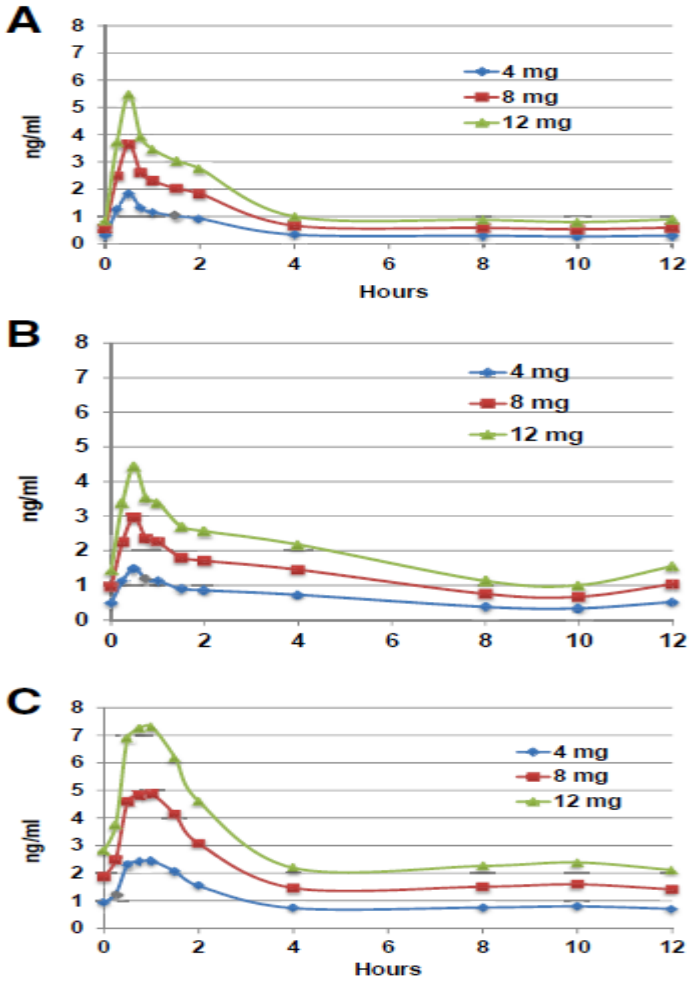
PK, pharmacokinetic.

Caritis et al. Dosing recommendations for buprenorphine during pregnancy. Am J Obstet Gynecol 2017.

TAKE HOME

Levels of buprenorphine decline over pregnancy. Anticipate the need for dose increases. Increase dose in response to craving and withdrawal symptoms. Reduce dose postpartum.

FIGURE 1
Median buprenorphine concentrations



Median buprenorphine concentrations according to dose in second (**A**) and third trimesters (**B**) and postpartum period (**C**) after sublingual dose of 4, 8, or 12 mg BID. All subjects were at steady state.

Caritis et al. Dosing recommendations for buprenorphine during pregnancy. Am J Obstet Gynecol 2017.

OBSTETRICS

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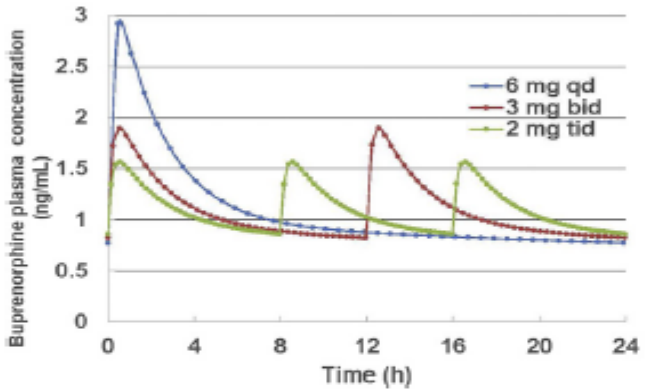
- Simulation of Buprenorphine
  - 6mg daily
  - 3mg BID
  - 2mg TID

TAKE HOME

Split the total daily buprenorphine dose and take smaller amounts of buprenorphine more frequently.

FIGURE 3
Simulated plasma concentrations of buprenorphine in nonpregnant subjects



Simulated plasma concentrations of buprenorphine in nonpregnant subjects utilizing physiologically based pharmacokinetic modeling. Values are means. Frequency of dosing includes 6 mg daily, 3 mg BID, and 2 mg TID.

BID, twice a day; *QD*, once a day; *TID*, three times a day.

Caritis et al. Dosing recommendations for buprenorphine during pregnancy. Am J Obstet Gynecol 2017.

BUPRENORPHINE PREGNANCY

- **National Institute on Drug Abuse**
  - **Clinical Trials Network**

- Lead Node: University of Cincinnati
- 10 sites across the country

- RCT Bup XR vs. Bup SL
- Illicit opioid use
- less severe NOWS (NAS)

BUPRENORPHINE PREGNANCY

Long-Acting BUP	Induction	Admin & Location	Dose	Frequency	Special Consideration	Pregnancy/ Breastfeeding
Brixadi (CAM 2038)	Naïve SL BUP or switch from SL BUP	Sub-cutaneous injection Upper Arm/Thigh/Buttock/Abdomen	8/16/24/32mg 64/96/128mg	*Weekly **Monthly	REMS	*Weekly: RCT **Monthly: Do not use (NMP teratogenic)
Sublocade	7 days of 8-24mg SL BUP before injection	Sub-cutaneous injection abdomen	100mg 300mg	***Monthly	REMS Refridge	***Monthly: Do not use

OPIOID ANTAGONIST – NARCAN

- Opioid Overdose Reversal

BUPRENORPHINE LOW DOSE INITIATION DURING PREGNANCY: OUTPATIENT SETTING

Bernese Method

Table 1. Buprenorphine Microdosing Protocol Used by Our Team

Day	Buprenorphine dosage	Methadone dose
1	0.5 mg[a] SL once/day	Full dose
2	0.5 mg[a] SL twice/day	Full dose
3	1 mg SL twice/day	Full dose
4	2 mg SL twice/day	Full dose
5	4 mg SL twice/day	Full dose
6	8 mg SL once/day	Full dose
7	8 mg SL in A.M. and 4 mg SL in P.M.	Full dose
8	12 mg SL/day	Stop

SL = sublingually.
[a]For our buprenorphine formulation, one-quarter of a 2-mg sublingual strip was used.

Terasaki, et al. *Pharmacotherapy.* 2019 Oct;39(10):1023-29.
Randhawa, et al. *CMAJ.* 2020 Jan 20;192(3):E73.

Ancillary Medications
until 24 hrs + on 8 mg SL TID

- Tizanidine 2-4 mg Q6h
- Hydroxyzine 50 mg Q6h
- Gabapentin 300 mg Q6h
- Dicyclomine 20 mg Q6h
- Mirtazapine 15 mg QHS
- Continue ancillary medications prn for 3-5 days

MEDICATION-ASSISTED WITHDRAWAL IS NOT RECOMMENDED

- **Medication-Assisted Withdrawal**
- 1,002 pregnant women undergoing Medication-Assisted Withdrawal
  - Relapse to drug use: 14-74%
- 1,126 pregnant women undergoing Medication-Assisted Withdrawal
  - Relapse to drug use: 0-100%
    - Rates depend on in/ex and lost to follow-up
  - Successful detoxification: 9-100%
    - Rates depend on type of treatment program

Summary: Treatment of Perinatal OUD

- **Comprehensive Integrated Treatment Including MOUD**

  Risk & Benefits of Medication Vs. Risk of Untreated Illness

  Shared Decision Making: Informed Treatment Choices

  Treatment Choices Prioritize Women's Health

  Continue Effective Treatments (Don't Switch)

  Use Most Effective Dose of the Medication (Ineffective: Risk/Risk)

  Anticipate Increasing Dose/Split Dose in Pregnancy (Education)

  Encourage Breastfeeding and Skin-to-Skin Contact

GOAL 1: PROVIDER
BUILDING FRONTLINE PROVIDER CAPACITY

GOAL 2: PATIENT
ACCESS TO MH/SUD CARE

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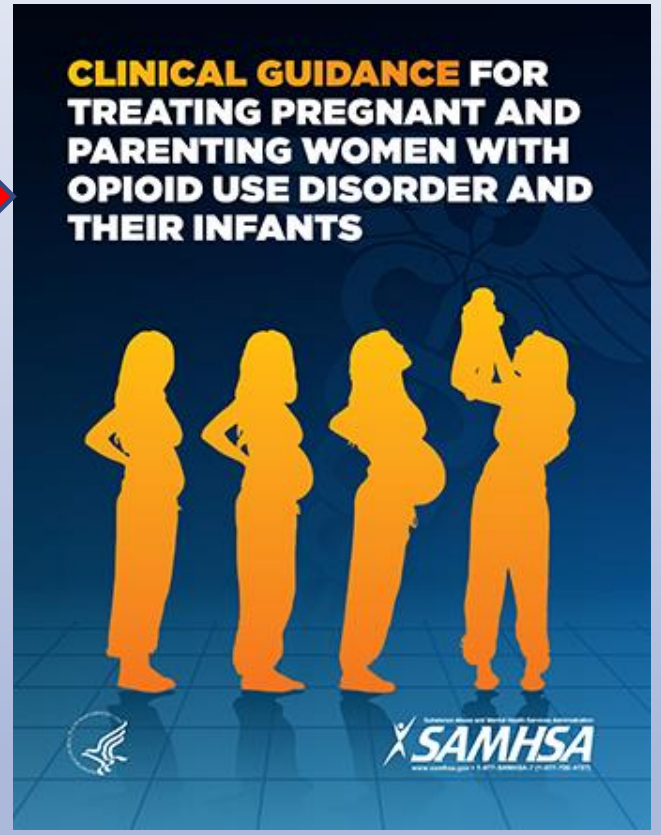
- **Mom's IMPACTT has 3 components and provides:**
  - **Real-time psychiatric consultation for providers** to support them in effectively managing maternal mental health and substance use disorders.
  - **Mental health and substance use disorder trainings** tailored to the needs of the hospital and/or outpatient practice's providers and staff.
  - **Brief Phone assessment by Care Coordinator** to provide appropriate referral to treatment and community-based resources.

SAMHSA Clinical Guide Recommendations

GREAT RESOURCE

https://store.samhsa.gov/



SHARED DECISION-MAKING AID

To assist MOUD Decisions During Pregnancy

- What are the current treatment recommendations
- Risks of Methadone or Buprenorphine
- Risk of Relapse
- Risk of Drug Use in Pregnancy

SHARED DECISION-MAKING AID

To assist MOUD Decisions During Pregnancy

Risk of Relapse- Individual

Reasons likely to relapse/ not relapse

Patient Preference

Reasons prefer/do not prefer pharmacology

Recommendation

Based on risk of relapse and preference

Plan-Delivery (Plan-Pain Management)

Breastfeeding

Postpartum Relapse Prevention

PAIN MANAGEMENT

Maintain standard of care as for birthing patient without OUD, while continuing MOUD

- Administering additional pain medication if necessary
- Avoiding opioid antagonist medication (Nubain, Stadol)
- Use of epidural or spinal anesthesia when appropriate
- Use of nonsteroidal anti-inflammatory drugs and acetaminophen

DELAYED PRENATAL & SUD CARE

- Typically present at approximately 20-24wga
  - Delays in prenatal care
  - Delays in treatment
- Lack of knowledge of pregnancy
- Fears: separation from baby, DSS case, other legal consequences, judgement
- Other social determinants of care: transportation, childcare, insurance
- Lack of understanding of what treatment looks like

TREATMENT OF OPIOID USE DISORDER IN PREGNANCY

Behavioral Interventions

- Motivational Interviewing
- Cognitive Behavioral Therapy
- Contingency Management

Management of Withdrawal

- Tizanidine 2-4 mg Q6h x 24-48hr (muscle relaxant)
- Hydroxyzine 50 mg Q6h x 24-48hr (anxiety)
- Gabapentin 300 mg Q6h x 24-48hr (severity of withdrawal)
- Dicyclomine 20 mg Q6h x 24-48hr (stomach cramping)

Medications OUD

- Buprenorphine/Naloxone (combined or mono)
- Methadone
- Naltrexone

Vs.

Risks of Untreated Opioid Use Disorder

- Maternal & Obstetric Health
- Newborn Health
- Child Development

Summary: Treatment of Perinatal OUD

- **Comprehensive Integrated Treatment Including MOUD**
- **MOUD**

  Risk & Benefits of Medication Vs. Risk of Untreated Illness

  Shared Decision Making: Informed Treatment Choices

  Treatment Choices Prioritize Women's Health

  Continue Effective Treatments to Reduce Risks of

  Destabilization, Withdrawal, Unnecessary Exposures