Management of Opioid Use Disorder: Care for Pregnant and Postpartum Women and Their Infants

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Outline

- National and International Guidelines
- Use of Medication in the Treatment of Opioid Use Disorder
- Neonatal Abstinence Syndrome
- Developmental Outcomes of Children Prenatally Exposed to Opioids
- Comprehensive Models of Care

Pregnant and Postpartum Women and Their Infants

- Two major focal points:
  - Antenatal focus is on ***mother*** and the pharmacological management of her opioid use disorder during pregnancy with methadone and buprenorphine
  - Postpartum focus is on the ***infant*** and the management of neonatal abstinence
- However, these must be placed in context of the complex bio-psycho-social problems associated with maternal substance use disorders and the array of services necessary for optimal outcomes for the mother/infant dyad.

Terminology

- Pregnant women with opioid use disorders or women with opioid use disorders who are pregnant
  - Disorder is not specific to pregnancy
  - Ignores experiences that contributed to their disorder
  - Leads to marginalization an stigma
- Medication assisted treatment or medication for addiction treatment (MAT)
  - Suggests that rather than being efficacious is a treatment that assists something else.

We must always keep a mother in mind in order for her to keep her child in mind

Guidelines

- Medication Assisted Treatment for Opioid Addiction in Opioid Treatment Programs, TIP 43, SAMHSA, 2005
- Substance Abuse Treatment: Addressing the Specific Needs of Women, TIP 51, SAMHSA, 2009
- Opioid Abuse, Dependence and Addiction in Pregnancy, ACOG and ASAM Joint Committee Opinion, 2012

Guidelines

- Concept of Trauma and Guidance for a Trauma Informed Approach, SAMHSA, 2014
- Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants, SAMHSA, 2016

All are available online

Medication for Addiction Treatment (MAT)

- The well being of the infant is improved with the well being of the mother

Maternal opioid use disorder and medication for addiction treatment

Understanding MAT

- Outline
  - Definitions
  - Role of medication in recovery
  - Role of methadone in recovery
  - Role of buprenorphine in recovery
  - Components of treatment

MAT

Medication for addiction treatment is the use of FDA approved medications in combination with evidence based behavioral therapies to provide a whole-patient approach to treating a substance use disorder

MAT

- Medications used to treat opioid use disorders
- Methadone
- Buprenorphine (mono and combination products)
- Naltrexone (not recommended for use during pregnancy)

Historical Context of Treatment Principles

- Methadone maintenance has been recommended for women with opioid use disorder who are pregnant since the early 1970's
- Over the past 40 years, the literature has established that methadone administered in appropriate doses, combined with counseling, psychiatric care and support services is an effective treatment

Historical Context

- The recognition of methadone as the standard of care can be traced historically in the USA through multiple federal publications:
  - Drug Dependence in Pregnancy: Clinical Management of Mother and Child, Services Research Monograph Series, NIDA, 1979
  - State Methadone Treatment Guidelines, CSAT, US DHHS, 1993
  - Effective Medical Treatment of Opiate Addiction, National Institutes of Health Consensus Development Panel, 1998

Historical Context

- Buprenorphine has been used in Europe since the 1990's.
- It was approved for use in the United States in 2002 and it is widely used in the US.
- 2012 Joint Committee Opinion: American College of Obstetricians and Gynecologists and the American Society of Addiction Medicine recommend the use of methadone or buprenorphine for pregnant opioid dependent women

MAT during Pregnancy

- Prevents erratic maternal opioid levels and protects the fetus from repeated episodes of withdrawal
- Associated with improved obstetrical care, increased growth, and reduced fetal and neonatal morbidity and mortality
- Supports and sustains recovery

Methadone and Buprenorphine

- Basic tenets of treatment are the same
  - Pharmacologically different
  - Schedule II vs. Schedule III
  - Different systems of care
  - Cost

MAT with Methadone

- Issues Specific to Methadone
  - Regulatory Schedule II Drug (may only be prescribed for MAT within an OTP except for hospitalization for medical condition)
  - Induction
  - Dose

Methadone Induction

- USA Regulatory Issues (42CFR 8.12)

Documented opioid dependence for a minimum of 1 year- pregnant women are exempt but must certify pregnancy

First dose ≤ 30mg

If withdrawal symptoms persist after 2-4 hours, initial dose can be supplemented with another 5-10mg

Maximum daily dose 40mg unless documented by physician that dose was insufficient to control withdrawal

Methadone Induction

- Difference in outpatient and hospital induction
- Inpatient allows for medical monitoring and comprehensive approach
- Outpatient often a practical necessity
  - Twice daily observation until patient is stabilized

Methadone Dose

- Dose should be based on the same criteria as non-pregnant patients
- Pregnant women may develop symptoms of withdrawal as pregnancy progresses and may require dose increase in order to maintain the same plasma level
- Split dose regimen may be used to facilitate steady state maintenance (often difficult to implement)
  - Increasing the daily medication regimen (2-6 doses per day) has been found to reduce the need for NAS treatment significantly to 29% *(McCarthy et al., J Addict Med 2015)*

Methadone Dose

- Dose should not be reduced during pregnancy to avoid NAS**
- No clear evidence of association between that maternal dose and severity of NAS
- Non-therapeutic maternal dose may promote supplemental drug use and increase risk to fetus

MAT with Buprenorphine

- Issues Specific to Buprenorphine
  - Regulatory Schedule III Drug
  - Transition from methadone to buprenorphine
  - Induction

Buprenorphine and DATA 2000

- Drug Addiction Treatment Act of 2000

Qualifying physicians in medical offices outside the OTP system may prescribe and/or dispense

Schedule III,IV, and V opioid medications for the treatment of opioid use disorders if such medications have been specifically approved by the FDA for that indication

Buprenorphine Induction

- Does not have the same regulatory restrictions
- Typically takes place over a 3 day period, beginning with 2mg or 4mg, usually with a maximum dose of

  8 mg Day 1

  12 mg Day 2

  16 mg Day 3

Buprenorphine Induction

- Dependence on short-acting or long acting opioids is issue
- Short-acting: minimum of 12-24 hrs between use and buprenorphine administration and exhibit early signs of withdrawal
- Long-acting: taper to ≤30mg for a minimum of 1 week. Last dose of methadone 24hr before buprenorphine and experiencing withdrawal
  - As such transition from methadone is especially difficult tin pregnant women

Differences in Maternal Treatment Medications on NAS

- MOTHER study designed to assess the efficacy of buprenorphine for reducing NAS relative to methadone
- Randomized Clinical Trial
  - Double-blind
  - Double-dummy
  - Flexible dosing

Summary of MOTHER NAS Results

- 57% of methadone-exposed and 47% of buprenorphine-exposed babies were treated for NAS.
- In comparison to 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

(Jones, et al. N Engl J Med, 2010)

Additional Studies

- Systematic review and meta analysis of 12 studies (including MOTHER) had better neonatal outcomes for buprenorphine exposed infants compared to methadone exposed infants for treatment duration, morphine dose, birth weight, length and head circumference
- No difference in need for treatment

(Brogly et al., 2014)

MOTHER Study Secondary Analyses

Two secondary analyses of MOTHER data

- To determine pre- and post-dosing effects of prenatal methadone compared to buprenorphine on fetal well-being *(Salisbury et al., Addiction, 2012)*
- To compare the profile of individual signs of NAS as a function of medication condition *(Gaalema et al., Addiction, 2012)*

Fetal Assessment Before and After Dosing with Buprenorphine or Methadone

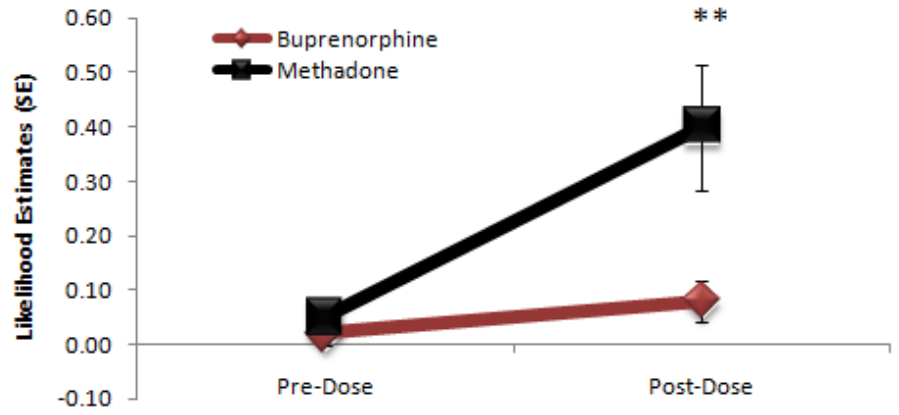
- *N*=81 of the 131 MOTHER participants who delivered were assessed 2 hours before and 2 hours after dosing during week 32 of their pregnancy
- Non-invasive assessment by fetal non-stress test (NST) and biophysical profile (BPP)

RESULTS

- Fetuses exposed to buprenorphine were more likely to have a reactive non-stress test with more fetal heart rate (FHR) accelerations than fetuses exposed to methadone treatment
- Medications did not differ on these measures immediately prior to dosing
- Buprenorphine dosing has less of a suppressive effect than does methadone on mean FHR, FHR variability, and the ability of the autonomic system to respond to integrate response to movement

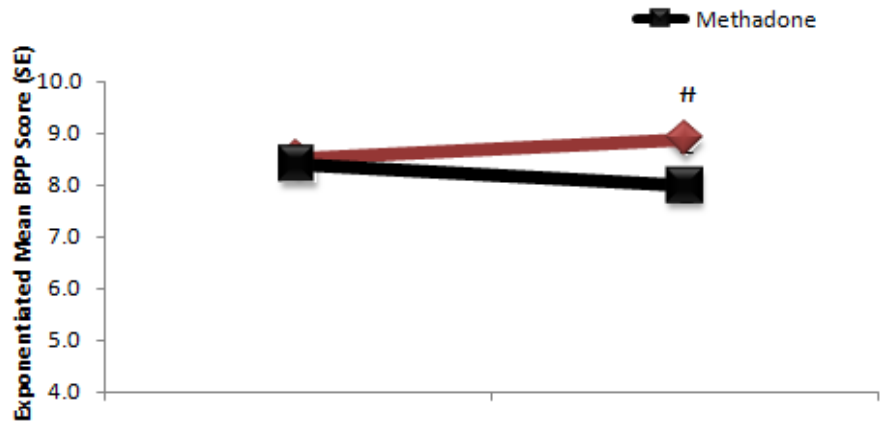
Fetal Assessment Before and After Dosing with Buprenorphine or Methadone

Figure 3. Non-Reactive Non-Stress Test



Group: p<=.002; Time: p<=001; Group x Time: p=.21, **p<.01

Figure 4. Biophysical Profile Score



Group: p=.018, Time: p=.203, Group*Time:p=.046; #p=.095

Differences in the Profile of Neonatal Abstinence Syndrome Signs in Methadone vs Buprenorphine Exposed Neonates

- The incidence and mean severity of the total NAS score and each individual sign of NAS were calculated and compared between medication conditions, as was the mean time until morphine treatment initiation among treated infants in each condition

Differences in the Profile of NAS Signs

- Three NAS signs (nasal stuffiness, sneezing, loose stools) were observed more frequently in neonates exposed to buprenorphine.
- Mean severity scores on the total NAS score and five individual signs (disturbed and undisturbed tremors, hyperactive Moro reflex, excessive irritability, failure to thrive) were significantly higher in neonates exposed to methadone, while sneezing was higher in neonates exposed to buprenorphine.
- Among treated neonates, methadone-exposed infants required treatment significantly earlier than buprenorphine-exposed infants (43:54 ± 5:52 hours vs. 65:56 ± 7:09 hours postnatal, respectively).

Methadone or Buprenorphine?

- Both have benefits and disadvantages

↑Buprenorphine: easier access to treatment, better outcomes for infant

↓Buprenorphine: behavioral treatment not always provided, ceiling effect, cost

↑Methadone: easier induction, lower cost, better treatment retention

↓Methadone: restrictive regulations, access to treatment often limited

Methadone or Buprenorphine?

- Opioid dependent women naïve to agonist treatment may be a good candidate for buprenorphine. If she does not respond to buprenorphine, transfer to methadone can easily be initiated.
- Women stabilized on buprenorphine or methadone who become pregnant should remain on their current medication
- Each woman's medical, psychological and substance use history must be considered in any treatment decision

Medication Assisted Withdrawal during Pregnancy

- Medication assisted withdrawal/detoxification used to provide transition from illicit opioids to drug free state
- Taper is a gradual transition from maintenance to a drug free state

Withdrawal during Pregnancy

- Historically, recommendations have been for withdrawal to be conducted only within the second trimester
- Recommendations based on 2 events that occurred in the early 1970's that identified safety issues with detoxification in pregnancy
- However, there are no systematic studies on whether withdrawal should only be initiated during this time period
- Data in 1994 indicated that with monitoring, can be conducted safely in any trimester *(Jarvis and Schnoll)*

Medically Supervised Withdrawal in Pregnancy: Contemporary Data

- *Dashe et al., Obstetrics and Gynecology, 1998*
  - Small study of 34 women
  - 20 (59%) were successful, i.e. no drug use at delivery
  - 12% late preterm delivery
  - Safety established; high relapse rate, no follow up data postpartum

Medically Supervised Withdrawal in Pregnancy: Contemporary Data

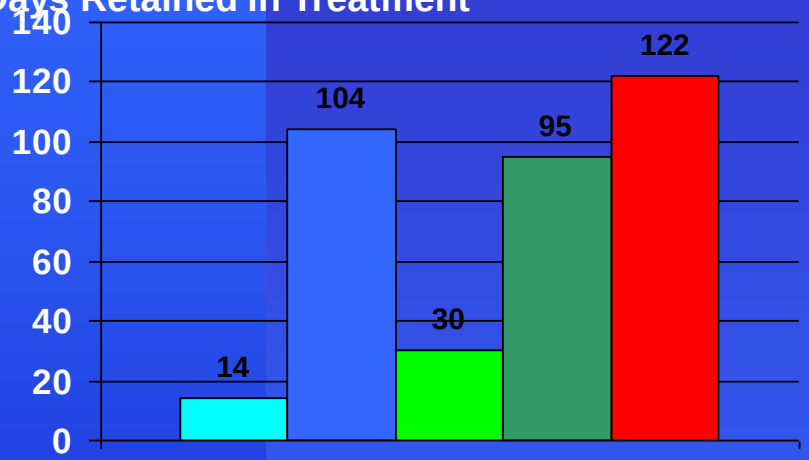
- *Jones et al., Journal of Substance Abuse Treatment, 2008*

Medication-Assisted Withdrawal

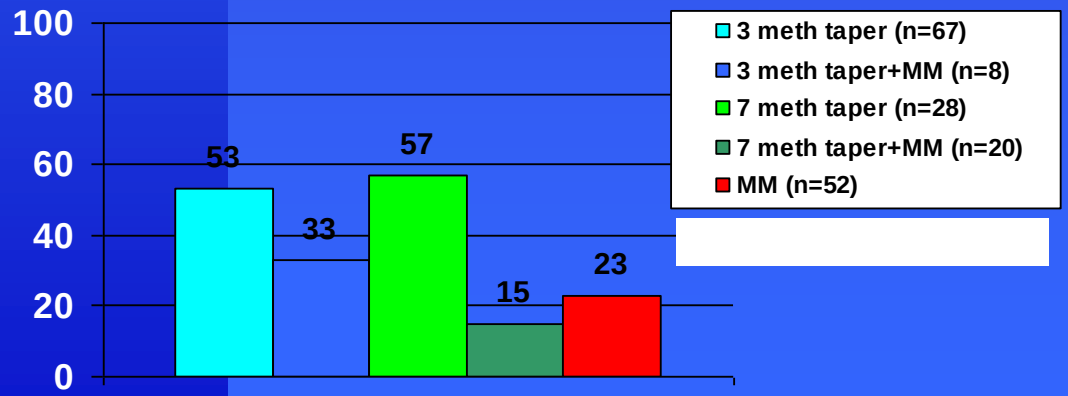
Chart review of 5 groups of patients:

- **3-day methadone-assisted withdrawal (MAW) alone (*n*=67)**
- **3-day MAW followed by methadone maintenance (MM) (*n*=8)**
- **7-day MAW alone (*n*=28)**
- **7-day MAW followed by MM (*n*=20)**
- **continuous MM (*n*=52)**

Days Retained in Treatment



Urine-positive Drug Screen Percentage at Delivery



Patients in the three MM groups:

−remained in treatment longer
−had fewer positive urine drug screening test results
−attended more obstetrical visits
−more often delivered at the program hospital than patients in the two MAW alone groups.

Medically Supervised Withdrawal in Pregnancy: Contemporary Data

- *Stewart et al., American Journal of Obstetrics and Gynecology, 2013*
  - N=95
  - No fetal distress or demise
  - 44% relapse rate
  - Only followed to delivery

Medically Supervised Withdrawal in Pregnancy: Contemporary Data

- *Bell et al., American Journal of Obstetrics and Gynecology, 2016*
  - Group 1: 108 incarcerated patients who underwent acute detoxification (Two fetal demises, R=23.1%*)
  - Group 2: 23 patients received inpatient medical detox, intense behavioral health follow-up (R=17.4%)
  - Group 3: 77 patient received inpatient medical detox, no behavioral health follow-up (R=74%)
  - Group 4: 93 patients received slow outpatient taper, continued behavioral health follow-up (17.2%)

Medically Supervised Withdrawal

- Women can be safely withdrawn during pregnancy
- Question is whether it should be done
  - Very high rate of relapse in opioid dependent women
  - Places fetus at additional risk

Medically Supervised Withdrawal

- Medication assisted withdrawal:

  Need to provide counseling and education on risk/benefits of maintenance.
- Taper:

  A thorough assessment is essential to determine if woman is appropriate candidate
- Should be conducted under supervision by physician accompanied by fetal monitoring
- Important to provide prenatal and postpartum behavioral health treatment

MAT vs. Withdrawal or Taper

- Recommendations in support of treatment rather than withdrawal
  - WHO 2014 Guidelines
  - American College of Obstetricians and Gynecologists and American Society of Addiction Medicine Joint Opinion 2012
  - Treatment improvement Protocol, US Department of Health and Human Services 2005

MAT and Concomitant Use/Misuse of Drugs

- Illicit drug use and prescription misuse
- Methadone and buprenorphine have no direct pharmacological effect on non-opioids
- Misuse of other drugs such as cocaine, marijuana, alcohol, and/or benzodiazepine must be treated as a separate problem
- Benzodiazepine misuse is the most difficult problem

Benzodiazepines

- Benzodiazepines are one of the most widely prescribed medications to women
- Generally used to treat insomnia and anxiety
- Women more likely than men to be prescribed benzodiazepines when presenting for symptoms such as stress or life changes
- Women are more likely to be prescribed benzodiazepines for a longer period of time
- Women with opioid use disorders have rates of anxiety up to 78% (*Green et al. 2009*)

Benzodiazepines

- National Survey of Drug Use and Health (NSDUH) reports on prescription misuse for pregnant women but does not provide data by drug category
- The Jefferson recruitment for the MOTHER study MOTHER had to exclude 44% of the 199 pregnant opioid dependent women screened for the study because of a benzodiazepine substance use disorder

Special Challenges

- Not all benzodiazepine use/misuse is the same and requires different management strategies
- Benzodiazepine use may be
  - Prescribed and used appropriately
  - Prescribed and misused
  - No prescription/ buys off the street
- These three categories are not always mutually exclusive

Special Challenges

- Benzodiazepines taken with methadone or buprenorphine can cause overdose (BZDs were present in 50% of PA's drug-related deaths in 2014)
- Prescription Drug Monitoring Program(PDMP)
- Medical withdrawal not often available to pregnant patients
- Slow taper is recommended to avoid withdrawal and/or exacerbation of psychiatric symptoms
- Medical assessment is needed to determine appropriate medication, e.g. Klonopin/SSRI, and/or non medication options, e.g. Mindfulness, etc.

Role of Medication in Recovery

- Opioid medications such as methadone and buprenorphine can be successful components in treating opioid use disorder, both in the general population and in pregnant women.
- Opioid medications are best provided in the context of a comprehensive treatment plan that includes behavioral treatment like individual counseling.
- A comprehensive treatment plan is developed following an assessment that determines which life areas have been affected by drug use and to what extent they have been affected.
- The patient and provider then develop specific goals for improved life functioning in each life area and a plan for how and when the goals will be met.
- Part of the plan may eventually include wellness indicators of when patients can taper off of their medication.