Medication Assisted Treatment as the Standard of Care for Opiate Dependent Pregnant Women

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Addiction is a Disease
ASAM Definition

- According to the American Society of Addiction Medicine (ASAM), addiction is “a primary chronic neurobiologic disease, with genetic, psychosocial, and environmental factors influencing the development and manifestations.
- Addiction is characterized by (four “C”s):
  - Impaired control over drug use
  - Compulsive use
  - Continued use despite harm
  - Craving

Source: Seikel, SE. Methadone treatment in pregnancy...That can’t be right, can it?, Northeast Florida Medicine, 2012, 63.
Definition of Addiction

- Addiction is an intense desire use a drug with an impaired ability to control the urges to take that drug, even at the expense of serious adverse consequences.

- Often addiction is stigmatized as a bad “choice” that is made voluntarily by the addicted person.

- Multiple studies and research show that repeated drug use leads to long-lasting changes in the brain that undermine voluntary control.

- There are environmental, genetic, and developmental factors that contribute to addiction.
Addiction is a Disease?

- Recent imaging studies have revealed an underlying disruption to brain regions that are important for the normal processes of motivation, reward, and inhibitory control of addicted individuals.

- The abnormal behavior with addiction is a chronic disease of the brain associated with dysfunction of brain tissue, just like cardiac insufficiency is a disease of the heart and abnormal blood circulation is a result of dysfunction of myocardial tissue.

- Drug experimentation and recreational use are volitional, but after addiction develops, control is markedly disrupted.

- Imaging studies consistently show specific abnormalities in the brain function of the addicted.

Source: Volkow et al. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications, Archives of Neurology, 2007, 64.
Similarities to Other Chronic Diseases

- The adaptations in the brain that result from chronic exposure are long lasting, and therefore addiction should be viewed as a chronic disease.

- Long-term treatment will be required for most cases, just as for other chronic diseases (hypertension, diabetes, asthma).

- Perspective on relapse: discontinuation of treatment is likely to result in relapse as with other chronic diseases. Relapse is not a failure of treatment, but is due to a lack of compliance or tolerance to an effective treatment.

- Rates of relapse and recovery in the treatment of drug addiction are equivalent to other medical diseases.

Understanding Addiction

- Addiction is a brain disease affecting 10% to 15% of the population.

- Working in medication assisted treatment (MAT), one can experience a transformation of a woman whose brain is being run by a limbic system in overdrive, to one with intact executive function and a prefrontal cortex that could override a thought of using.

- Addiction is a brain disease...not a moral failing.

Source: Seikel, SE. Methadone treatment in pregnancy...That can’t be right, can it? Northeast Florida Medicine, 2012, 63.
Hypofrontality

- Nora Volkow’s work at the National Institute of Drug Abuse (NIDA) shows evidence of a limbic system that has significantly increased activity of positron emission tomography (PET) images.

- The prefrontal cortex in patients with addictive disorders has diminished cellular activity.

- In neuroimaging, this is called “hypofrontality.”

- Scientists could predict relapse in cocaine addicts by “how dark”, or the degree of hypofrontality, in these patients.

The Process of Addiction

- When the mu opiate receptor is chronically activated over a period of time, it results in structural changes in the brain – altered gene expression.

- Once there is new gene expression, new metabolic pathways are activated from new enzymes and the brain has changed, most likely permanently.

- In Narcotics Anonymous (NA), there is the saying “once an addict, always an addict” and “you can’t change a pickle back into a cucumber.”

Functionally...

Dopamine D2 Receptors are Decreased by Addiction

Cocaine

Meth

Alcohol

Heroin

Control

Addicted

DA D2 Receptor Availability
Brain Reward Pathways

- The VTA-nucleus accumbens pathway is activated by all drugs of dependence including alcohol.
- This pathway is important not only in drug dependence, but also in essential physiological behaviors such as eating, drinking, sleeping, and sex.

Risks to Women With Substance Use Disorders

• Developing physical, mental or social problems
• Human immunodeficiency virus (HIV)
• Sexually transmitted diseases
• Hepatitis
• Spontaneous abortions
• Malnutrition
• Subjected to physical or sexual abuse
• Suffers from depression
Factors in Chemical Dependency in Women

• Family instability, troubled current relationships and in family of origin
• Family history of drug and alcohol use
• Homelessness or transiency
• Childhood sexual abuse
• Having a chemically dependent partner
• Having a dual diagnosis of both drug addiction and mental illness (anxiety or depression)
• Being a victim of violence
Opioid Misuse During Pregnancy is a Serious and Growing Concern

- High rates of infection
- Poor pre-natal care
- Increased 1st trimester spontaneous abortions/3rd trimester premature labor (opiate withdrawal)
- Untreated substance abuse in mothers
- Interruption of maternal/fetal dyad
- Low birth weight, which is an important risk factor for later developmental delay
Getting the Prenatal Dose Right: Induction and Stabilization
Goals for Pharmacotherapy

• Prevention or reduction of withdrawal symptoms
• Prevention or reduction of drug craving
• Prevention of relapse to use of addictive drug
• Restoration to or toward normalcy of any physiological function disrupted by drug abuse
• Blockade of euphoric effects of illicit self-administered opiates

Methadone Simulated 24 Hr. Dose/Response At Steady-State in Tolerant Patient

- "Loaded"
- "High"
- Normal Range "Comfort Zone"
- "Abnormal Normality"
- Subjective w/d
- "Sick" Objective w/d

Dose Response

Time

0 hrs. 24 hrs.
Profile for Potential Psychotherapeutic Agent

• Effective after oral administration
• Long biological half-life (>24 hours)
• Minimal side effects during chronic administration
• Safe, no true toxic or serious adverse effects
• Efficacious for a substantial percent of persons with the disorder

Effects of Withdrawal

- Opioid Withdrawal Syndrome during pregnancy can lead to fetal distress and premature labor owing to increased oxygen consumption by both the mother and fetus.

- Minimal symptoms in the mother may indicate fetal distress, as the fetus may be more susceptible to withdrawal symptoms than the mother.

- Rates of pre-term labor may be as high as 29% to 41% with opioid use during pregnancy

- Methadone prevents the withdrawal syndrome and helps stabilize the pregnancy.

Acceptance as the Standard of Care

• Methadone has been accepted since the late 1970s to treat opioid addiction during pregnancy.

• In 1998, a National Institute of Health consensus panel recommended methadone maintenance as the standard of care for pregnant women with opioid addiction.

• Recent literature supports buprenorphine as another option for safe medication-assisted treatment for opioid addiction (MAT) in pregnant patients.
Methadone Maintenance Treatment

• Full mu-opioid agonist.
• Methadone is the only medication currently approved for the treatment of opioid addiction in pregnancy (US).
  – Maintenance with methadone during pregnancy produces the same benefits as treatment in the non-pregnant patient.
• Recommended standard of care over no treatment or medication-assisted withdrawal.
• Medically supervised withdrawal is not the standard of care due to the poor outcomes (Jones, 2008) and the potential catastrophic consequences of relapse.
• A pregnant patient CAN taper off of methadone (opioid agonist therapy) but should not be permitted to experience significant abstinence syndrome (Luty, J, Nilolaou V, Bearn J. 2004).
Dosing During Pregnancy

- The dose is adjusted as necessary to an effective dose. The dose is effective when it prevents withdrawal symptoms and decreases cravings.

- The dose does not correlate with neonatal abstinence syndrome (NAS) symptoms, so maternal benefits of methadone are not offset by harm to the newborn (dose over 60mg often necessary).

- The dose often needs to be increased during the 3rd trimester, owing to larger plasma volume, decreased plasma protein binding, increased tissue binding, increased methadone metabolism, and increased methadone clearance of the mother.

- Splitting the dose may be an option for effective treatment.

The Right Dose Throughout Pregnancy (Is the Dose that Stops Withdrawal)

- Increased blood volume
- Larger tissue reservoir
- Methadone loss to amniotic fluid
- Altered maternal metabolism
- Metabolic activity of fetus

- Patient may require progressive increases throughout pregnancy
- Split dosing is an option to maintain adequate blood levels with fewer increases (Kaltenbach, 1998; Jarvis, 1999)
- Counseling is essential to address cravings, stress, and anxiety
Dosages Relative to Neonatal Abstinence Syndrome

- Historically, treatment providers have based dosing decisions on the need to avoid or reduce the incidence of NAS (Kaltenbach et al., 1998).

- This low-dose approach emerged from several 1970s studies (Harper et al., 1977) and has been contradicted by more recent studies (Brown et al., 1998).

- There is no compelling evidence supporting reduced methadone dosages to avoid NAS.
On the Contrary, Higher Doses of Methadone Have Been Associated With

- Increased weight gain
- Decreased illegal drug use
- Improved compliance with prenatal care by pregnant women in MAT
- Increased birth weight
- Increased head circumference
- Prolonged gestation
- Improved growth of infants born to women in MAT (De Petrillo and Rice, 1995)

***Reduced methadone dosages may result in continued substance use and increased risks to both expectant mothers and their fetuses.
Benefits of Maintenance with Opioid Agonist Therapy in Pregnancy

WOW!
I get to give birth
AND
change diapers!
Benefits of Opioid Maintenance

- Medical withdrawal is not recommended because of the high rates of relapse to illicit prescription opiate and heroin use and increased risk to the fetus of intrauterine death
- Decreases fluctuations between intoxication and withdrawal (premature labor and spontaneous abortion)
- Reduction of exposure to harmful compounds in heroin and access to illicit Rx opiates is unpredictable
- Improved maternal health and nutrition
- Reduction in criminal activity
- Decreased disruption of the maternal-child dyad
- Allows the mother to participate in prenatal care and addiction treatment and allows the woman and her family to prepare for arrival of the infant

Medication Assisted Withdrawal (MAW)

- Smaller consecutive doses of an opioid agonist like methadone to provide a smoother transition from illicit opioid use to a medication free state
- Indicated for the following:
  - Patient refuses treatment unless medication-free at delivery
  - Inability to receive agonist therapy in their community
  - Need to ingest a medication that is incompatible with methadone
Advantages of MAT with Methadone vs. MAW

• Superior relapse prevention
• Reduced fetal exposure to illicit drug use and other maternal behaviors
• Enhanced compliance with obstetrical care
• Enhanced neonatal outcomes including heavier birth weight (Kaltenbach et al., 1998)
Methadone Maintenance vs. Methadone Taper During Pregnancy: Maternal and Neonatal Outcomes

- Retrospective study of 175 pregnant clients at the Center for Addiction and Pregnancy (CAP) at Johns Hopkins Bayview Medical Center in Baltimore, Md. from 1995 to 2001
- Compared 3 groups of participants
  - Women receiving 3 day MAW
  - Women receiving 7 day MAW
  - Women receiving MAT
- Showed that MAW is not in the best interest of the mother or child because MAW clients had poorer maternal outcomes than MAT clients

Source: Jones et al., 2008
Maternal Outcomes

• The methadone maintained groups remained in treatment at CAP an average of 106.7 days and the medication free groups an average of 20.6 days.

• Methadone maintained groups attended an average of 8.3 obstetrical visits vs. medication free groups averaging only 2.3 days.

• Methadone maintained groups were 7.1 times more likely to deliver at CAP.
MAT and NAS

• There is no evidence that higher doses are harmful to the fetus.

• The neonate has a high probability of having NAS (Neonatal Abstinence Syndrome) – anecdotally about 75%.

• Delivery should be arranged for a hospital where the neonate can be appropriately managed for NAS, if necessary.
Weaning To Avoid NAS?

• Poor compliance
• Recidivism
• Use of concurrent medication
• Jail
• Risk of infection related to intravenous drug use

*** Best outcomes for mom and baby with MAT throughout pregnancy ***
Dosage of Methadone and NAS

- In a retrospective review of pregnancies that were maintained on methadone therapy in one hospital, 100 mother/neonate pairs on methadone therapy were identified.
- Women who received an average methadone dose of greater than 80 mg were similar to women maintained on dosages of less than or equal to 80 mg in:
  - Having infants with similar NAS scores
  - Needs for neonatal treatment for withdrawal
  - Similar duration of withdrawal when it occurred in the neonate
- The authors concluded that maternal methadone dosage does not correlate with neonatal withdrawal; therefore maternal benefits of effective methadone dosing are not offset by neonatal harm.

Methadone vs. Buprenorphine

• Opioid maintained patients who become pregnant should be maintained on the current agent
• Suboxone can be changed directly to Subutex
• Even though it is a category C drug, buprenorphine may be used with pregnant patients in the US under certain circumstances
• Buprenorphine should only be initiated when:
  - Patient cannot tolerate methadone
  - Methadone program is not accessible
  - Patient is adamant about avoiding methadone
  - Patient is capable of informed consent
Buprenorphine

- Pharmacological advantages led to prospective open-label and controlled studies of its use in prenatal treatment.
- The results of some of these studies suggested that neonates exposed to buprenorphine might be less likely to require treatment for NAS than those exposed to methadone.
- These studies have had inconsistent results with respect to NAS outcomes.
- Improved pregnancy outcomes seen with methadone appear to be duplicated on buprenorphine.
Buprenorphine

- Methadone is the treatment of choice for opioid-dependent pregnant women.
- Buprenorphine is an alternative and along with methadone is a category C drug.
- This allows a risk benefit clinical decision to start or continue to maintain pregnant patients on sublingual buprenorphine when methadone treatment is not an option or is unacceptable to the patient.
- MOTHER Study – promising for evidence of less severe NAS.

Buprenorphine

• There have been 31 published reports of buprenorphine, a partial-mu opioid agonist, exposure during pregnancy that were reviewed and summarized (Jones et al., 2008).

• Overall, the studies report approximately 522 neonates prenatally exposed to buprenorphine, with a wide range of therapeutic doses from 0.4 to 24 mg sublingual tablets/day.

• Generally, the pregnancies were uneventful, without physical teratogenic effects, and with low rates of prematurity, suggesting that buprenorphine is relatively safe and effective for this population.
MOTHER Study

• The Maternal Opioid Treatment: Human Experimental Research Project seeks to develop guidelines based on risk-benefit ratios
• Buprenorphine is used alone (no naloxone!)
• Transferring a patient to buprenorphine is challenging and there is no medication transition procedure that avoids the risk of withdrawal, which carries the risk of fetal distress, miscarriage, and stillbirth. It needs to be done in a hospital setting with morphine (not practical).
• Issues with pain management during labor and delivery

MOTHER Project

• Given the calls to increase representation of pregnant women in medication research, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) project was initiated.

• A multicenter, randomized, controlled trial comparing buprenorphine with methadone for the treatment of opioid-dependent pregnant patients.

• Prior to this only 2 randomized, double-blind studies have been conducted comparing methadone with buprenorphine (Fisher et al., 2006; Jones et al., 2005).
Landmark Study

• Neonatal abstinence syndrome after methadone or buprenorphine exposure, Jones et. Al, 2010, New England Journal of Medicine

• A double blind, double dummy, flexible-dosing, randomized, controlled study in which buprenorphine and methadone were compared for use in the comprehensive care of 175 pregnant women with opioid dependency at 8 international sites.

• A comparison of the 131 neonates whose mothers were followed to the end of pregnancy according to treatment group (with 58 exposed to buprenorphine and 73 exposed to methadone) showed the buprenorphine group
  – Required significantly less morphine (mean dose, 1.1 mg vs. 10.4 mg)
  – Had a significantly shorter hospital stay (10.0 days vs. 17.5 days)
  – Had a significantly shorter duration of treatment for the NAS (4.1 days vs. 9.9 days)
Measured Neonatal Study Outcomes

Primary Neonatal Outcomes
• Number of neonates requiring treatment for NAS
• Peak NAS score
• Total amount of morphine needed for treatment of NAS
• Length of hospital stay
• Head circumference

Secondary Neonatal Outcomes
• Number of days during which medication was given for NAS
• Weight and length at birth
• Preterm birth (< 37 weeks gestation)
• Gestational age at delivery
• 1 and 5 minute APGAR scores
Primary Outcomes With Significant Differences

• The mean total dose amount of morphine needed for the treatment of NAS averaged 10.4 mg in the methadone group and 1.1 mg in the buprenorphine group.

• On average, neonates exposed to buprenorphine required 89% less morphine than did neonates exposed to methadone.

• The average amount of days for the infant’s stay in the hospital was 17.5 vs 10.0 days, so infants born to mother’s on buprenorphine spent on average 43% less time in the hospital.
Secondary Outcomes With Significant Differences

• One of the 7 neonatal outcomes differed in that neonates exposed to buprenorphine spent, on average, 58% less time in the hospital receiving medication for NAS than did those exposed to methadone (4.1 days vs. 9.9 days).

• There were no significant differences in any of the nine maternal secondary outcomes.
Figure 2. Mean Neonatal Morphine Dose, Length of Neonatal Hospital Stay, and Duration of Treatment for Neonatal Abstinence Syndrome.
MAT as a Solution...

- Methadone or MAT is necessary early in recovery for patients to learn new skills:
  - Coping skills
  - Parenting skills
  - Relapse prevention
  - Ability to ask for help through an extensive network

- Women in MAT have the ability to engage recovery. The network of support begins with her counselor and grows to include women in recovery in community-based 12 Step Programs.
Not Just Another Addiction!

- Stereotypes about methadone being “just another addiction” can have prejudicial influence on medical decisions.
- Methadone is considered the gold standard maintenance treatment for opioid-dependent pregnant women.
- The dose needs to be adequate – contrary to expectations, higher doses are not associated with increased risks of neonatal abstinence.

Staying in Treatment

- It is important to reduce early treatment dropout in pregnant women.
- Participation in treatment is associated with better maternal and neonatal outcomes.
- Drug craving and withdrawal were important precipitants of relapse, especially for heroin users who did not receive methadone maintenance.

Source: Kissin et al., Identifying pregnant women at risk for early attrition from substance abuse treatment, Journal of Substance Abuse Treatment, 2004, 27(1).
Postpartum Management

**Moms!**

*Not all superheroes wear capes!*
Analgesia and Anesthesia

• Provision of pain control and anesthesia can be complex and challenging
• Chronic opiate use leads to cross tolerance of anesthetics and other depressants-chronic receptor stimulation
• Erroneous assumption: daily maintenance dose of methadone alone will provide analgesia

Analgesia and Anesthesia

• During labor and postpartum, pain control in opioid-dependent pregnant women should be similar to that of non-substance using women
• Acute intra-partum and post-partum pain should not be treated with additional doses of methadone
• Confirm ante-partum methadone dose on arrival to labor and delivery

Source: Seligman et al, 2014
Analgesia and Anesthesia

• Higher than usual opioid analgesic doses may be required due to cross tolerance and patient’s increased pain sensitivity.

• Mixed agonist and antagonist opioid analgesics should NOT be administered. They may displace methadone from the mu receptor and precipitate acute withdrawal.
  – Pentazocine (Talwin)
  – Nalbuphine (Nubain)
  – Butorphanol (Stadol)

Source: Seligman et al, 2014
Analgesia and Anesthesia

- Oxycodone-acetaminophen (Percocet) usually provides adequate analgesia post-op.
- If it does not control pain adequately, hydromorphone (Dilaudid) can be given.
- Injectable NSAIDs (Ketorolac) can provide good analgesia without the need for additional narcotics in many cases.
- Regional anesthesia is safe.

Source: Seligman et al, 2014
Breastfeeding on Methadone

Alex Grey
“Nursing”
1985
Oil on Linen
Breast-Feeding on Methadone

- Despite the fact that women were on relatively high doses of methadone (ranging from 25 to 180 mg/day) levels in breast milk were small and no adverse events were detected.
- Women should not be discouraged from breast-feeding if they are not using illicit drugs and do not have special contraindications.
- The American Academy of Pediatrics (AAP) endorses breastfeeding for mothers on methadone without contraindications.

Source: McCarthy et al., Methadone levels in human milk. Journal of Human Lactation, 2000; 16(2)
Breast-Feeding

• Mothers maintained on methadone can breast-feed if they are not HIV positive, are not abusing substances, and do not have a disease or infection in which breast-feeding is contraindicated (Kaltenbach et al., 1993).

• Hepatitis C is no longer considered a contraindication for breast-feeding.

• The AAP has a long-standing recommendation that methadone is compatible with breast-feeding only if mothers receive no more than 20 mg in 24 hours.

• Studies have found minimal transmission of methadone in breast milk, regardless of maternal dose (Geraghty et al., 1997)

• McCarthy and Posey (2000) found only small amounts of methadone in breast milk of women maintained on daily doses up to 180 mg and argued the 20 mg/day limit.
Breast-Feeding

• Methadone doses of 25 to 180 mg/d → milk concentrations in milk from 27 to 260 ng/ml.
• Based on estimated milk intake of 500 ml/d in an infant, average daily methadone ingestion is 0.05 mg.
• In an 11 lb baby, the ingested amount is thus less than 1% of the maternal weight-adjusted dose.
• Methadone clearance in neonates is slower than adults, but the infant dose will not exceed 5% of the maternal weight-adjusted dose (Glatstein et al., 2008 Canadian Family Physician 54(12): 1689-90).
• AAP recommendations
  – 1994: doses > 20mg/day contraindicated
  – 2001: methadone, regardless of dose, removed from the contraindicated list, data supported.
• Breastfeeding shouldn’t impact dosing decisions.
Comprehensive
Coordinated Care Plan
Model
The Continuum of Care

- OATS – Opiate Addiction Treatment Services
- Zero Exposure Case Management
- Coordination of Care with Obstetrical Providers
- Education and Outreach
- Treatment Team Approach
- Monthly Support Groups
- Coordination with Pediatricians/Neonatology
Additional Services

• Gender Specific Treatment-Dual Enrollment
  – Women’s Residential Service
  – Women’s Outpatient Services
  – Outpatient Programs

• Hillsborough County Sheriff’s Office/Child Protection Investigations and Eckerd Referrals/Collaboration

• Nurturing Pregnancies and Newborns Initiative
  – Funded by the Children’s Board
Zero Exposure

- Case management services for pregnant clients
- Link clients to OB-GYN for appropriate prenatal services
- Conduct and gather pre-natal screenings
- Evaluate the need for substance abuse treatment services and provide appropriate referrals
- Develop and maintain referral sources appropriate for pregnant and post-partum women
- Engage and link clients to appropriate community services
- Provide outreach services to identified clients
**Approach to the Pregnant Client**

- Pregnant women who abuse alcohol or illicit drugs are more stigmatized than non-pregnant women, and may deny their drug use, its harmful effects, and the need to seek help.

- As the addicted pregnant woman may be wary of health care providers due to previous experiences, prevention services, diagnosis, and referral to treatment should be available within a prenatal clinical setting.

- Those who provide health care to the substance-using pregnant women will have the best results for engaging patients in treatment if they are sensitive to the feelings of the patients and approach them in a non-judgmental way.

Recovery is a Staged Process

• Trans-Theoretical Model of Change (Prochaska and DiClemente)

• Change is achieved over time and requires progression through 6 sequential stages:
  – Precontemplation
  – Contemplation
  – Preparation
  – Action
  – Maintenance
  – Termination
Keys to Engagement in Treatment

• Women are put on an equal relationship with staff, avoid authoritarian attitudes
• Approach with collaborative attitude
• Comprehensive history-taking
• Engage women as early as possible in pregnancy
• Promote collaborative, comprehensive continuity approach
• Provision of an extended period of postnatal support for at least 6 months to women and their children
Take Home Points

- MAT is the standard of care for opiate dependent pregnant patients for best outcomes for mom and baby.
- Mother arrives with negative UDS, the ability to parent and bond with the infant.
- With proper pre-natal education mothers can have realistic expectations of NAS management by the NICU team and be more likely to continue to engage effective treatment.
- There are many opportunities in the continuum of care (from addiction specialist to neonatology) for the mother to be supported and properly educated on the benefits of staying in effective MAT treatment for opiate dependence.
Questions???

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