FDA Presentation: Maternal Perspective on Opioid Medication Assisted Therapy

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Outline

- Describe patients who need treatment / candidates for medication-assisted therapy with methadone or buprenorphine (MAT).
- Care that a patient may get if they receive treatment through an integrated addiction program.
- Literature review-based discussion of pregnancy outcomes of women treated during pregnancy compared with those who were not.
- Patient counseling of benefit and risk of medication-assisted therapy with regard to pregnancy outcome.
- Impact of FDA labeling (“boxed warning” on methadone & buprenorphine)
  - On prescriber’s willingness to prescribe
  - On patient’s willingness to take treatment
DEFINITIONS

- **DRUG ADDICTION** (NIDA, 2010)
  - a compulsive drive to take a drug despite serious adverse consequences.
  - A chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.

- **SUBSTANCE USE DISORDER (SUD)** in DSM5
  - A disorder in which the use of one or more substances leads to a clinically significant impairment or distress.
DEFINITIONS

DRUG DEPENDENCE (NIDA, 2010)
- Dependence develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug. When the drug is withdrawn, several physiologic reactions occur, collectively known as the withdrawal syndrome. These can be mild (e.g. for caffeine) or even life-threatening (e.g. for alcohol).

Although prolonged use of opioid drugs change brain structure and function, resulting in drug dependence, addiction may or may not be present.
Who needs treatment?
Who are candidates for medication-assisted therapy

Women who require opioid drug treatment for opioid dependence can be divided into 3 populations:
Who needs treatment? Who are candidates for medication-assisted therapy?

First,

Patients who become pregnant and are addicted to either legal or illegal opioid drugs (or both). These include:

- Women who abuse street opioids: heroin, methadone, all forms of narcotic tablets and patches.
- Women who misuse opioid prescriptions or are over-prescribed opioid drugs.

Note: Heroin is cheaper than most opioid tablets and patches and can be snorted, so frequent transition to heroin occurs where available.
Who needs treatment? Who are candidates for medication-assisted therapy?

This first group became addicted to opioid drugs due to:

- Recreational drug use which escalated to addiction
- Self-medication for mental illness (up to 75%)
- Self-medication for history of or current trauma (40-59%)
- History of acute pain issues for which opioid prescriptions were given.
- Involvement in sex trafficking.
Who needs treatment? Who are candidates for medication-assisted therapy?

Second,

Chronic pain patients who become pregnant and are taking long-acting opioid medications in a prescribed manner. These include

- women with medical conditions, such as sickle cell disease,
- women with history of severe injury, and
- women with chronic pain of less clear etiology
Who needs treatment?
Who are candidates for medication-assisted therapy?

Third,

Chronic pain patients who abuse opioids and/or other drugs of abuse and become pregnant.
Who needs treatment? Who are candidates for medication-assisted therapy (MAT)?

Pregnant women addicted to opioids (first group) are definite candidates for MAT (either methadone or buprenorphine).

- This is considered the standard of care in pregnancy (Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: SAHMSA/CSAT treatment).

Women already on MAT should continue, although the dosing needs in pregnancy are controversial.

- Due to increase blood volume during pregnancy, methadone dosage may need to be increased in advancing pregnancy in order to avoid opioid withdrawal symptoms.
- Some methadone providers increase methadone dosage empirically in pregnancy, regardless of withdrawal symptoms.
Who needs treatment? Who are candidates for medication-assisted therapy?

Detoxification from opioids has been done under direct medical supervision in pregnancy, but is not recommended due to:

- The high failure rate in maintaining drug-free status (up to 90%)
- Concerns about in utero fetal detoxification, although it does not appear to result in fetal death in utero.

(Jones HE et al. Am J Addict 2008;17:372-86.)

Detoxification is done, where available, for the following reasons:

1. Patient refusal of maintenance therapy.
2. Unavailability of medication-assisted therapy close enough to her residence.
3. Requirement of a long-term residential or intensive-outpatient treatment program to have patient drug-free prior to admission.
Who needs treatment? Who are candidates for medication-assisted therapy?

- The documented chronic pain patients (second group) often need continuation of their opioids medications in pregnancy, although appropriate dosage needs to be individualized and adjusted during pregnancy, as needed.
  - Medication-assisted therapy and referral to a drug treatment program is usually not appropriate.
  - However, many chronic pain programs do not accept and may discharge pregnant women.
  - Many prenatal care providers are not comfortable prescribing the opioid medications.
  - Is this due to the “boxed warning” for use of these drugs in pregnancy?
Who needs treatment? Who are candidates for medication-assisted therapy?

The third group of pregnant women, who have both ongoing chronic pain and opioid addiction are difficult to treat.

- MAT with methadone maintenance has not been recommended for use in chronic pain patients due to different dosages and dosing schedules used in MAT (to avoid withdrawal symptoms) and in treatment of chronic pain.
- Most methadone programs do not allow their clients to have ongoing narcotic prescriptions.
- Very few “dual-diagnoses” programs.
Methadone Administration

- Methadone is only administered/distributed for MAT through properly licensed narcotic treatment programs (state-registered methadone programs)
  - Requires a physician who manages the methadone dosage.
  - Requires RNs or pharmacists to administer/distribute the methadone
  - May be a private or publically-funded program.
  - Methadone is usually dispensed in liquid form.
  - Programs have set hours for administration of methadone
  - Usually client goes to the methadone program location

- Outside of these methadone programs, physicians may only prescribed methadone
  - while a patient is hospitalized
    - Usually with verification from methadone program
  - For pain relief as outpatient (designated on the prescription)
Methadone Administration

- In addition to providing methadone as MAT, methadone programs are required to
  - Do periodic toxicology screens (usually urine).
  - Provide periodic assigned drug counseling.

- Methadone is administered on a daily basis until a stable dose is achieved and toxicology screens are negative (except for methadone) for a period of time.

- Clients may then “earn” take-home” doses of methadone
  - Starts with 1 “take-home” dose per week; may proceed to up to a month’s supply at a time.
  - Client may be required to have a “lock-box” in which to keep “take-home” doses secure.
  - Diversion control plan: ex.: Periodic recalls may be done, at which time client must bring in all unused doses of methadone.
Buprenorphine Administration

- Buprenorphine was approved for MAT to be prescribed in an office or clinic setting by a specially-licensed physician.

- In order to prescribe buprenorphine on an out-patient basis, the provider must complete an 8-hour training course and apply to have an “X” designation added to their DEA number.

- Each prescriber is limited to 30 patients receiving buprenorphine prescriptions the first year, and 100 patients for each year thereafter.
  - The goal is to provide buprenorphine for MAT within a primary care practice, and not to create clinics/practices for the sole purpose of distributing buprenorphine.
Buprenorphine Administration

- Initially, the locations for administering methadone and prescribing buprenorphine were to be separate.
  - Methadone in a registered methadone program
  - Buprenorphine in a clinic/office setting.

- However, steps have been taken to allow methadone programs to prescribe / administer buprenorphine
  - To provide optimum MAT for a given patient without the patient changing programs.
An Integrated Addiction Program

- Care of the opioid-addicted pregnant women is a multi-disciplinary effort to optimize both perinatal outcome and maternal sobriety!
  - Prenatal care
  - Evaluation and treatment for co-morbidities
    - Psychiatric, medical, obstetrical
  - Substance abuse treatment and counseling
  - Nutritional counseling
  - Social service involvement
  - Pediatric Services
Challenges in providing care

Drug-associated life-style complications:

- Poor nutrition
- Cigarette smoking (80-93%)
- Homelessness
- Multi-generational substance use/abuse
- Unemployment
- Lack of transportation
- Poor social supports
- Lack of child care
- Violent social environment
- Family problems
  - Unstable partners and other family members
  - Parenting Difficulties
Challenges in providing care

- Tremendous prejudice towards drug-addicted pregnant women
  - Within society
  - Within the healthcare system

- Limited or no reimbursement for additional services provided within either an obstetrical practice, a methadone program, or a practice/clinic providing buprenorphine therapy.

Challenges in providing care

- Limited responsibility
  - Example: methadone programs are required to refer pregnant women to prenatal care, but are not required to facilitate referral or follow-up to ensure prenatal care is being received.

- Limited communication among providers of prenatal care, drug treatment, and mental health treatment.
  - Restricted access to Psychiatric and Drug Treatment records / providers
    - Special consents required by law.
An Integrated Addiction Program

- There are few integrated addiction treatment programs in the US for pregnant women with opioid addiction.

- Many challenges in establishing an on-site multi-disciplinary team
  - Differing philosophies of care
  - Infrastructure
  - Institutional commitment
An Integrated Addiction Program

- Differing philosophies of care:
  - OB care: protocol-driven, but individualized; focus on optimizing care through delivery; presence of an innocent passenger.

  - Substance abuse treatment: more programmatic, with more restrictions on individualization of care; focus on providing care as long as pt. is enrolled in program; variable consideration for fetal well-being.
One model of care: Center for Addiction and Pregnancy (CAP)

Obstetrical Evaluation and Care
  • Including high-risk obstetrical care

Substance Abuse Treatment
  • Methadone and buprenorphine maintenance
  • Intensive Outpatient Programming (IOP)

Mental Health/Psychiatric consultation
  • Domestic Violence / PTSD Counseling

Pediatric Health Care

Residential Service: a 16 bed housing unit

Referral and follow-up for in-patient detoxification
  • Opioids, Benzodiazepines, Alcohol
Intensive Outpatient Program

Representative Topics in an Integrated Program:

- Importance of prenatal care
- Consequences of drug use during pregnancy
- Improving self-esteem
- Coping with depression
- Relapse prevention
- Parenting skills training
- Life skills training
- HIV Prevention
- STD Prevention
- Smoking Cessation
An Integrated Addiction Treatment Program

- Cannot optimize obstetrical/medical care unless substance abuse issues are stabilized, and vice versa.
Pregnancy Outcomes

- Only a few studies are available (mainly from the 1990’s) comparing pregnancy outcomes of women treated with medication-assisted therapy with those who were not treated.
- Those who received methadone maintenance therapy had contact with the health care system and were more likely to receive some prenatal care, possibly some counseling, psychiatric care, etc.
- Prenatal care alone is known to result in improved pregnancy outcomes.
- So, difficult to assess the specific impact of medication-assisted therapy on pregnancy outcomes.
Perinatal Complications attributable to opioid use/abuse

- Preterm delivery
- Preeclampsia
- Third trimester bleeding
- Malpresentation
- Nonreassuring fetal status
- Passage of meconium
- Low birth weight
- In utero fetal death and Neonatal death
- Puerperal morbidity
- Neonatal Abstinence Syndrome
- SIDS (74-fold increase in 1 study)
Pregnancy Outcomes

- In 1998, a National Institutes of Health consensus panel recommended methadone maintenance as the standard of care for pregnant women with opioid addiction. (National Institutes of Health Consensus Development Panel 1998)

- In fact, methadone has been accepted since the late 1970s to treat opioid addiction during pregnancy. (Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In:SAMHSA/CSAT treatment improvement protocols. Rockville, MD, 2008.)
Pregnancy Outcomes

Comprehensive methadone maintenance treatment that includes prenatal care reduces the risk of obstetrical and fetal complications, in utero growth retardation, and neonatal morbidity and mortality

(Finnegan L P. Treatment issues for opioid-dependent women during the perinatal period. Journal of Psychoactive Drugs. 1991;23(2):191–201.)
Pregnancy Outcomes

- Methadone maintenance therapy significantly:
  - Reduces fluctuations in maternal serum opioid levels, so it protects a fetus from repeated withdrawal episodes
  - Eliminated need for illicit opioid use
  - Reduces neonatal morbidity and mortality
  - Increases birth weight


Pregnancy Outcomes

- The appropriate dose range of methadone in pregnancy and its effect on NAS/NOWS has been controversial, but the preponderance of data has not shown a link between lowering methadone dose and decreased severity of NAS/NOWS.

- In fact, reduced methadone dosages may result in continued substance use and increase risks to both expectant mothers and their fetuses. (Kaltenbach K et al, 1998.)
Pregnancy Outcomes

- Higher methadone dosages have been associated with
  - increased maternal weight gain,
  - with increased birth weight and head circumference,
    prolonged gestation, and
  - improved infant growth.


- The dose range included in most studies is 20-140mg, so there is little data on the effects of very high dosages (>180mg).
Recent studies have focused on

- assessing the efficacy of both methadone and buprenorphine for medication-assisted therapy during pregnancy
- the rising effects of increased prescription opioid use during pregnancy
Pregnancy Outcomes

The MOTHER Study

- Double-blind, double-dummy, flexible dosing, randomized, controlled study.
- 175 patients.
- 8 international sites

Pregnancy Outcomes

The MOTHER Study

131 Neonates followed post-delivery.

- Requiring NAS treatment
  - 47% - 57%
- Mean dose of morphine needed:
  - 1.1mg - 10.4mg
- Mean hospital stay:
  - 10.0 days - 17.5 days
- Mean duration of treatment:
  - 4.1 days - 9.9 days
The MOTHER study

- Methadone and buprenorphine are both beneficial as MAT when considering neonatal outcomes and treatment.

- Conclusion:
  Use of Buprenorphine is an acceptable treatment for opioid dependence in pregnant women.
Pregnancy Outcomes

In considering Methadone and Buprenorphine for Management of Opioid Dependence in Pregnancy

- Both are efficacious in preventing relapse to illicit opioid use.
- Buprenorphine may have only minimal effect on suppressing fetal cardiac activity and fetal movement.
- The incidence and severity of NAS/NOWS after in utero buprenorphine exposure are at least comparable relative to methadone.

Long-term sequelae to in utero opioid exposure

- Difficult to study due to losses to follow up and many confounding factors, particularly continued maternal substance use/abuse and associated lifestyles.

- Behavioral and cognitive effects.
- Growth abnormalities
- Effects of preterm delivery
- Predisposition to alcohol and illicit drug use.
- Predisposition to cardiac disease
Patient Counseling on Medication-assisted Therapy

Goals

- Cessation of Illicit Drug Use
- Stabilization of Intrauterine Environment
- Stabilization of Patient’s Environment
- Increased compliance with Prenatal Care and Substance Abuse Treatment Programming and Counseling
- Enhanced Pregnancy Outcomes
Patient Counseling on Medication-assisted Therapy

Benefits

- Improved Pregnancy Outcomes
  - Lower risk of preterm delivery.
  - Lower risk of low birth weight.
  - Lower risk of in utero fetal death.
  - Lower risk of emergency Cesarean delivery for non-reassuring fetal status.
  - Elimination of fetal/infant risk from contaminant drugs found in street heroin.

- Lower risk of SIDS

- Concomitant avoidance of other street drugs (cocaine, benzodiazepines) will improve pregnancy outcomes.
Patient Counseling on Medication-assisted Therapy

Risks

- Infant is still at risk for NAS/NOWS, but recognized and appropriately treated, it is usually a self-limiting condition. (NAS should be discussed in detail.)

- Improper evaluation and treatment for NAS/NOWS may lead to worse neonatal outcomes, including poor growth, and infant death, as well as altered trajectories in child development.

- Children are still at higher risk for development, emotional, and behavioral concerns.

- If not residential, patient needs transportation for daily methadone dosing.
Methadone Maintenance

- It is viewed as a therapeutic adjunct, to be used together with drug treatment counseling.
- Average dose is 60 mgs.
  (Range 20 – 140 mg.)
- Has been used for decades in opioid-addicted pregnant women.
Patient Counseling on Medication-assisted Therapy

**Buprenorphine Maintenance**

- A high safety profile clinically
- Is now considered an acceptable form of MAT in pregnancy.
- Physical dependence may still occur with buprenorphine, as with other opioids.
- Withdrawal symptoms may occur upon cessation after prolonged administration.
- Varying dosing schedules (several times/day -> several times/week)
- It is as efficacious as methadone in terms of neonatal outcome, including NAS/NOWS.
Impact of FDA labeling

On Prescribers’ willingness to prescribe

- Perceived increased liability if prescribed to pregnant women, especially liability for poor neonatal outcome.
- Perceived need to limit dose of opioid agonist.
- Increased “burden” to educate patient (and family) about NAS/NOWS.
- Increased need to communicate with prenatal care provider and/or hospital pediatric staff.
- Limited ability of prescriber to ensure patient attends prenatal care and follows the advice of the prenatal care provider.
Impact of FDA labeling on patient’s willingness to take treatment (medication-assisted therapy)

- Fear of worse pregnancy outcomes on medication-assisted therapy.
  - Patient may try to self-detoxify to avoid medication-assisted therapy. This approach often leads to failure and later entry into treatment - very problematic since pregnancy is very time-sensitive.

- Fear of increased stigma.
  - Loss of family support, housing, children.
Impact of FDA labeling

On patient’s willingness to take treatment

- Perceived increased need to hide pregnancy from MAT provider.

- Concern about finding a prenatal provider who accepts patients on medication-assisted therapy.