Medication Assisted Treatment

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Operation PAR, Inc.
Medication Assisted Patient Services (MAPS)
Operation PAR’s Medication Assisted Patient Services (MAPS) Program consists of 6 Opioid Treatment Programs (OTP) and 4 Satellite Clinics (aka Medication Units), providing Medication Assisted Treatment (MAT) in Florida:

**Operation PAR MAPS Locations:**

- Spring Hill (Primary OTP)
- Port Richey (Primary OTP)
- Clearwater (Primary OTP)
- St. Petersburg (Satellite)
- Largo (Satellite)
- Bradenton (Primary OTP)
- Sarasota (Primary OTP)
- Pt. Charlotte (Satellite)
- N. Ft. Myers (Primary OTP)
- Ft. Myers (Satellite)
METHADONE IS NOT CRYSTAL M ETH!!!

Methadone is a central nervous system depressant. Crystal Meth, aka Methamphetamine, is a central nervous system stimulant.
What Are Opiates/Opioids?

- Opiate is an older term classically used in pharmacology to mean a drug derived from opium (poppy plant).
- Opioid, a more modern term, is used to designate all substances, both natural and synthetic, that bind to the opioid receptors.
- Central nervous system depressants with a HIGH potential for abuse.
- Medical use: relieve/alleviate pain (analgesics)
- Some examples of common opioids:
  - Codeine – an ingredient in some cough syrups and in one Tylenol® product
  - Hydrocodone – Vicodin®, Lortab®, or Lorcet®
  - Oxycodone – Percocet®, OxyContin®, or Percodan®
  - Hydromorphone – Dilaudid®
  - Morphine – MSContin®, MSIR®, Avinza®, or Kadian®
  - Propoxyphene – Darvocet® or Darvon®
  - Fentanyl – Duragesic®
  - Buprenorphine – Suboxone®, Subutex®
  - Methadone
  - Heroin
- Routes of administration: injection, snorting/inhalation, smoking, oral
From 1898 through to 1910, diamorphine was marketed under the trademark name **Heroin** as a non-addictive morphine substitute and cough suppressant. In 1924, the United States Congress banned its sale, importation, or manufacture.
Comparison of Drug Caused Deaths
2015 to 2017

Note: Not all drugs are included in the above chart.
*Reporting of fentanyl analogs by all districts began in 2016.
Strengthening of neural pathways

Learned behaviors are reflected physically in the brain through the strengthening of neural pathways.

“The more often a pathway is used, the more sensitive the pathway becomes and the more developed that pathway becomes in the individual brain. As these pathways develop, the collective group of used pathways become a map of how an individual thinks, reasons, and remembers.”

- Neural Pathway Development by Dr. Gene Van Tassell

Every time I repeat an action or thought, I am engaging the same neuronal pathway in the brain.

Think about the natural creation of a footpath in the woods.
DOPAMINE

Dopamine is a neurotransmitter -- a chemical released by neurons to send signals to other nerve cells. It is directly involved in the regulation of motor control, pleasures related to motivation and also emotional arousal.

The reward circuitry was designed by evolution to reward: food, sleep, sex, friendship, novelty, etc.

All addictive drugs directly or indirectly affect dopamine neurotransmission in the nucleus accumbens.

Variations in dopamine levels tell all kinds of structures in your brain when something you want is within reach, getting closer, slipping away or not working for you anymore.
Opioid addiction is **NOT** the same as physiological dependence.
HOW OPIOID TOLERANCE / DEPENDENCE DEVELOPS

1. Person uses opioid.

2. Opioid molecules link to mu receptors on brain cells in the Locus Ceruleus (LC) and suppress the neurons’ release of noradrenaline (NA), resulting in drowsiness, slowed respiration, and low blood pressure. (familiar effects of opioid intoxication)

3. With repeated exposure to opioids, the LC neurons adjust by increasing their level of activity (thus increasing baseline NA levels).

4. Opioid receptors gradually become less responsive to opioid stimulation, affecting the mesolimbic reward system – preventing the patient from obtaining pleasure from normally rewarding activities such as eating.

5. When opioids are not present to suppress the LC brain cells’ enhanced activity, the neurons are now releasing excessive amounts of NA, triggering jitters, anxiety, muscle cramps, and diarrhea (aka Opioid Withdrawal)

**VTA** = Ventral Tegmental Area (produces dopamine, sends to NAc)

**NAc** = Nucleus Accumbens (pleasure/motivation center)

**PFC** = Prefrontal Cortex (consciousness, will power)

**LC** = Locus Ceruleus (produces noradrenaline; stimulates wakefulness)
Symptoms of Opioid Withdrawal

- Diarrhea
- Excessive perspiration
- Shaking, muscle spasms
- Vomiting, nausea
- Irritability
- Insomnia, difficulty sleeping
- Dilated pupils
- Increased heart rate
YOU HAVE KLEPTOMANIA.

CAN I TAKE SOMETHING FOR IT?
Pharmacotherapy Treatment Options

Opiate Agonists
• Methadone
• Buprenorphine (Suboxone/Subutex)

Suboxone = Buprenorphine with Naloxone
Subutex = Buprenorphine without Naloxone

Opiate Antagonists
• Naltrexone
• Vivitrol (Naltrexone XR)
• Naloxone (Narcan)
Naloxone (Narcan, Evzio)

- Opioid receptor antagonist – binds to opioid receptors and reverses or blocks the effects of other opioids.
- It can be administered by injection or through a nasal spray.
- Administering naloxone in cases of opioid overdose can cause withdrawal symptoms when the person is dependent on opioids; this is uncomfortable without being life threatening.
- Naloxone only works if a person has opioids in their system; the medication has no effect if opioids are absent.
- Effects last ~ 20-45 minutes.

Naltrexone

- Opioid antagonist
- Daily pill form
- Used to treat both Alcohol Use Disorder and Opioid Use Disorder.
- Does not produce tolerance or withdrawal
- Requires full detoxification from opioids prior to initiating treatment (otherwise competitively displaces opioid medications from their binding sites, precipitating withdrawal).
- Poor treatment adherence has primarily limited the real-world effectiveness of this formulation. As a result, there is insufficient evidence that oral naltrexone is an effective treatment for opioid use disorder.
- Contraindicated in acute hepatitis or liver failure.
- FDA pregnancy category C – meaning its effects on the fetus are unknown.


Vivitrol®
(Extended-Release Injectable Naltrexone)

• 380 mg intramuscular injection once every 4 weeks

• Patient must be opioid free for 7 to 10 days (or at least 14 days for patients who have been taking methadone for more than 3 to 4 weeks)

• Enhanced Medication Compliance due to extended-release formulation.

• Contraindicated in acute hepatitis or liver failure. However, due to its lack of first-pass metabolism, significantly reduces liver exposure to the drug, reducing the risk of potential liver toxicity.

• Individuals are at risk for overdose of opioids if they use large amounts of opioids to overcome naltrexone’s opioid blockade (in effort to feel the effects of the drugs).
<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Methadone</th>
<th>Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partial opioid agonist</strong></td>
<td>Full opioid agonist</td>
<td>Full opioid agonist</td>
<td>Full opioid agonist</td>
</tr>
</tbody>
</table>
| **Long half-life (24 to 60 hours)** | Long half-life  
~ 24 hours for opioid-tolerant  
~ up to 55 hours in opioid-naive | Long half-life | Short half-life (2 to 6 minutes)  
*Morphine’s half-life is 1-5 hours  
Oxycodone’s half-life is 4-6 hours* |
| **Ceiling effect/Plateau of efficacy; good safety profile** | No ceiling effect  
(useful in patients dependent on high doses of opioids) | No ceiling effect | No ceiling effect |

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**Figures:**

**Left:** Opioid Use With or Without Buprenorphine Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Buprenorphine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fudala et al. 2003</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Kakko et al. 2003</td>
<td>90%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Right:** Opioid Use With or Without Methadone Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Methadone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yancovitz et al. 1991</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Vanichseni et al. 1991</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Schwartz et al. 2006</td>
<td>80%</td>
<td>20%</td>
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<tr>
<td>Kinlock et al. 2007</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Gruber et al. 2008</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Dolan et al. 2003</td>
<td>50%</td>
<td>50%</td>
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</table>

For people who are not addicted to or dependent on opioids, the effects of partial (buprenorphine) and full (methadone) agonists are indistinguishable. However, at a certain point, the increasing effects of partial agonists reach maximum levels. For this reason, people who are dependent on high doses of opioids are better suited to treatment with a full agonist, such as methadone.

-Addiction Treatment Forum: http://atforum.com/2013/02/buprenorphine-vs-methadone/
Functional State (Heroin)

"High"

"Straight"

"Sick"

Days

AM
PM
AM
PM
AM


Functional State (Methadone)

"High"

"Straight"

"Sick"

Days

AM
PM
AM
PM
AM

Methadone Special Properties/Characteristics

- Long acting medication (24-36 hour half-life for opioid tolerant individuals)
- Blocks euphoric effects of short-acting narcotics
- Prevents withdrawal symptoms and “drug hunger”
- Allows normalization of disrupted physiology
- Does not provide a euphoric rush or “high”
- Has no adverse effects on mental capability, intelligence, or employability.
- It is not sedating or intoxicating (at an appropriate dosage), nor does it interfere with ordinary activities such as driving a car or operating machinery.
- Patients are able to feel pain and experience emotional reactions.
- Tolerance develops extremely slow (if at all) over long periods of continued use. It is not unusual for a patient to be maintained on the same dosage for several years without needing an increase.
- When taken under medical supervision, long-term maintenance causes no adverse effects to the heart, lungs, liver, kidneys, bones, blood, brain, or other vital body organs.
- Produces very few serious side effects, although some patients experience minor symptoms such as constipation, water retention, drowsiness, skin rash, excessive sweating, and changes in libido. However, once methadone dosage is adjusted and stabilized, these symptoms usually subside.
Methadone / Buprenorphine Maintenance Treatment Goals

1. Establish *adequate* dosage which will accomplish three objectives without causing any sedation/impairment:
   i. Suppress uncomfortable opioid withdrawal symptoms.
   ii. Extinguish cravings for illicit “street opioids.”
   iii. Block effects of illicit opioids if any are taken.

2. Identify and address any other problems that may be contributing to the opioid dependency and/or impeding their ability to function normally and productively in society (e.g. employment, medical/mental health issues, polysubstance abuse, criminal activity, social support, etc.)
Dose Stability

Concentration

Multiples of elimination half time

Steady State Concentration

toxic range

therapeutic range

subtherapeutic range

Image source: www.icjournal.org
What is Split Dosing?
If a patient has been maintained on a stable methadone dosage and misses a single day of dosing, will they go into severe opioid withdrawal?

For long-acting opioids like methadone, **mild** withdrawal symptoms will typically start about 30 hours after last administration. Severe symptoms of withdrawal can be expected approximately 72 hours after last administration.
What’s the difference between methadone received from an Opioid Treatment Program (OTP) and the methadone prescribed through a private physician?

Although the chemical make-up of methadone prescribed at a private physician’s office is technically the same as the methadone administered at an OTP, there are two key differences:

1. An OTP can only dispense/administer methadone in the form of either liquid or 40mg tablet. Private Physicians may only prescribe methadone in 10mg pill form.
2. An OTP can only prescribe methadone for the treatment of opioid use disorder (dependence/addiction). Private Physicians can only prescribe methadone for the treatment of pain.
Myth: Soon after starting treatment, patients will become addicted to methadone and will have no choice but to continue taking it or suffer through severe methadone withdrawal; “liquid handcuffs”.

Truth: Individuals must already be physically opioid dependent (with few rare exceptions) in order to be admitted to an OTP.

Although there may be some differences in the degree at which different opioid receptor types are activated by different opioid drugs, in a practical sense there really isn’t a significant difference between the dependency caused or maintained by different opioid drugs. There is no “oxycodone dependency” vs “heroin dependency” vs “methadone dependency”. Cross tolerance among different opioid substances is what allows for methadone treatment to work on those who may have become opioid dependent through the abuse of other opioids.

Any patient currently maintained on methadone has the freedom to abruptly discontinue treatment and go right back to using the same opioid substance that made them opioid dependent in the first place.
• **Myth**: Patients will be on methadone/buprenorphine forever. They have no motivation to quit.

• **Truth**: While it is true that some patients may be on methadone for a long term basis, this is an individual decision and based on several factors: concomitant medical issues, motivation for change, positive changes in recovery environment and maladaptive behaviors, strong support system, dose stability.

• Methadone alone will not “cure” addiction. It is a *supplement* to other behavioral and cognitive changes that must occur to sustain recovery. As with all other types of treatment modalities, some patients are motivated for change and others are not. At the very least, while in treatment, our patients are no longer spreading disease and robbing you to support their addiction. They can become productive members of society.

• The primary focus should not be how soon can they get off of methadone/buprenorphine. **The focus should be on whether or not they are able to achieve and maintain a healthy, productive life.** If they require continued methadone treatment in order to sustain that progress, why should that be considered any different from other maintenance medications used to treat other medical conditions like hypertension or diabetes?
Methadone blockade limitations & Drug Interactions

- Methadone ONLY blocks the euphoric effects of other opioid substances. It will NOT prevent someone from feeling the effects non-opioid substances. Non-opioid nervous system depressants like benzodiazepines and alcohol are particularly dangerous to take in combination with methadone.
What are some possible causes for a methadone patient to be sedated or impaired?

One or more of the following conditions would likely account for why a methadone maintenance patient presents as sedated or impaired:

A. They took another psychoactive drug (which may or may not be legally prescribed to them) – most likely a Central Nervous System (CNS) depressant like alcohol or a benzodiazepine. It is also possible they may have supplemented their methadone dose with additional street-purchased methadone.

B. Their dosage of methadone is simply too high (and the prescribing physician is unaware).

C. They may have untreated (or inadequately treated) medical and/or mental health condition(s) whose symptoms may overlap or mimic symptoms typically caused by the abuse of a psychoactive drug.

D. They may not have slept adequately the night before for a variety of, or combination of reasons, e.g. Up with a sick child, fighting with a significant other/family member, etc.

Signs of over-medication may include (not limited to):
• Slurred speech
• Sedation or excessive sleepiness
• Nodding or feeling “loaded”
• Heavy or drooping eyelids
• Constricted/pinpoint pupils

It is neither normal nor acceptable for any methadone maintenance patient to be sedated or impaired in any way.

(if you witness such behavior, please report it to the clinic or prescribing physician immediately)
MAT and Pregnancy

- Pharmacotherapy, combined with behavioral interventions, helps people who misuse opioids avoid experiencing withdrawal symptoms or overwhelming cravings when the opioid misuse is stopped.
- By blocking cyclic withdrawal symptoms associated with the misuse of short-acting opioids, methadone or buprenorphine can provide a more stabilized intrauterine environment.
- In addition, starting on pharmacotherapy can help the pregnant woman stop injecting drugs, a primary route of infection for people who use drugs.
- By controlling the symptoms of OUD (e.g., withdrawal, cravings), the pregnant woman can regain control, reengage in important obligations and activities in her life, and rebuild a stable social environment for herself and her family.
- Behavioral interventions are also recommended to provide maximum support for long-term recovery.
Methadone and Pregnancy

- The “Gold Standard” of care for pregnant women with opioid use disorder is methadone maintenance.

  However...

- Buprenorphine is an approved medication for the outpatient treatment of opioid use disorder since 2002 and is being used with increasing frequency for maintenance treatment of pregnant women with opioid use disorder.

- Evidence suggests buprenorphine may cause a less severe withdrawal syndrome in the neonate compared to methadone.
MOTHER Study
Multisite Randomized Controlled Trial

- Compared maternal and neonatal outcomes in opioid-addicted women treated with methadone vs. buprenorphine (86 buprenorphine / 89 methadone)

- Outcomes for Buprenorphine treated arm:
  - Less infant morphine needed for NAS
  - Shorter infant hospital stays
  - BUT
  - Higher maternal dropout rate compared to methadone, mostly due to drug dissatisfaction.
The Challenge of Methadone Dosing in Pregnancy

- There is significant genetic diversity for the enzymes that metabolize methadone (3A4, 2D6) resulting in different individual metabolic rates. (Eap et al., 1998)
- Pregnancy accelerates methadone metabolism. CYP3A is consistently and significantly increased in all stages of pregnancy. (Tracy et al., 2005)
- Absolute clearance of methadone is greater during pregnancy than post-partum. (Pond et al., 1985)
- Methadone elimination is significantly more rapid for pregnant compared to non-pregnant patients (half life 19 vs. 36 hrs). (Jarvis et al., 1999)
- Serum methadone dilution and perhaps decreased absorption as pregnancy progresses decreases effective serum levels. (Jarvis et al., 1999)
Medically Supervised Withdrawal Is NOT Recommended

- Pregnant women with OUD should not be encouraged to withdraw from pharmacotherapy for OUD during their pregnancy or shortly after delivery.
- Pharmacotherapy is the recommended standard of care, and it is the best option for a pregnant woman with OUD.
- Remaining on pharmacotherapy will help her avoid a return to substance use, which has the potential for overdose or death.
- A decision to withdraw from pharmacotherapy should be made with great care on a case-by-case basis, and additional supports such as close observation should be put in place.
- Withdrawal of pharmacotherapy for OUD and tapering during pregnancy have a high failure rate (American Society of Addiction Medicine, 2015; Jones, O’Grady, Malfi, & Tuten, 2008; Substance Abuse and Mental Health Services Administration [SAMHSA], 2014; World Health Organization, 2014), and expectant women with OUD often return to opioid misuse and its attendant risks (e.g., Kaltenbach, Berghella, & Finnegan, 1998; Mattick, Breen, Kimber, & Davoli, 2009).
- A Norwegian study (Ravndal & Amundsen, 2010) of the mortality risk after inpatient medically supervised withdrawal in a nonpregnant population found that the elevated risk of dying from an overdose within the first 4 weeks of discharge was so dramatic that prevention measures should be instituted.
Neonatal Abstinence Syndrome (NAS)

- A potentially serious medical condition
- Affects vital functions in the neonatal period that permit growth and normalcy such as
  - Feeding
  - Elimination
  - Sleep
- Symptoms mimic other serious neonatal conditions
  - Septicemia, encephalitis, meningitis
  - Post-anoxic CNS irritation
  - Hypoglycemia
  - Hypocalcemia
  - Cerebral hemorrhage
What NAS is NOT:

- “Born Addicted”
- “Hooked Newborns”
- “Littlest Victims”
- “Heroin Babies”
- “Addicted Babies”
- “Oxy Babies”
- “Oxy Tots”
- “Tiny Addict”
- “Methadone or Bup Babies”

Babies don’t have compulsive substance seeking behavior in spite of adverse consequences.

They do have a transient but potentially serious physiologic disturbance from abrupt discontinuation of prenatal opioid exposure when the umbilical cord is cut.
Methadone and Neonatal Abstinence Severity

- **POPULAR BELIEF:** “DOSE OF METHADONE INFLUENCES THE INCIDENCE AND SEVERITY OF NEONATAL ABSTINENCE”

- Evidence-based studies show no association between NAS severity and:
  - Maternal methadone dose
  - Trimester of methadone initiation
  - Duration and amount of methadone exposure
  - Duration of maternal drug use prior to pregnancy
  - No apparent relationship between maternal methadone dose (10-100 mg/day) and frequency or severity of abstinence associated seizures

(Numerous authors: Cleary et al., 2010; McCarthy, 2012; Berghella et al., 2003; Newman et al., 2011; Jones et al., 2010; Herzlinger, et al. 1977)
Postnatal Environment and NAS Severity

- The opioid exposed baby is usually separated from the mother, admitted for observation in a quiet, dimly lit environment, or more likely to a NICU and treated for abstinence, if necessary.
- Separation from the mother and sensory deprivation have not been studied as independent predictors of improvement in NAS.
- Separation might contribute to increased NAS Symptoms, decreased maternal attachment and neonatal abandonment.
Rooming-in of the Opioid Exposed Baby with Mother: Advantage in NAS?

- Newborns who roomed in (RI) with their methadone or heroin using mothers versus those who received traditional care in the NICU were compared in Vancouver, BC

- Incidence of treatment and hospital stay:
  - RI = 11%
  - NICU = 45%

- Hospital stay:
  - RI = 7 days
  - NICU = 13 days

Abrahams et al., 2007;
Hodgson and Abrahams, 2012
Can breast feeding influence neonatal opioid abstinence expression? Welle-Strand et al., 2013

- Norwegian national cohort of 124 women treated with methadone or buprenorphine. (1999-2009)
- 77% of women on opioid maintenance treatment initiated breastfeeding
- Breastfed infants exposed to methadone prenatally had a lower incidence of NAS requiring treatment (53% vs. 80%)
- Breastfed infants exposed to Methadone or Buprenorphine needed shorter pharmacological treatment of NAS than neonates who were not breastfed.
SAMHSA: No Known Risk of Increased Birth Defects With Pharmacotherapy for OUD

- The woman should be informed that experts do not agree on whether intrauterine exposure to buprenorphine (e.g., Subutex), buprenorphine/naloxone (e.g., Suboxone), or methadone results in lasting developmental or other problems for the infant.
- A woman receiving either buprenorphine or methadone should be informed that the benefits of pharmacotherapy for OUD during pregnancy outweigh the risks of untreated OUD.
- Healthcare professionals may want to reassure women that, to date, research has not shown that buprenorphine and methadone can cause an increase in birth defects and has minimal long-term neurodevelopmental impact.
- She should be informed that tobacco and alcohol exposure are known to be harmful to her and the fetus and should be provided with support to limit or preferably discontinue exposure to these substances.
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- Deborah Moore for the TimesUnion. 24 August 2014 Heroin: A brief history of unintended consequences.
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