Methadone
A Standard, Standby, and Still a Solution for OUD

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Disclosure Information

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Purpose of the Webinar

- The use of opioids for OUD emerged in the 1950s
- Methadone Maintenance Treatment (MMT) became the grand-daddy of maintenance due to the Vietnam War
- MMT is still important and valuable a half century later
- Methadone has unique chemistry, brain effects, side effects, and impact on behavior.
- We will review
  - pharmacology & clinical indications
  - MMT federal law requirements
  - patient selection, practice guidelines
  - counseling recommendations
  - contraindications, adverse effects, abuse risks
  - and treatment completion.

Objectives

As a result of this workshop, participants will be able to:

- Describe the brain receptor actions and time-course of methadone in addiction treatment
- Implement clinically effective coordination of methadone with psychosocial treatment
- Collaborate in the initiation, stabilization, maintenance and discontinuation of methadone in suitable patient populations
The U.S. Opioid Epidemic

- 4.3 million aged ≥12 used past mo. nonmedical Rx pain meds
- 435,000 used heroin in the past month
- Overdose: leading U.S. cause of personal injury-related death
- Since 1999 opioid overdose deaths quadrupled
- 2014: 1.5 times more US deaths from OD vs. MVA
- 2014: Heroin OD deaths rose 26%; fentanyl doubled
- 2015, 27 million (8% of total population ≥12) met SUD criteria
- <10% of these received any specialized care

Pathophysiology

Cortex
Role:
- Decision making
- Thinking
- Reasoning
- Learning

Limbic Region
Role:
- Basic Drives
- Experience of Reward, Euphoria

Interventions
- Psychosocial Therapies
- 12 Step Programs
- Monitoring

Interventions
- Agonist Medications
- Antagonist Medications

Healthy Opioid Receptor Activity

Endorphins
- Pain relief
- Stress relief
- Emotional bonding

Dopamine
- Eating when hungry
- Drinking when thirsty
- Rewards survival behavior

Opioid Agonists & Partial Agonists

Agonists
- Opioid analgesics
- Illicit opioid (e.g., heroin)
- Methadone
- Activates opioid receptors
- Excess dopamine release

Partial Agonists
- Buprenorphine
- Same as agonists, but ceiling effect – about half the reward of full agonists
**Full and Partial Agonists vs. Antagonists**

An agonist has an active site of similar shape to the endogenous ligand binding to the receptor and producing the same effect.

An antagonist is close enough in shape to bind to the receptor but not close enough to produce an effect. It also takes up receptor space and so prevents the endogenous ligand from binding.

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**Specific Binding**

[^18F]cyclofoxy (m ligand)

- **Normal Control**
- **Methadone Maintained Patient**

30-35% receptor occupancy for methadone >80 mg/day

*Kling et al., JPET 2000*
Neurobiology of Opioid Use Disorder

- Opioids: at substantia nigra & VTA interneurons, rapidly & briefly bind MOP-r, GABAergic inhibition of DA neurons
- ↑Dopaminergic Reward: Initial positive reinforcement; later, regulatory changes via mRNA or protein/peptides
- Recurrent withdrawal negatively reinforces recurrent use, via regulatory changes that persist for weeks/months
- Negative Reinforcement: mediated via
  - Upregulation of the KOP-r/dynorphin system (may underlie aversion, dysphoria/anhedonia, and depression-like or anxiety-like states)
  - Stress-responsive brain areas via the hypothalamo-pituitary-adrenal (HPA) axis

(Kreek et al., J Clin Investigation 2012)
Goals of Anti-Opioid Pharmacotherapy

- **Detoxification**: detox without continued meds dominates, but research & experience prove this to be inadequate care
- **Early recovery protection**: period of highest risk for OD
  - Death rates upon prison release = 12-100x general population
  - Harm reduction, e.g., from HIV and HEP C transmission
- **Anti-craving**: stabilize urges/impulses to use long enough to permit counseling effects to take hold
- **Stress Response Normalization**: OUD disrupts ACTH/Cortisol
- **Extinction**: of both positive and negative cue response
- **Biological Stabilization**: Eating, diurnal cycle, sexual function, capacity for self-care / activities of daily living / treatment retention, general healthcare, relationship bonding
- **NOT Recovery**: Disease acceptance, coping skills, rehab

Methadone: Detox (180 d) vs. Maintenance

- Patients given 6-month withdrawal management with Methadone have significantly & dramatically worse dropout from treatment vs. those in long-term Methadone Maintenance Treatment (MMT)

(Sees et al., 2000)
Patients given 6-month withdrawal management with Methadone have significantly & dramatically worse heroin relapse vs. those in long-term Methadone Maintenance Treatment (MMT) (Sees et al., 2000)

Methadone: Detox (180 d) vs. Maintenance

Rationale for Opioid Agonist Treatment

- (Opioid Substitution, or Opioid Maintenance Treatment)
- Stabilizes neuronal circuitry in OUD
  - Mu occupation with potent blockade
  - Cross-tolerant, long-acting (23 hours)
- Prevents withdrawal and craving
- Extinguishes compulsive behavior
- Reduces injection behavior, spread of HIV and HCV
- Reduces criminal behavior
- Safe for use in pregnant women
History

• Early 1960s: Methadone Maintenance Treatment (MMT) eliminates withdrawal, stabilizes craving, drug & IV use, ID
• Vietnam war ends; ~50% of US GIs used opium in the field
• Nixon’s “Drug Czar” Jerome Jaffe advances MMT nationwide
• 4-5 fold reduction in mortality with MMT (Joseph et al, 2000, Mt. Sinai J Med, vol 67)
• Adverse events: physical dependence, long/difficult withdrawal, sedation/respiratory depression, fatal OD
• Regulations control sites, staffing and procedures
• Diversion is problematic, particularly after AIDS epidemic

MMT: Reduction in Crime

Among 6 different MMT programs, crime days per year among patients before treatment (black bars) vs. during MMT

(Adapted from Ball & Ross, The Effectiveness of Methadone Maintenance Treatment, 1991)
MMT: Reduction in HIV Seroconversion

Among 138 patients in MMT (black bars), HIV infection rates were significantly lower than 88 patients who were not in MMT.


Treatment vs. Addiction

<table>
<thead>
<tr>
<th></th>
<th>Methadone/Buprenorphine</th>
<th>Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Oral or SL</td>
<td>IV, IN</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>30 minutes</td>
<td>Immediate</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>24-36 hours</td>
<td>3-6 hours</td>
</tr>
<tr>
<td><strong>Euphoria</strong></td>
<td>Absent</td>
<td>Marked</td>
</tr>
</tbody>
</table>
### Agonists vs. Antagonists: Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>AGONIST</th>
<th>ANTAGONIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain physiological dependence and potential for withdrawal</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Potential for tolerance development</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Euphoric effects/abuse/diversion</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Compatible with ongoing illicit opioid use</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>May alter use of other drugs</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Extinction of heroin-reinforced behaviors/ reversal of underlying neurobiology</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>indefinite</td>
<td>?</td>
</tr>
<tr>
<td>Cultural/ideological barriers to availability</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Professional/public opposition</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*Not offering medication after they stop drug use puts patients at increased risk of overdose and death.*

### Agonists vs. Antagonists: Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>AGONIST Agents</th>
<th>ANTAGONIST Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of physiological opioid dependence</td>
<td>Methadone (full)</td>
<td>Buprenorphine (partial)</td>
</tr>
<tr>
<td>Potential for tolerance development</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Compatible with ongoing illicit opioid use</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Diversion issues</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Requires Opioid Detoxification</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Risk of Opioid Withdrawal - Initiation</td>
<td>no</td>
<td>✓</td>
</tr>
<tr>
<td>Risk of Opioid Withdrawal - Discontinuation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pain Management Issues</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA Scheduling- Abuse Liability</td>
<td>CII</td>
<td>CIII</td>
</tr>
<tr>
<td>Risk of Opioid Withdrawal - Initiation</td>
<td>no</td>
<td>✓</td>
</tr>
<tr>
<td>Risk of Opioid Withdrawal - Discontinuation</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pain Management Issues</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Agonists vs. Antagonists: Clinical Considerations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>FDA Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>agonist</td>
<td>For maintenance treatment of opioid addiction.(^1)</td>
</tr>
<tr>
<td>Suboxone</td>
<td>partial agonist</td>
<td>For the maintenance treatment of opioid dependence.(^2)</td>
</tr>
<tr>
<td>ReVia</td>
<td>antagonist</td>
<td>In the treatment of detoxified, formerly opioid-dependent individuals.(^3)</td>
</tr>
<tr>
<td>Vivitrol</td>
<td>antagonist</td>
<td>For the prevention of relapse to opioid dependence, following opioid detoxification.(^4)</td>
</tr>
</tbody>
</table>

\(^1\) Methadone full Prescribing Information. Roxane Laboratories. \(^2\) Suboxone full Prescribing Information, Reckitt Benckiser. \(^3\) ReVia full Prescribing Information, Duramed Pharmaceuticals, Inc. \(^4\) VIVITROL full Prescribing Information, Alkermes, Inc.

All MATs are FDA-approved as in combination with psychosocial therapy.
Agonists vs. Antagonists: Key Differences

<table>
<thead>
<tr>
<th>Prescribing Considerations</th>
<th>Extended-Release Injectable Naltrexone</th>
<th>Buprenorphine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of Administration</td>
<td>Monthly</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Intramuscular injection in the gluteal muscle by healthcare professional.</td>
<td>Oral tablet or film is dissolved under the tongue. Can be taken at a physician’s office or at home.</td>
<td>Oral (liquid) consumption usually witnessed at an OTP, until the patient receives take-home doses.</td>
</tr>
<tr>
<td>Restrictions on Prescribing or Dispensing</td>
<td>Any individual who is licensed to prescribe medicine (e.g., physician, physician assistant, nurse practitioner) may prescribe and order administration by qualified staff.</td>
<td>Only licensed physicians who are DEA registered and who either work at an OTP or have obtained a waiver to prescribe buprenorphine may do so.</td>
<td>Only licensed physicians who are DEA registered and who work at an OTP can order methadone for dispensing at the OTP.</td>
</tr>
<tr>
<td>Abuse and Diversion Potential</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Additional Requirements</td>
<td>None; any pharmacy can fill the prescription.</td>
<td>Physicians must complete limited special training to qualify for the DEA prescribing waiver. Any pharmacy can fill the prescription.</td>
<td>For opioid dependence treatment purposes, methadone can only be purchased by and dispensed at certified OTPs or hospitals.</td>
</tr>
</tbody>
</table>

Methadone

- Full Mu-opioid agonist, slow onset & long duration (23 hrs)
- Extensive research shows benefit of treatment initiation
- Widely used in harm reduction: Anti-HIV & -HepC
- Start at 20-40 mg; titrating up until no craving or illicit use
- Average dose 80-100 mg daily
- Only available in ~1,600 federally certified programs
- Lipophilic, so fat tissue accumulation causes long withdrawal
- Must be used as a long-term treatment
- Cardiac risk: Prolongs QTc with risk of Torsades de Pointes
Methadone

- **Onset**: Slow; patient starts to ‘feel’ the dose 30-45 minutes later
- **Peak**: Delayed; single dose effect peaks at 2-4 hours post ingestion
- **Steady State**: Methadone deposits rise in tissues over 3-7 days. Thus, during induction phase, each dose’s effect will be stronger & last longer until steady state is achieved.

![Clinical Dose Effect](adapted from JT Payte/PCSS-O)

Methadone vs. BUP vs. No MAT

- **Estimated Days of Opioid Use**: MMT > BUP >> No MET (N = 795)  
  (Hser et al., 2015 – START Study)

![Estimated Days of Opioid Use Per Month](BUP treatment, MET treatment, No BUP or MET treatment)

**The number of participants in each type of treatment varied in each month and is therefore not indicated in the figure; on average over the follow-up period, each month there were about 14.2% of the participants in BUP treatment, 30.5% in MET treatment, and 45.3% in neither BUP nor MET treatment.**
Methadone: For Whom?

- Demographics alone: don’t provide much guidance
- Age of opioid use initiation
  - May have some value,
- Addiction history
  - Length & severity (i.e. heroin use, injection history)
  - Premorbid functioning
  - Patients with anxiety often find Methadone calming

Methadone: For Whom?

- Long history with chaotic lifestyle
- IV route of drug administration
- Needs close, daily supervision
- May have difficulty persisting with treatment
- High risk for diverting medication
- May benefit from take home contingency management
- Wants to continue some subjective sense of opioid dependence
- Has chronic pain problems & needs/expects opioids
- Pregnant or planning to become pregnant
- Is prepared for long-term or even lifelong dosing
**Methadone: Dosing**

- MMT doses >60 mg/d frequently required for heroin abstinence
  
  \[(JC\ Ball, 11/18/1988. \text{ Adapted from JT Payte MD)}\]

<table>
<thead>
<tr>
<th>Methadone Dose (mg/day)</th>
<th>Percent Heroin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

- MMT has a dose-effect curve. In studies, 60-80 mg / day is associated with near elimination of opioid + tox screens
- Average U.S. doses for heroin use disorder treatment: 60-120 mg
- Examine a MMT Clinic average dose:
  - If average is 50mg, are drug screens too often positive?
  - If average is >120mg, are patients over-sedated, drowsy?
    
    \[(Judith\ Martin\ MD,\ PCSS-O)\]
- Doses must be individualized. After a single dose, 28-fold differences in blood levels can occur between subjects, due to liver enzyme genetic variability
- Doses are not affected by Marijuana use
Methadone: Concerns

- No evidence for a pre-determined treatment: Longer Retention = Better Outcomes
- Recommended Duration: >1-2 yrs of sobriety before taper, reassess dosing every 6 mos.
- Difficult discontinuation upon treatment cessation
  Even long-term tapering can fail with final 20 mg
- Can be lethal in overdose
  - low threshold for unintentional overdose due to long half-life
  - no ceiling for respiratory depression
- Stigmatized by some in 12 step groups, criminal justice system, and other health care providers as “just substituting one drug for another.”

Methadone: Guidance to Patient & Family

Patients need advice on:
- The challenge of getting through withdrawal successfully
- Symptoms following induction on MAT
- Necessary duration of treatment (i.e., 12+ mos.)
- What will get in their way? Internal beliefs? Situational issues?
- What systems of care are needed to support the patient through this process successfully?
Opioid Treatment: Changing Approach

<table>
<thead>
<tr>
<th>Methadone Clinic</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Criteria:</td>
<td>• Criteria:</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>DSM IV or 5</td>
</tr>
<tr>
<td>12 months prior use</td>
<td>No past use time criteria</td>
</tr>
<tr>
<td>• Dose regulated</td>
<td>• MD sets dose</td>
</tr>
<tr>
<td>• Age &gt; 18</td>
<td>• Age &gt; 16</td>
</tr>
<tr>
<td>• Limited take homes</td>
<td>• Take homes (30 days)</td>
</tr>
<tr>
<td>• Tx Services “required”</td>
<td>• Services must be “available”</td>
</tr>
</tbody>
</table>

U.S. Treatment System (2014)

- 1,800,000 Rxed with MMT or OBOT
- Dramatic growth in OBOT since 2004
  - Agent 2004 2014
    - MMT: 241,000 336,000
    - BUP: 42,000 1,526,000
- 30,000 US physicians waivered for OBOT
- 9,600 US physicians certified for ≤100 pts
- 1,300 MMT programs licensed

(IMS 2015; SAMHSA)
Withdrawal Management

- Opioid withdrawal management alone – is not treatment
- Opioid WM w/methadone must be done inpatient or in an OTP
- BUP: To avoid precipitated withdrawal, wait for mild–mod WD
- BUP + low dose NTX-PO (accelerated WD) shows promise
- Clonidine: not FDA-approved; 0.1–0.3mg q6–8 hrs PO to 1.2mg qD
- Clonidine Transdermal: delayed response may require PO on day 1
- Hypotension may limit dose; may combine with other WD Sx meds
  Anxiety - BZs, diarrhea - loperamide, pain – acetaminophen/NSAIDs, nausea – ondansetron
- Ultrarapid opioid detox (UROD) – high mortality

Kampman & Jarvis. ASAM National Practice Guideline for Medications in OUD, JAM 2015

Buprenorphine: Switching from MMT to BUP

Switching from MMT to BUP may be appropriate...

- If patient experiences intolerable side effects
- Or is unsuccessful in attaining /maintaining treatment goals w/MMT
- Should be on low doses of methadone before switching
- Low dose methadone (≤30–40mg per day) generally tolerate transition to BUP with minimal discomfort, whereas higher doses may produce significant discomfort in switching medications

Kampman & Jarvis. ASAM National Practice Guideline for Medications in OUD, JAM 2015
## Methadone: Drug Testing

- Urine sample required at each visit.
- Leave belongings (coats, bags, etc.) outside bathroom
- No handwashing until urine handed off in bio-hazard bag
- No toilet flushing until urine handed off to gloved Assistant
- Questionable urine: automatic repeat, same day
- Random observed urines: Optimal, but only by same sex staff, & rarely routine. Oral swabs are better.
- If chain of custody required, can refer to a lab or higher LOC
- Validity checks: Urine temperature, pH; Oral swab witnessing
- If signs of TAMPERING: Repeat test; counsel, consider higher LOC

## Methadone: Safety & Management

- **Induction**: “Start low, go slow”
- **Mortality**: higher in the 1st 10 days & with higher induction doses. Induction risk: 7X greater than active heroin use.
- **Tolerance**: Methadone induces its own metabolic rate over time. Eventual dose need – usually much higher than initial tolerance. No direct measure of tolerance to methadone.
  - Estimate based on history & physical, & toxicology tests. First Dose Limited in Regulation,
  - Maximum 1st dose = 30mg
  - Maximum total dose during 1st day of treatment = 40mg
Methadone: Safety & Management

- **OD Death Risk:**
  - No prior MMT
  - Concurrent BZs/EToH use
  - Recently abstinent (e.g., incarcerated)
  - Can’t be observed for hours after 1st dose
- **Avoid:** Sedation, respiratory depression (stay within tolerance)
- **Minimize:** Constipation, sweating, hypogonadism
- **Check:** Medication interactions, QT/cardiac risk

Methadone: Safety & Management

- **Check:** Medication interactions, QT/cardiac risk
- Methadone effects change when blood levels change
- Inactive metabolite, so metabolism is sensitive to liver enzymes (CYP 350)
- **Med Interactions:** In general, determine dose changes clinically, if symptom/signs appear after new meds are added or withdrawn
  - Anticonvulsants (dilantin, phenobarbital)
  - HIV medication (efavirenz)
  - Rifampicin
  - QT prolonging drugs (antipsychotics)
  - Many others
Methadone: Regulatory Issues

- Diagnosis of opioid use disorder (addiction) is required
- Day 1: Dosing is limited
- Unobserved doses are initially prohibited
- Specially licensed facilities only, subject to accreditation
- Must have a diversion control plan
- Must have mandated testing & counseling
- Must have a DEA license for MMT & approved DEA storage safe
- Must perform medication reconciliation to standards
- Clinical care standards – for both patient & public safety
- Clinical options – limited; documentation requirements – high

Methadone: Take Homes

- 8 criteria defined in 42CFR part 8
- Obstacles to take homes are:
  - Non-compliance with:
    - Counseling
    - Dosing
    - Abstinence
  - Criminality, homelessness, or unemployment
  - If eligible, gradually build up from 1 day per week to monthly
  - May be ‘exceptions’; physicians often involved in these decisions
Methadone: Treatment Plan Objectives

- Physical withdrawal will be concluded
- Craving will be negligible; not distracting from recovery efforts
- Dose will block any lapse of opioid use
- Body & mind: alert, stable & normalized throughout the 24 hr day
- Patient able to engage in recovery & personal growth efforts

Methadone: Addressing Relapse

- Conduct periodic, random urine tox screens for BUP
- “5-panel” tests detect methadone, oxycodone, heroin (NOT BUP)
- Warning Signs:
  - Negative opioid urine test for methadone
  - Ongoing BZ/barb/CNS depressants, stimulants, alcohol
  - Impairment, sedation, OD, unsafe med/hazardous behaviors
  - Presenting intoxicated, or hospitalization due to drug use
- MMT is a harm reduction model – so no automatic discharge
- Revise treatment plan, increase monitoring & supports
- If continued use despite intensified treatment plan → ↑LOC

(adapted from JT Payte/ PCSS-O)
**Methadone: Discontinuation**

- Warning: Patients who discontinue MMT and then resume opioids risks craving, relapse, & overdose, & increased risk of death
- 95% relapse when attempting to taper off (Nosyk, et al. 2013). Tolerance is lost in ~3 weeks.
- Weiss et al., AGP 2012 treated BUP patients who were dependent on opioid analgesics for 3 mos., followed by a 1 mo. BUP taper 92% relapsed to opioid use again within 8 weeks
- Therefore, agonist taper & discontinuation must be slow, is indefinite in duration, & requires close monitoring even after MMT
- MMT taper is generally accomplished over several months
- Patients should remain in treatment for ongoing monitoring past the point of discontinuation
  
  Kampman & Jarvis. ASAM National Practice Guideline for Medications in OUD, JAM 2015

**Switching from BUP to MMT**

- Consider if patient is not stabilizing on BUP despite intensified care
- Consider if patient is unhappy without perceived opioid effects
- When considering a switch from BUP to MMT, there is no required time delay because addition of a full mu-opioid agonist to a partial agonist does not create withdrawal

  Kampman & Jarvis. ASAM National Practice Guideline for Medications in OUD, JAM 2015
Methadone: Pain Management

- Temporary ↑ in MET dose w/TID dosing may be effective
- For severe acute pain, switch to high-potency opioid (fentanyl)
- Monitor closely and consider, e.g., regional anesthesia
- Prior to elective surgery, consult with the surgeon & anesthesiologist – MMT should continue thru & beyond surgery

Kampman & Jarvis. ASAM National Practice Guideline for Medications in OUD, JAM 2015

Pregnancy

- 0.1% of pregnant women self-report illicit opioid use; but prescription misuse has more than doubled, 1992 – 2008
- Prenatal opioid exposure, with complex environmental conditions, is associated with many adverse outcomes
- Prenatal methadone: usual treatment, BUT...
  – is associated with neonatal abstinence syndrome (NAS)
- NAS requires medical intervention for possible GI, respiratory, CNS, autonomic nervous system, and breastfeeding dysfunction and prolonged hospitalization
- BUP (vs. methadone) NAS: less morphine need & hospitalization
- BUP monotherapy is preferred in pregnancy
- Methadone is excreted at low levels in breast milk

BUP vs. MMT: Mortality

(Kimber et al., Lancet Psychiatry 2015; 2:901-8)

- Retrospective cohort study (n=32,033) in Australia
- BUP had less all-cause & drug-related mortality than MMT in the 1st 4 weeks (adjusted all-cause MRR 2.17, 95% CI 1.29-3.67)
- After 4 weeks, mortality risk did not differ
- In the 4 weeks after treatment cessation, all-cause mortality did not differ, but drug-related mortality was lower for methadone (adjusted all-cause MRR 1.12, 0.79-1.59; adjusted drug-related MRR 0.50, 0.29-0.86).
- In the initial high risk of death period (1st 4 weeks of opioid substitution therapy, BUP seemed to reduce mortality
- Little difference between BUP vs. MMT was noted thereafter

BUP vs. MMT: Cognitive Function

During Month 1 of Treatment:

- Delayed reaction time & verbal memory deficits: Methadone > BUP > CTRLs (Rapeli P et al. ISAM 2006)

After Maintenance is Established:

- = Reaction time: MMT 100 mg vs. CTRLs (Gordon, Psychopharm 1970)
- ‡ Working memory: MMT 70 mg (Mintzer & Stitzer. DAD 2002)
- ‡ Verbal memory: MMT 35 vs. 17.5 mg (Curran et al. Psychopharm 2001)
- ‡ Visual memory vs. CTRLs: MMT 66 mg & BUP 9 mg (Pirastu et al. DAD 2006)
BUP vs. MMT: Treatment Retention

Mean retention on BUP:
Yser, Addiction 2014: 66 days
Baser, AJMC, 2011: 69 days
Fishman, CPDD 2011: 9.6 wks (adolescents/young adults)
92% relapse within 8 wks of taper (Weiss et al., 2011)

- 31 RCTs (N=5,430); evidence: mod to high
- Flexible dose MMT: better retention vs. BUP doses <16 mg
- BUP: when high dose MMT isn’t tolerated
- BUP advantages: relative safety, alternate-day administration, convenience & access
- No need for more MMT vs. BUP RCTs

(Mattick et al., Cochrane 2014)
BUP vs. MMT: Retention (Flexible Dosing)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buprenorphine</th>
<th>Methadone</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>1.1.1 Double-blind flexible dose studies</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Johnson 2000</td>
<td>32</td>
<td>55</td>
<td>40</td>
<td>55</td>
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<tr>
<td>Mattick 2003</td>
<td>96</td>
<td>200</td>
<td>120</td>
<td>205</td>
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<tr>
<td>Pettjean 2001</td>
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<td>27</td>
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<td>31</td>
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<tr>
<td>Strain 1994a</td>
<td>47</td>
<td>84</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>Strain 1994b</td>
<td>13</td>
<td>24</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td>398</td>
<td>47.2%</td>
<td>47.2%</td>
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<tr>
<td>Total events</td>
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<td>248</td>
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<td></td>
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<tr>
<td>Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 4.94$, df = 4 ($P = 0.29$); $I^2 = 19%$</td>
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<tr>
<td>Test for overall effect $Z = 2.83$ ($P = 0.009$)</td>
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</tbody>
</table>

1.2 Open label flexible dose studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buprenorphine</th>
<th>Methadone</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td>Fischer 1999</td>
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<td>Kistensen 2005</td>
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<td>Linzeris 2004</td>
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<td>Magura 2009</td>
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<td>Neri 2005</td>
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<td>Sokos 2008a</td>
<td>28</td>
<td>64</td>
<td>34</td>
<td>76</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>307</td>
<td>296</td>
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<td>52.8%</td>
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<tr>
<td>Total events</td>
<td>164</td>
<td>189</td>
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<tr>
<td>Heterogeneity: $\tau^2 = 0.08$, $\chi^2 = 18.72$, df = 5 ($P = 0.002$); $I^2 = 73%$</td>
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<td>Test for overall effect $Z = 1.91$ ($P = 0.05$)</td>
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</tr>
</tbody>
</table>

(Mattick et al., Cochrane 2014)

BUP vs. MMT: Retention

- 31 RCTs (N=5,430); evidence: mod to high
- Flexible dose MMT: better retention vs. BUP doses <16 mg
- BUP: when high dose MMT isn’t tolerated
- BUP advantages: relative safety, alternate-day administration, convenience & access
- No need for more MMT vs. BUP RCTs

(Mattick et al., Cochrane 2014)
“We find that all of us, as a society, are to blame, but only the defendant is guilty.”

**MMT vs. BUP Conclusions**

- MMT flex-dose: better retention
- BUP: preferred when high dose MMT cannot be administered or tolerated
- BUP advantages: relative safety, alternate-day administration, convenience & access
- “There does not appear to be any need for further randomized control trials of the relative efficacy of methadone compared with buprenorphine.”

(Mattick et al., Cochrane 2014)
Healthcare Costs in Opioid Dependence: Comparison of Four Agents

O Baser¹, M Chalk², DA Fiellin³, DR Gastfriend⁴

¹ STATInMED Research, Inc. & U of Michigan, Ann Arbor, MI
² Treatment Research Institute, Philadelphia, PA
³ Yale University Medical School, New Haven, CT
⁴ Alkermes, Inc., Waltham, MA

Funding: through a contract from Alkermes Inc. to Ingenix Pharmaceutical Services Inc. and STATinMED Research, Inc.

Objective: 6-month retrospective insurance claims study (N=10,413) using instrumental variable analysis to control for baseline group differences to determine total healthcare costs (all meds + inpt + outpt)

Medication Costs

- Direct cost of methadone = $1/day
- Overall cost MMT = $10-20/day
- Direct cost of buprenorphine (SL) = $4-$30/day
- Direct cost of XR-naltrexone (IM) at $600-1200 per injection (monthly) = $20-40/day
6-Mo TOTAL Healthcare Costs
(Inpatient + Outpatient + Pharmacy)

P-value vs. XR-NTX: ‡ P<0.001

Inpatient Admission Rates
Real-World 6 Month Outcomes After Treatment Initiation

P-value vs. XR-NTX: * P<0.05; † <0.01; ‡ P<0.001

Baser et al., Am J Manag Care 2011b
Attitudes: Harmful & Helpful

- Attitudes that do a disservice to patients:
  - “If you’re using drugs, you’re not really sober; I did it the hard way”
  - “If you just work the program, you won’t need any drugs”
  - “You can’t treat a drug problem with a drug”
  - “If you are on drugs, you can’t speak at a meeting”

- Attitudes that are justified by the science:
  - We don’t withhold medication from heart disease patients, saying: “You have to stop smoking & lose weight on your own, like I did”!
  - Chronic diseases, like hypertension & asthma have meds. If we want addiction to be treated as equal to other medical illnesses, we need to accept the role of medicine in addiction treatment, too.
  - Opioid patient on XR-NTX: “I never understood it before... but now I know how it is that non-addicts can just ignore drugs. And suddenly I see what it means that I really do have an addiction.”

Is OST a Necessity for OUD Recovery?
(Merlo et al., JSAT 2016, 64:47-54)

- A 5-year, retrospective review of 702 physicians in 16 programs (N=702; 85.5% male; age=24-75). Alcohol Only (n=204), Any Opioid with or w/o alcohol use (n=339), 3) Non-Opioid drug use with or w/o alcohol (n=159)
- Of 22.1% of physicians who had a positive test, 2/3rds had just 1 + test, and only 1/3rd had >1 + test. Results were similar in all 3 groups.

CONCLUSIONS:

- MDs with OUD in PHPs have long-term abstinence from opioids, alcohol, and other drugs
- Without OST via abstinence-based psychosocial treatment with extended, intensive management after discharge
Q&A

• How to determine necessary MMT dose?
  – Difficult: patient subjective self-report
  – Balanced by objective function (incl. collaterals) and drug testing

• Are there head-to-head trials of MMT vs. XR-NTX?
  – No; only BUP vs. XR-NTX (1 good-sized & 1 large trial)

Conclusions: MAT in Opioid Use Disorder

- Opioid dependence is a chronic disease requiring long-term rehabilitation with both meds AND counseling.
- The goals of treatment/rehabilitation are: saving lives, stabilizing behavior and establishing social functioning.
- Agonists & antagonists are superior to counseling alone.
- All FDA-approved agents are appropriate 1st-line approaches.
- Therefore, programs should provide ALL options, so that patients can be informed of and offered ALL options.
- Low initial costs can become high costs longer-term, and high initial costs can result in lower costs longer-term, therefore, cost should NOT be a consideration in clinical care.
- Patient choice may be the BEST basis for drug selection.
- If one agent is unsuccessful, other options should be tried.
Case 1 (Part I)

Johnny is a 34 yo male; hurt back working in the coal mines and was Rxed opioids; use escalated and he began using multiple oxycodone with APAP 30/500 mg tabs IV daily. Met criteria for Opioid Dependence, LFTs less than 3x normal.

Tried BUP from a doctor and received a prescription: “It didn’t work for me. I just stopped taking it and used, and took it some more and then stopped and used. It was too easy to game it. I need more. I don’t want that medicine”.

Case 1 (Part II)

Johnny did extremely well with methadone at a maximum dose of 85 mg per day and began a gradual dose reduction.

At 3 years he on 70 mg and has been eligible for 27 take homes per 28 days, but opts to get 13 in 14 days (“I don’t trust myself with more. I need to come here to keep myself honest”).

He has an opportunity to change jobs from underground mining to hauling coal locally, which requires a commercial driver’s license. He is willing to change to BUP, recognizing he is now doing well presenting every 2 weeks to clinic.
Case 1 (Part III)

Johnny made the change from methadone to BUP, stabilized at 12 mg qd for a year and gradually tapered to 4 mg qd. Attempts to lower the dose have failed.

Continues to choose present q 2 weeks to clinic, although eligible for monthly visits and has been encouraged to find support outside of clinic

Local mines have closed, and he has the option for work in another state. Plans to come home once monthly. Will have insurance with new job, and has saved substantial money since he stopped using street opioids and began treatment 6 years ago.

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