The safety and efficacy of long-term buprenorphine and methadone for opioid use disorder

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Conflicts of Interest

No conflicts of interest
Learning Objectives

1. Understand the use of buprenorphine and methadone medication-assisted therapy (MAT) for opioid use disorder (OUD), through different phases of treatment (e.g. induction, stabilization, and maintenance)

2. Recognize the long-term benefits of continued engagement in treatment (treatment retention) in MAT for OUD

3. Compare and contrast the safety and efficacy of continued MAT for OUD

4. Understand regulatory and operational considerations of buprenorphine for OUD in a variety of treatment settings
Flow

Background
- Substance use disorder
- Chronic disease model
- MAT-first approach

Buprenorphine
- Efficacy
- Safety
- Office-based prescribing considerations & models

Methadone
- Efficacy
- Safety

Relative safety and efficacy
- Comparative safety/efficacy
- Special populations
- MAT versus non-OAT interventions

Conclusions
- Regulatory considerations
- MAT supply / demand
- Other considerations for using MAT

PollEverywhere
1) Text SCOTTCOON065 to 22333 once to join, then A,B,C,D
2) Respond at www.pollev.com/scottcoon065
Substance Use Disorder

DIAGNOSIS, REWARD SYSTEM AND HISTORY OF DISEASE

ST. LOUIS COLLEGE OF PHARMACY
Substance Use Disorder

- **Loss of control**: Taking larger amounts for longer than intended; wanting to cut down/quit but unable to; increasing time getting, using, & recovering from drug; craving

- **Continued use despite negative consequences**: Failure to carry out obligations at work, school or home; continued use despite social/interpersonal problems; stopping or reducing other important activities; recurrent use in hazardous situations; use despite medical or psychological consequences

- **Physical dependence** including tolerance, withdrawal

Tolerance and withdrawal to an opiate ≠ Opioid use disorder
A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period of time than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance.
10. Tolerance,* as defined by either of the following:
   a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect
   b. A markedly diminished effect with continued use of the same amount of an opioid
11. Withdrawal,* as manifested by either of the following:
   a. The characteristic opioid withdrawal syndrome
   b. The same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms

*This criterion is not met for individuals taking opioids solely under appropriate medical supervision. Severity: mild = 2–3 symptoms; moderate = 4–5 symptoms; severe = 6 or more symptoms
What have we been doing?

- Detoxification model of treatment for opioid use disorder (OUD)
- Overreliance on residential and group therapy as treatment
- Approached with an acute care model
- Use of medication as last resort
- Waiting for patient to “hit rock bottom” to be motivated to change

OUD is a chronic disease that involves changes in the way the brain functions. Absence of the drug does not fix the underlying brain chemistry.
Relapse rates with chronic illness

- Hypertension (50-70%) 60%
- Asthma (50-70%) 60%
- Substance Use Disorders (40-60%) 50%
- Type 1 Diabetes Mellitus (30-50%) 40%

- Consequences of relapse can be life-threatening with any chronic disease
- Opioid use disorder is a chronic condition and medications are used to prevent withdrawal symptoms and cravings for opioids
James is a 65 year old cis-male patient diagnosed with rheumatoid arthritis, coronary heart disease, generalized anxiety disorder, and tobacco use disorder.

Social History: smoking 1 pack per day for nearly 40 years

Quit attempts: he has quit tobacco cold-turkey x2 (lasting 1 year each)

Medication History: sertraline 100mg daily, atorvastatin 40mg daily, sulfasalazine 1000mg twice daily

At this current visit with you, he states that he is ready to quit smoking.

PLAN:

- Refer the patient to outpatient treatment program where he will be coached on non-pharmacologic smoking abstinence techniques
Case #1

Would this patient benefit from being offered pharmacotherapy?
Case #1

- James continues to smoke despite intensive behavioral counseling
  - He cites the initial withdrawal and continued cravings as the primary reasons he was unsuccessful
  - Fagerstrom score: 9 (high dependence)

PLAN:
- Rapid detoxification using nicotine replacement
- After detoxification is complete, return to outpatient rehabilitation
Case #1

**Withdrawal symptoms**

- Total score
- Quit day 1.5 - 1.9
- Day 7 1.6 - 1.9
- Day 14 1.7 - 1.9
- Day 21 1.8 - 1.9
- Day 28 1.7 - 1.9

**Urges to smoke**

- Total score
- Quit day 2.0 - 3.5
- Day 7 2.5 - 3.5
- Day 14 2.5 - 3.5
- Day 21 2.5 - 3.5
- Day 28 2.5 - 3.5

Withdrawal scored 1-5, urges scored 1-6
What have we been doing?

- Detoxification model of treatment for Opioid Use Disorders
- Overreliance on residential and group therapy as treatment
- Approached OUD with acute care model
- Use of medication as last resort
- Waiting for patient to “hit rock bottom” to be motivated to change

Why doesn’t this work?
Medication Assisted Therapy (MAT) myths and stigma

- Addiction is a choice
- People won’t get clean until they hit rock bottom
- Opioid agonist therapy (or MAT) is just trading one addiction for another
- You are not clean if you are using any opiate, even for MAT
- Methadone is just as dangerous as heroin
- Opioid agonist therapy prevents functioning in society, including holding a job
50 - 70% of substance use disorders are attributed to genetic predisposition.

25 - 36% of the genetic influences of multiple substance use disorders (alcohol, nicotine and cannabis) are attributed to overlapping factors.
Environmental and genetic factors are essential to understanding risk for substance use disorder

- Risk factors include personal history of other SUDs, family history of SUD, history of mental illness, exposure to trauma

Personal choices contribute, but no one wants to have a substance use disorder

Substance exposure is a requirement
Medication-first model

- Relief from withdrawal symptoms and stabilization
- Reduced craving
- Allows patient to engage in psychosocial treatments
- Increased retention in treatment
- Reduced death from overdose
Case #2
Analogy using depression

- Marta is a 42 year old cis-female patient diagnosed depression and generalized anxiety disorder
- Medication History: ibuprofen 200mg as needed
- PHQ-9: 18 (moderately-severe), [-] suicidal ideation
- At this current visit with you, expresses concern

PLAN:
- Refer the patient to outpatient treatment program where she will receive specialized medical care for her depression and will be taught to abstain from feelings of depression
- If necessary, she may receive pharmacotherapy contingent on her attending a minimum of 50% of the required behavioral health counseling sessions
Flow

- Substance use disorder
- Chronic disease model
- MAT-first approach

Buprenorphine

- Efficacy
- Safety
- Office-based prescribing considerations & models

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Buprenorphine

SAFETY, EFFICACY, BARRIERS, DIVERSION
PRESCRIBING MODELS AND CONSIDERATIONS

ST. LOUIS COLLEGE OF PHARMACY
# Buprenorphine Dosing

<table>
<thead>
<tr>
<th>Brand-name</th>
<th>Buprenorphine SL</th>
<th>Buprenorphine +naloxone SL</th>
<th>Buprenorphine SubQ</th>
<th>Buprenorphine implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subutex (tablet)</td>
<td>Suboxone (film)</td>
<td>Sublocade</td>
<td>Probuphine</td>
<td></td>
</tr>
<tr>
<td>Zubsolv (tablet)</td>
<td>Bunavail (film)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dosing**
- Typically given in 2-4mg increments during induction while patient presents in mild withdrawal (COWS 5-24)
- 100-300 mg injected SubQ
- 4 implantable devices (74.2 mg each)

**Half-life (hours)**
- Film: 27.6 ± 11.2 hr; tablet: 37 hr
- 43-68 days
- 24-48 hr

**Time to peak**
- Film: 2.5-3, tablet: 0.5-1 hours
- 24 hours
- 12 hours

**Safety concerns**
- CNS depression, precipitated withdrawal, accumulation in moderate-severe hepatic impairment, QTc increase (minor)

**Major safety concerns (formulation-specific)**
- n/a
- Naloxone has extensive first pass metabolism, but is active if used IV. Avoid in pregnancy
- Administration error-prone (SubQ given as IV/IM)
- Implant migration, protrusion, expulsion and nerve damage (due to improper insertion)

**Clinical considerations**
- Absorption is pH dependent (higher absorption with lower pH), diversion and misuse may occur more frequently with non-co-formulated products
- Start after induction with PO/SL for ≥ 7d
- Start after stable PO/SL dose ≤ 8mg for ≥ 3 months

**Maintenance target doses and range (mg)**
- Stabilization: 12-16mg/day, though doses up to 24mg may be necessary (benefit unclear >24)
- 100mg/month, may increase to 300mg if needed
- Equivalent of 80mg x4 (320mg)/6 months
Buprenorphine\textsuperscript{1,4,5}

- Increases retention in recovery versus placebo at all doses
  - Less effective for retention versus methadone at lower doses
  - Doses $\geq 16$ mg per day reduce illicit drug use versus placebo
- Reduces risk for mortality and a variety of morbidities associated with disease
- Treatment for maternal OUD lowers risk of preterm birth, low birth weight and small head circumference

...but there are barriers to prescribing
Prescribing barriers
Buprenorphine

Reasons for not being waivered or not prescribing to capacity

- Reimbursement insufficient: 15% waivered, 5% non-waivered
- Not enough education about OUD: 15% waivered, 1% non-waivered
- Concerned about precipitating withdrawal: 12% waivered, 2% non-waivered
- Don't believe in OAT: 14% waivered, 3% non-waivered
- No time for more patients: 12% waivered, 10% non-waivered
- Concerned about diversion: 26% waivered, 10% non-waivered
- Don't want to be inundated with BUP/NLX requests: 30% waivered, 9% non-waivered

...but prescribing doesn’t have to be alone
**Collaborative opioid prescribing (CoOP)**

**linking opioid treatment programs with office-based buprenorphine prescribers**

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"Adaptive Stepped Care System"

- Addiction treatment program:
  - Initial assessment
  - Induction/stabilization
  - Ongoing counseling

- Primary care site:
  - Office-based buprenorphine prescribing

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<table>
<thead>
<tr>
<th>Step</th>
<th>Opioid Agonist Medication</th>
<th>Prescribing or Dispensing Location</th>
<th>Prescribing or Dispensing Frequency</th>
<th>OTP Counseling Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stable OBOT</td>
<td>Buprenorphine</td>
<td>OBOT office prescription</td>
<td>1 month prescription</td>
<td>Low</td>
</tr>
<tr>
<td>2. Intensive OBOT</td>
<td>Buprenorphine</td>
<td>OBOT office prescription</td>
<td>1 week prescription</td>
<td>Intensive</td>
</tr>
<tr>
<td>3. Intensive OTP</td>
<td>Buprenorphine</td>
<td>OTP dispensary</td>
<td>Daily dispensing</td>
<td>Intensive</td>
</tr>
<tr>
<td>4. Methadone OTP</td>
<td>Methadone</td>
<td>OTP dispensary</td>
<td>Daily dispensing</td>
<td>Intensive</td>
</tr>
</tbody>
</table>
**Benefits (Baltimore, MD)**

**Outcome: overdose deaths**

- **1995-2002**
  - No significant association between heroin overdose deaths and the number of **methadone** patients ($P = 0.957$)

- **2003-2009**
  - Significant negative association between heroin overdose deaths and the number of **buprenorphine** patients during this period was significant ($P < 0.001$)
Benefits (France) \(^9\)

Outcome: Heroin overdoses

- Prescribers are not required to receive special training for buprenorphine
- There is no limit to the number of patients a prescriber may treat
- There are no requirements for urine drug testing or counseling
Deaths Attributable to Methadone vs Buprenorphine in France\textsuperscript{10}


Number of attributed deaths / total (for each drug respectively)

<table>
<thead>
<tr>
<th>Year</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>0.0017</td>
<td>0</td>
</tr>
<tr>
<td>1995</td>
<td>0.0125</td>
<td>0.0017</td>
</tr>
<tr>
<td>1996</td>
<td>0.0025</td>
<td>0.0001</td>
</tr>
<tr>
<td>1997</td>
<td>0.003</td>
<td>0.0001</td>
</tr>
<tr>
<td>1998</td>
<td>0.0007</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Benefits (Maintenance vs. Detox)\textsuperscript{11}

Outcome: retention and abstinence

- Participants randomized to:
  - Fixed-dose buprenorphine (16 mg/day) for 12 months, or
  - 6-day buprenorphine taper followed by placebo
- All patients participated in cognitive-behavioral group therapy and received weekly individual counselling sessions
- 15/20 (75%) retention in buprenorphine group vs. 0/20 (0%) retention in detox
- Urine screens were about 75% negative for opioids and other drugs in the patients remaining in treatment

![Graph showing retention rates over time for buprenorphine and control groups. The graph indicates a significant difference (p=0.0001) between the two groups.](Graph.png)
**Benefit (Maintenance vs. Detox)**

Outcome: retention and abstinence from opioid use in youth (14-21)

Retention in Treatment: Detox vs. Maintenance

- **Baseline:**
  - Detox: 84%
  - Maintenance: 70%
- **4 weeks:**
  - Detox: 74%
  - Maintenance: 63%
- **8 weeks:**
  - Detox: 27%
  - Maintenance: 52%
- **12 weeks:**
  - Detox: 21%
  - Maintenance: 55%

**Any opioid use: Detox Taper vs. Maintenance**

- **Baseline:**
  - Detox Taper: 45%
  - Maintenance: 38%
- **4 weeks:**
  - Detox Taper: 26%
  - Maintenance: 19%
- **8 weeks:**
  - Detox Taper: 26%
  - Maintenance: 19%
- **12 weeks:**
  - Detox Taper: 21%
  - Maintenance: 19%
## Risks

### Diversion and misuse

<table>
<thead>
<tr>
<th>Reason for Use of Illicit Buprenorphine</th>
<th>Actively Prescribed Buprenorphine</th>
<th>Not Actively Prescribed Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>To get high</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>To save money</td>
<td>8%</td>
<td>29%</td>
</tr>
<tr>
<td>To treat depression</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>To reduce pain</td>
<td>15%</td>
<td>47%</td>
</tr>
<tr>
<td>To treat anxiety</td>
<td>33%</td>
<td>42%</td>
</tr>
<tr>
<td>To prevent withdrawal</td>
<td>67%</td>
<td>90%</td>
</tr>
<tr>
<td>To prevent cravings</td>
<td>88%</td>
<td>97%</td>
</tr>
</tbody>
</table>

Whether persons did/didn’t have a Rx for themselves, top reasons for use were similar.

### Craving

“[C]onstant, intrusive, involuntary obsession that will persist until the drug is ingested”
### Risks

#### Adverse Effects

<table>
<thead>
<tr>
<th>System</th>
<th>Side effect (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Hypertension (1-5%), peripheral edema (1-5%)</td>
</tr>
<tr>
<td>CNS</td>
<td>Fatigue (≥5%), headache (4% to ≥5%), dizziness (2% to ≥5%), drowsiness (1% to ≥5%), anxiety (1%-%), depression (1-5%), falling (1-5%), insomnia (1-5%), opioid withdrawal syndrome (1-5%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea (9-10%), diarrhea (≥5%), xerostomia (≥5%), vomiting (4 to ≥5%), constipation (3 to ≥5%), abdominal pain (1-5%), decreased appetite (1-5%), gastroenteritis (1-5%)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>UTI 1-5%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Upper respiratory tract infection (≥5%), bronchitis (1-5%), nasopharyngitis (1-5%), oropharyngeal pain (1-5%), paranasal sinus congestion (1-5%), sinusitis (1-5%)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Hyperhidrosis (1-5%), pruritus (1-5%), skin rash (1-5%), hot flash (1-5%)</td>
</tr>
</tbody>
</table>
Flow

- Substance use disorder
- Chronic disease model
- MAT-first approach

- Efficacy
- Safety
- Office-based prescribing considerations & models

**Background**

**Buprenorphine**

**Methadone**

**PollEverywhere**

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Methadone

SAFETY AND EFFICACY

ST. LOUIS COLLEGE OF PHARMACY
Methadone Dosing

<table>
<thead>
<tr>
<th>Methadone</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>Start with low dose (20-30mg) in opioid tolerant persons (lower if non opioid tolerant) and gradually increase over days to weeks (e.g. +20mg q3day) based on withdrawal symptoms. Equianalgesic conversion is discouraged</td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td>8-59 hrs (avg. 24hrs)</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
<td>1-7.5 hrs</td>
</tr>
<tr>
<td><strong>Safety concerns</strong></td>
<td>QTc prolongation (dose dependent, especially when &gt;120mg), respiratory depression, accumulation with severe hepatic disease (may precipitate encephalopathy)</td>
</tr>
<tr>
<td><strong>Clinical considerations</strong></td>
<td>Many drug interactions, No ceiling effect, NMDA receptor antagonist, Equianalgesic conversions (e.g. morphine milligram equivalent) varies based on dose (non-linear kinetics). Tablets are dissolved into suspension</td>
</tr>
<tr>
<td><strong>Common side effects</strong></td>
<td>Sleep disruptions, N/V, constipation, xerostomia, sweating, sexual dysfunction, menstrual irregularities, weight gain</td>
</tr>
<tr>
<td><strong>Maintenance target doses and range (mg)</strong></td>
<td>80-120mg</td>
</tr>
</tbody>
</table>
Methadone\textsuperscript{1}

- Oldest therapy available for OUD
- High doses (80-120 mg/day) are associated with better outcomes
- Methadone treatment increases retention in recovery, reduces crime, the spread of infectious diseases, illicit opioid use, and death from overdose.

Source: Infect Chemother. 2008 May-Jun;40(3):133-139
Federal guidelines for outpatient treatment programs\textsuperscript{28}

- 42 CFR 8.12(e) Patient admission criteria:
  - Maintenance treatment: “...[The] person is currently addicted to an opioid drug, and that the person became addicted at least 1 year before admission for treatment.”
    - “If clinically appropriate, the program physician may waive the requirement of a 1-year history of addiction... for patients released from penal institutions (<6 mo from release), pregnant patients, or previously treated patients (< 2 years after discharge)”
  - < 18 years old: “[I]s required to have had two documented unsuccessful attempts at short-term medical withdrawal (detoxification) or drug-free treatment within a 12-month period to be eligible for methadone maintenance treatment.”
  - “A program shall not admit a patient for more than two detoxification [\textit{to a medication-free state or antagonist therapy}] treatment episodes in one year”
    - “Detoxification services should be accompanied by relapse prevention counseling, overdose prevention education as well as a naloxone kit (naloxone dose and syringes) or an FDA-approved naloxone auto injector.”
    - “The treatment and aftercare plans should always include a strategy to transition to medication-assisted treatment if needed”
Methadone clinic

Are we doing the best we can to minimize stigma for our patients?

Source: Deluth News Tribune

Source: Inlander
Risks
Diversion and misuse

Report **diverting methadone** in the last year

**YES** 14%

**NO** 86%

Reasons for diverting methadone (%)

- To help someone: 80%
- To buy other drugs: 25%
- To trade methadone for other drugs: 13%
- To buy other items (not drugs): 8%
- Other: 6%
Risks

Diversion and misuse

Circumstances under which participants obtained illicit methadone (%)

- Needed methadone, but not in treatment: 12%
- Top-up prescription: 27%
- Missed prescriber/agency appointment: 28%
- Other: 37%
- Missed pharmacy pick-up: 50%

How can we be more available?
Flow

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- Efficacy
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Relative safety and efficacy
- Comparative safety/efficacy
- Special populations
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Relative safety and efficacy

METHADONE AND BUPRENORPHINE

ST. LOUIS COLLEGE OF PHARMACY
## Opioid agonists for OUD\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine +/- naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic activity</td>
<td>Full agonist</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>Formulations</td>
<td>Oral</td>
<td>SL, injectable, and subdermal</td>
</tr>
<tr>
<td>Dosing</td>
<td>Daily</td>
<td>Daily, monthly, bi-annually</td>
</tr>
<tr>
<td>Safety</td>
<td>Safe when taken as directed; arrhythmia and overdose possible (dose dependent)</td>
<td>Very safe when taken as directed overdose risk is low</td>
</tr>
<tr>
<td>Considerations</td>
<td>Dispensed from an Opioid Treatment Program (OTP) certified by SAMHSA</td>
<td>MDs, NPs, &amp; Pas can rx; must have DEA DATA 2000 waiver</td>
</tr>
<tr>
<td>May work well for:</td>
<td>Have a long history of addiction; need high levels of daily structure</td>
<td>May not need daily supportive structures</td>
</tr>
</tbody>
</table>

*See TIP63, EXHIBIT 2.14 for detailed breakdown of MAT considerations*
Opioid agonist receptor activity

Partial agonists have lower risk for respiratory depression.

Partial agonists have lower risk for experiencing the euphoric effects of an opiate.
### Buprenorphine vs. Methadone

**Outcome: retention**

#### Flexible-dose:
- Methadone favored over flexible-dose buprenorphine (RR 0.83; 95% CI 0.73 to 0.95)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>buprenorphine</th>
<th>methadone</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1 Double-blind flexible dose studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson 2000</td>
<td>32</td>
<td>32</td>
<td>64</td>
<td>10.2%</td>
<td>0.80 [0.61, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Mattick 2003</td>
<td>96</td>
<td>96</td>
<td>192</td>
<td>13.5%</td>
<td>0.82 [0.68, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Pettit 2001</td>
<td>15</td>
<td>15</td>
<td>30</td>
<td>7.9%</td>
<td>0.62 [0.43, 0.88]</td>
<td></td>
</tr>
<tr>
<td>Strain 1994a</td>
<td>47</td>
<td>47</td>
<td>94</td>
<td>10.4%</td>
<td>0.99 [0.76, 1.30]</td>
<td></td>
</tr>
<tr>
<td>Strain 1994b</td>
<td>13</td>
<td>13</td>
<td>26</td>
<td>6.1%</td>
<td>0.97 [0.59, 1.61]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>390</td>
<td>390</td>
<td>780</td>
<td>47.2%</td>
<td>0.83 [0.72, 0.95]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>203</td>
<td>248</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> Tau² = 0.00; Chi² = 4.94, df = 4 (P = 0.29); I² = 19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect: Z = 2.43 (P = 0.009)**

#### Low-doses:
- Low-dose methadone favored over low dose buprenorphine (RR 0.67; 95% CI 0.52 to 0.87)
  - Methadone > buprenorphine

#### Medium-doses:
- Medium-dose buprenorphine versus medium-dose methadone (RR 0.87; 95% CI 0.69-1.10)
  - No Difference

#### High-doses:
- High-dose buprenorphine versus high-dose methadone (RR 0.79; 95% CI 0.20 - 3.16)
  - No Difference
There were significant fewer people remaining in treatment with buprenorphine versus methadone (P < 0.01 for all time points).

However, most of the attrition occurred within the first 12 months and then remained constant.
Buprenorphine vs. methadone

Outcome: [-] urine drug screen

**Flexible-dose**
Flexible-dose buprenorphine versus flexible-dose methadone
(SMD -0.11; 95% CI -0.23 to 0.02)
No Difference

**Medium-doses**
Medium-dose buprenorphine versus medium-dose methadone
(SMD 0.25; 95% CI -0.08 to 0.58)
No Difference

**Low-doses**
Low-dose buprenorphine versus low-dose methadone
(SMD -0.35; 95% CI -0.87 to 0.16)
No Difference

**High-doses**
High-dose buprenorphine versus high-dose methadone
No studies reporting urine data
Unknown
Buprenorphine vs. methadone\textsuperscript{17}

Outcome: relapse (by self-reported days of opioid use)

- Methadone and buprenorphine both had similar efficacy in limiting illicit opioid use while in treatment, as compared to no MAT
Relapse was similar for buprenorphine and methadone, lower than for non-opioid agonist behavioral health therapy.
“While patients should be offered psychosocial support, they should not be denied agonist maintenance treatment should they refuse such support.” (Ref 20)
Buprenorphine vs. methadone\textsuperscript{17,20}

Outcome: mortality

<table>
<thead>
<tr>
<th></th>
<th>Death/n</th>
<th>5-year incidence</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>26/450</td>
<td>0.0578</td>
<td>P=0.10</td>
</tr>
<tr>
<td>BUP</td>
<td>23/630</td>
<td>0.0365</td>
<td></td>
</tr>
</tbody>
</table>

Mortality rate / 1000 person-years (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>In treatment</th>
<th>Out of treatment</th>
<th>Risk Reduction (out vs in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>2.6 (2.1-3.3)</td>
<td>12.7 (6.9-23.4)</td>
<td>4.9 times</td>
</tr>
<tr>
<td>BUP</td>
<td>1.4 (1.0-2.0)</td>
<td>4.6 (3.9-5.4)</td>
<td>3.3 times</td>
</tr>
</tbody>
</table>

- Incidence was low, not powered to show difference
- Cox regression hazard ratio (adjusting for age, gender, race/ethnicity, cocaine use at baseline) showed no difference between groups
- Risk reduction was greatest with methadone, but overall mortality rate was significantly lower with buprenorphine (both in and out of treatment)
- Limited conclusions based on these data due to confounding and bias from cohort design
**Buprenorphine vs. methadone**

Outcome: mortality

<table>
<thead>
<tr>
<th>Treatment provider</th>
<th>In treatment</th>
<th>Out of treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist</td>
<td>13.4 (9.2-19.5)</td>
<td>46.5 (28.2-76.5)</td>
<td>P=0.26</td>
</tr>
<tr>
<td>GP/mixed</td>
<td>8.6 (5.4-13.7)</td>
<td>24.4 (13.1-45.5)</td>
<td></td>
</tr>
</tbody>
</table>

Similar outcome on mortality regardless of treatment provider
Buprenorphine vs. methadone

Outcome: Adverse Events

- Typically similar between groups, some trials have reported more sedation with methadone
- Due to buprenorphine's partial agonist activity, respiratory depression is less likely
- QTc prolongation is possible with either...but there's a big difference between the two
Buprenorphine versus methadone

Effects on QT-interval

Proportion exceeding QTc limits

Mean QTc, ms

Levomethadyl acetate group
Methadone hydrochloride group
Buprenorphine hydrochloride group

Interval, wk

Subjects, %

Week

4 8 12 16
The SAMHSA Expert Panel:

- Screening for structural heart disease, arrhythmia, and syncope
- EKG for all patients prior to starting, within 30 days after starting, and then annually
  - A dose is not specified (i.e. low dose and high dose treated similarly)
- Discuss risks/benefits if QTc is 450-500 ms
- Consider discontinuing if > 500 ms
Special Populations

ANTEPARTUM/POSTPARTUM, INTRAVENOUS USE
Unintended pregnancy rates are estimated to be as high as 80% in women with SUDs.

Methadone and buprenorphine (without naloxone) are similar in safety / efficacy to mother and fetus. The WHO makes strong recommendation for either.

Drop out (pictured below) was similar, though a non-significant trend favored methadone (p=0.06)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Methadone Events</th>
<th>Total</th>
<th>Buprenorphine Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer 2006</td>
<td>3</td>
<td>9</td>
<td>1</td>
<td>9</td>
<td>2.8%</td>
<td>3.00 [0.38, 23.68]</td>
<td></td>
</tr>
<tr>
<td>Jones 2005</td>
<td>4</td>
<td>15</td>
<td>6</td>
<td>15</td>
<td>16.9%</td>
<td>0.67 [0.23, 1.89]</td>
<td></td>
</tr>
<tr>
<td>MOTHER Study</td>
<td>16</td>
<td>89</td>
<td>28</td>
<td>86</td>
<td>80.3%</td>
<td>0.55 [0.32, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>113</td>
<td></td>
<td>110</td>
<td></td>
<td>100.0%</td>
<td>0.64 [0.41, 1.01]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 23 35

Heterogeneity: $\chi^2 = 2.44$, df = 2 (P = 0.29); $I^2 = 16$

Test for overall effect: $Z = 1.91$ (P = 0.06)
MAT during Pregnancy

- Serious fetal harms were similar between methadone

- A 60% lower risk for preterm birth was seen with buprenorphine vs. methadone (HR 0.4, 0.18-0.91, I² 0%)
Neonatal Abstinence Syndrome\textsuperscript{31,32}

- A large meta-analysis of RCTs found:
  - A 10% lower risk for NAS (RR 0.9, 95\%CI 0.81-0.98) with buprenorphine
  - An 8-9 day shorter NAS treatment duration (-8.46 days, 95\%CI -10.64 to -3.83) with buprenorphine
  - A lower morphine [NAS treatment] dose requirement (not significant) with buprenorphine

  ...but results are confounded by the difference in disease severity, which often dictates the treatment selection (i.e. buprenorphine or methadone)

- A recent cohort analysis that adjusted for measured (parity, maternal race, age, delivery year, employment, HCV, smoking, marital, and insurance status) and unmeasured confounding variables (i.e. severity of addiction) found:

  - NAS risk was 30\% higher for infants exposed to methadone versus buprenorphine (RR 1.3, 95\%CI 1.2-1.5) in utero

- Longitudinal studies have not shown long-term developmental sequelae to in-utero exposure to methadone (up to 5 years)
MAT should continue postpartum

- Patients are more vulnerable and relapse is more frequent
  - Loss of insurance and access to treatment
  - New childcare responsibilities
  - Custody concerns

- Significant MAT dose reductions postpartum should not be done routinely, but should be titrated to signs and symptoms of sedation
Breast feeding

<table>
<thead>
<tr>
<th><strong>Buprenorphine</strong></th>
<th><strong>Methadone</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal plasma : breast milk ratio = 1.0</td>
<td>Maternal methadone dose 25 to 180 mg/day leads to breast milk concentration 27 to 260 ng/mL (corresponding to a relative infant dose = 0.05 mg)</td>
</tr>
<tr>
<td>Poor oral bioavailability, so the relative infant dose is 10-20% the mother’s buprenorphine dose</td>
<td>Two infant deaths have been attributed (both infants were genetically pre-disposed)</td>
</tr>
<tr>
<td>Breast milk and plasma concentrations of buprenorphine or metabolites are generally undetectable</td>
<td></td>
</tr>
</tbody>
</table>

In both cases, infant plasma levels are undetectable to low

**Benefit vs. risk**
HIV seroconversion was significant lower among intravenous drug users (IVDU) receiving methadone maintenance versus no treatment over 18-months of observation (Rate: 3.5% versus 22%)
Other special populations

- Adolescents (parental consent inpatient/outpatient)
- Other mental health comorbidities
- Polysubstance use disorders
- Chronic pain (buprenorphine partial agonist, methadone outpatient for pain)
- Persons in correctional facilities
Flow

Background
- Substance use disorder
- Chronic disease model
- MAT-first approach

Buprenorphine
- Efficacy
- Safety
- Office-based prescribing considerations & models

Methadone
- Efficacy
- Safety

Relative safety and efficacy
- Comparative safety/efficacy
- Special populations
- MAT versus non-OAT interventions

Conclusions
- Regulatory considerations
- MAT supply / demand
- Other considerations for using MAT

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PollEverywhere
1) Text **SCOTTCOON065** to **22333** once to join, then **A,B,C,D**
2) Respond at **www.pollev.com/scottcoon065**
Conclusions

Treatment shortage and general MAT considerations
Exceeding capacity

A CAPACITY DEFICIT

 OTP = outpatient treatment program

<table>
<thead>
<tr>
<th>Year</th>
<th>Remaining persons with OUD</th>
<th>Maximum potential buprenorphine patients</th>
<th>Patients receiving methadone in OTPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>14%</td>
<td>55%</td>
<td>14%</td>
</tr>
<tr>
<td>2009</td>
<td>14%</td>
<td>52%</td>
<td>14%</td>
</tr>
<tr>
<td>2010</td>
<td>15%</td>
<td>44%</td>
<td>15%</td>
</tr>
<tr>
<td>2011</td>
<td>15%</td>
<td>39%</td>
<td>15%</td>
</tr>
<tr>
<td>2012</td>
<td>13%</td>
<td>39%</td>
<td>13%</td>
</tr>
</tbody>
</table>
“Health systems were completely unprepared and treatment is still dominated by abstinence-focused programs, where no regulatory standards have to be met.”

“Furthermore, among other factors, prejudice against the most effective treatments for opioid addiction—opiod substitution therapy (OST)—has translated into lack of treatment for those in need.”
MAT vs. Behavioral Health\textsuperscript{18, 19}

Outcome: total expenditure

- Methadone cost: $0.60 to $1.20 per effective dose ($0.005-$0.01/mg)
- Buprenorphine cost: $0.8 to $8 per effective dose ($0.10-$1/mg)
Principles of long-term MAT

- Medication prescription should not be stopped unless it is worsening the patient’s condition
- Longer treatment results in longer retention and survival
- Psychosocial supports such as individual or group counseling may be encouraged, but should not be required
  - Peer recovery coaches/peer support services appear to be beneficial, but strong evidence supports MAT efficacy with/without psychosocial support
- Urine drug screening should be routinely conducted, but results should not affect patient access to MAT (unless the patient will be harmed)
Treatment selection

Considerations:
- Potential side effects, contraindications
- Treatment availability and requirements
- Affordability
- Patient preference
- Special circumstances / populations

Patient characteristics are not reliable in predicting response to respond to one treatment versus another

Effective recovery needs to address associated medical, psychological, social, vocational, and legal problems
References


The safety and efficacy of long-term buprenorphine and methadone for opioid use disorder

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