Best Practices for Pharmacological Treatment of Opioid Use Disorders

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Overdose

• MMWR published in 2016 (Rudd et al.)
  – Since 2000, there has been a 200% increase in deaths involving opioids
  – In 2014, there were approximately 1.5x more drug overdose deaths than deaths from motor vehicle crashes

• In Allegheny County, heroin-related deaths increased 46% from 2014 to 2015
Overdose Deaths - 2000

Age-adjusted Death Rates for Drug Poisoning by State, 2000

Overdose Deaths - 2014

Overdose Deaths in Appalachia
2003-2014

Overdose Deaths Since 2001

Opioid use disorder over the years

• Opioid Use Disorder (OUD)
  – NESARC data for US adults comparison of 2001-2002 to 2012-2013
    • prescription opioid use increased by 161%
    • prescription opioid use disorder has increased by 125%
  – In 1960s, about 80% started using heroin
  – Now, 75-80% who use heroin started with opioid pills
    • Mars SG et al. (2014). "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting.
The changing face of heroin use in the last 50 years

-- Cicero et al. 2014
Treatment
Components of Comprehensive Drug Abuse Treatment

The best treatment programs provide a combination of therapies and other services to meet the needs of the individual patient.
FDA Approved Medications for Opioid Use Disorder

- **Full agonist**
  - Methadone

- **Partial agonist**
  - Buprenorphine/naloxone
  - Buprenorphine

- **Antagonist**
  - Naltrexone
  - Naltrexone-XR
Medication-Assisted Treatment (MAT) for OUD

- Evidence-based treatments to:
  - Reduce transmission of hepatitis C
  - Reduce transmission of HIV
  - Decrease illicit opioid use
  - Decrease criminal behavior
  - Reduce sexual risk behaviors (e.g., trading sex for money/drugs)
  - Improve physical and mental health
  - Improve social functioning
  - Retain people in treatment
  - Decrease overdose and death

-- References 7-21
Medication Assisted Treatment (MAT)

• One of many tools in the “recovery toolbox”
• Reduce cravings which can help stabilize and strengthen coping capacity
• Increase periods of abstinence and instill a sense of self-efficacy to help sustain recovery
• Allow patients to focus on behavioral therapies
• Improve clinical outcomes for patients and reduce impact on families/loved ones
Methadone
Methadone

- Synthetic, slow-acting, full mu-opioid agonist
- Used for treatment of addiction since 1960s
- Only available through licensed Opioid Treatment Programs (OTP) – cannot prescribe tabs to patient
- Dispensed daily initially, with ability to progress to receiving “take-home doses” – half-life 24-36 hrs
Methadone – Aims of Treatment

- Alleviate withdrawal symptoms
- Block euphoric effects of self-administered opioids
- Eliminate cravings for opioids
Methadone Treatment Criteria

• At least 1 year history of opioid use disorder (mod-severe)
  – Exceptions
    • Pregnant women
    • Released from correctional facility within last 6 months
    • Previously treated patients up to 2 years after discharge

• Person under 18
  – OK in some states if detoxed twice or had psychosocial treatment within 12 months; parents must consent in writing
  – In PA – more restrictive regulations for minors – only if pregnant
Methadone Induction

- Day 1: Starting dose 10-30 mg
- 3-7 days to reach steady state
  - Dose changes no more than 5 mg every 5 days
- Greatest risk of overdose death during induction
  - 42% methadone clinic deaths occur during first 2 weeks
  - Risk increases with
    - Overestimating a patient’s tolerance
    - Concurrent substance use (sedatives, alcohol, other opioids)
- Maintenance dose is the one that provides stability (typically 80-120 mg)
Methadone Simulated 24 Hr. Dose/Response (at steady-state in tolerant patient)

Subjective w/d

Objective w/d

“Comfort Zone”

“High”

“Dopesick”

Payte (1998) Opioid Agonist Treatment of Addiction
Methadone

- **Take-home criteria:**
  - Absence of recent drug & alcohol abuse
  - Regular attendance at clinic
  - Absence of behavioral problems at clinic
  - Absence of recent criminal activity

- **Stable home environment & relationships**
  - Acceptable time in maintenance tx
  - Assurance of safe storage
  - Rehabilitative benefit of take-homes outweighs risk of diversion
Methadone Metabolism

- Metabolized by the liver CYP3A4, CYP2C19, CYP2D6, CYP2C9
- Many potential drug-drug interactions
  - Increase or decrease serum methadone
  - QTc prolongation: avoid quetiapine and ziprasidone
- “Boosting” – clonazepam (3A4) or diazepam (2C19, 3A4) taken 1 hour after receiving methadone in order to get high from methadone (Stitzer et al., 1981)
Methadone Potential Adverse Effects

- Low energy
- Back pain
- Swelling
- Chills
- Hot flashes
- Malaise
- **Weight gain**
- Constipation
- Dry Mouth
- Blurred vision

- QT prolongation
- Abnormal dreams
- Anxiety
- Decreased libido
- Depression
- Euphoria
- Headache
- Insomnia
- Somnolence
- Sexual dysfunction

- Cough
- Rhinitis
- Yawning
- Postural hypotension
- Bradycardia
- Hyperprolactinemia
- Amenorrhea
- Sweating
- Rash
- Urinary retention
**Methadone**

- **Urine drug testing**
  - Federal regulations: at least 8x/year
  - Must screen for presence of methadone metabolite
  - Methadone is synthetic so must test for it specifically (in addition to “opiates”)
  - Must also specifically screen for oxycodone (synthetic)
  - Test for other any other drugs of concern
Methadone in Hospital

- When patient is admitted to hospital on methadone always
  - Get a release signed and call their OTP to verify
    - 1. Methadone dose
    - 2. Date of last dose (if patient hasn’t dosed in >3 days, dose is typically dropped to 30 mg or less)
  - This ensures you will not dose a patient with methadone who is not enrolled in a clinic
  - This will decrease the chance that you will overdose the patient on methadone

- On discharge patient is not discharged with methadone tablets under any circumstance
Sedatives and Other Opiates

- Patients on methadone are not to be prescribed benzodiazepines, benzodiazepine receptor agonists or barbiturates.
- If a patient is on methadone and has pain, he/she may be prescribed a short course of opioids when care is coordinated with the clinic.
Buprenorphine
Buprenorphine

• In 2000, DATA was passed which allowed physicians to treat patients with opioid dependence with schedule III-V drugs which were specifically approved by the FDA for opioid dependence

• In 2002, FDA approved buprenorphine and buprenorphine/naloxone for treatment of opioid dependence
Buprenorphine/Naloxone

• Buprenorphine – partial mu-opioid agonist which partially binds to the opioid receptor
  – Has very high affinity for mu receptor
  – Has slow dissociation from mu receptor

• Because it is a partial mu agonist it has a ceiling effect, which means larger doses do not result in larger effects, so safer in overdose (with some exceptions)

• Naloxone – opioid antagonist which is not active if the medication is taken as directed
Buprenorphine vs. Methadone

![Graph comparing opioid effects of buprenorphine and methadone](image-url)
Buprenorphine Formulations

- Product must be labeled to opioid use disorder (withdrawal or maintenance)
  - Buprenex (IV, IM – pain med)
  - Butrans (transdermal - pain med)
  - Belbuca (buccal strip – pain med)
- Buprenorphine ("Subutex" tabs, Probuphine subdermal)
- Buprenorphine/naloxone (Suboxone Film, bup/nx tabs, Zubsolv, Bunavail)
  - Naloxone 2-10% bioavailable
ZUBSOLV
PROBUPHINE

Implants placed under the skin of the upper arm
Buprenorphine Induction

• Must be in visible opioid withdrawal to initiate (or risk precipitated withdrawal)

• Patients converting from methadone to buprenorphine need
  – Methadone dose of 30 mg or lower
  – No methadone for 72 hours prior to starting buprenorphine

• Induction is typically 4-8 mg of buprenorphine

• Induction is usually accomplished in a matter of a few days
Buprenorphine Treatment

- Patients come to office weekly to start
- Get 1-week supply of medication
- Give urine specimen each visit
- Need to do some form of psychosocial treatment (typically an insurance requirement)
- When stable, advance treatment as physician feels comfortable, that is, giving 2-week supply of medication
- If there is a lapse, then resume weekly visits
Buprenorphine Maintenance

• Maintenance doses on average are 12-20 mg
• Patients are being successfully maintained at lower doses
• Medicaid typically pays for no more than 16 mg daily
• Take daily but could take every other day ($T_{1/2}=36$ hrs)
• Concerns for risk of diversion at higher doses
• PET study by Greenwald et al. (2003) showed
  – 78.9-91.5% of mu receptors were occupied at 16 mg
  – 84.1-98.4% of mu receptors were occupied at 32 mg
Effects of Buprenorphine Maintenance Dose on Opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-Dependent Volunteers

Greenwald et al., 2003
Buprenorphine Potential Adverse Effects

• Diaphoresis
• Constipation
• Headache
• Insomnia
• Nausea, vomiting
• Hypotension
• Sexual dysfunction
• Seizures
• Hepatitis, hepatoxicity
Controls – 6 day bup taper, daily dosing of placebo + relapse prevention
Buprenorphine – 16 mg bup + relapse prevention
Methadone vs. Buprenorphine

• Methadone
  – Needs high level of monitoring
  – Dependent on several substances
  – History of selling/diverting
  – No insurance or limited means
  – Previously failed buprenorphine or been on high dose methadone

• Buprenorphine
  – Can be trusted with one-week supply of medication
  – Not dependent on several substances
  – Low risk of diverting
  – Has insurance or means to pay for treatment
  – Has history of prolonged QT interval or taking meds that prolong QT interval
PRACTICAL ADVICE FOR PATIENTS YOU MAY SEE
Methadone in hospital

• When patient is admitted to hospital on methadone always
  – Get a release signed and call their OTP to verify
    1. Methadone dose
    2. Date of last dose (if patient hasn’t dosed in >3 days, dose is
typically dropped to 30 mg or less)
  – This ensures you will not dose a patient with methadone who is not
enrolled in a clinic
  – Check for methadone in urine toxicology
  – This will decrease the chance that you will overdose the patient on
methadone

• On discharge, patient is not discharged with a script for
methadone tablets under any circumstance
Buprenorphine in hospital

- When patient is admitted to hospital on buprenorphine always
  - Get a release signed and call their doctor/clinic or pharmacy to verify
    1. Buprenorphine/naloxone dose
    2. That they are still in treatment
    - Check the PDMP
    - Check for buprenorphine in urine tox (if available)
    - This ensures you will not be giving a patient buprenorphine who is not prescribed it or was discharged from treatment
- On discharge, they will return to their doctor for script, you probably aren’t going to write for it
Talk to patients about overdose

• Have you ever had an accidental overdose?
  – What were the circumstances, what happened, how did you survive?
• Have you ever witnessed an overdose?
  – What did you do?
• What do you do to protect yourself from overdose?
• What are some risk factors for overdose?
• Have you heard about naloxone/Narcan for reversal of overdose?
• Prescribe naloxone
  – www.prescribetoprevent.org
  – http://pcssmat.org/prescribing-naloxone-to-patients-for-overdose-reversal/
Sedative-hypnotic-anxiolytics

- Patients on methadone are generally not to be prescribed benzodiazepines, benzodiazepine receptor agonists or barbiturates
  - Some clinics have various policies which allow
- Patients on buprenorphine are not to be prescribed benzodiazepines
  - Insurance companies won’t cover buprenorphine
  - Some clinics and/or doctors have policies against benzodiazepines due to the high abuse of these medications in conjunction with buprenorphine
  - Similarly, benzodiazepine receptor agonists and barbiturates should not be prescribed with buprenorphine
Opioids

- If a patient is on methadone or buprenorphine and has pain, he/she may be prescribed a short course of opioids when care is coordinated with the clinic/physician.
- Tramadol is considered an opioid:
  - Schedule IV
  - Opioid-like activity is through metabolite desmethyltramadol
  - High doses activity is like propoxyphene; supratherapeutic doses it is like morphine
  - Has characteristic opioid withdrawal syndrome
Urine toxicology

• Must screen for opiates
• Must also specifically screen for oxycodone (synthetic)
• Test for other any other drugs prevalent in area or of concern
• Methadone
  – Federal regulations state at least 8x/year; state says monthly
  – Screen for presence of methadone and EDDP
• Buprenorphine
  – Typically every office visit, varies by practice
  – Screen for presence of buprenorphine and norbuprenorphine
Sleuthing
## Urine toxicology – examples, assorted patients

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<th>Norbup</th>
<th>Other</th>
<th>Cr</th>
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<td>83</td>
<td>585</td>
<td>Neg</td>
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<td>684</td>
<td>1840</td>
<td>Neg</td>
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<td>227</td>
<td>404</td>
<td>Neg</td>
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<td>&gt;2000</td>
<td>Neg</td>
<td>154.1</td>
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<td>Neg</td>
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<td>7/14/16</td>
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<td>26</td>
<td>THC, Codeine, Morphine, Hydromorphone</td>
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</table>
Urine toxicology – examples, one patient

- “Test not performed, an empty specimen container was received.”
- “Test not performed, specimen leaked in transit.”

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<thead>
<tr>
<th>Date</th>
<th>Bup</th>
<th>Norbup</th>
<th>Other</th>
<th>Cr</th>
<th>Observed</th>
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<td>Neg</td>
<td>64.4</td>
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<td>8/1/16</td>
<td>37</td>
<td>25</td>
<td>Neg</td>
<td>63.9</td>
<td></td>
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<tr>
<td>8/8/16</td>
<td>21</td>
<td>147</td>
<td>Pos morphine</td>
<td>59.9</td>
<td>x</td>
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<tr>
<td>8/15/16</td>
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<td>173</td>
<td>Neg</td>
<td>66.3</td>
<td>x</td>
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<td>&gt;2000</td>
<td>Neg</td>
<td>Neg</td>
<td>87.2</td>
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| 10/3/16  | Neg | Neg    | Morphine
Codeine
Hydromorphone
Hydroxyalprazolam
Cocaine |     | x      |
OPIOID USE IN PREGNANCY
During opioid intoxication mother may have periods of respiratory depression, aspiration, overdose, which may in turn result in:

- Hypoxemia
- Acidosis
- Intrauterine growth restriction (IUGR)
- Intrauterine fetal demise (IUFD)
What happens when an expectant mother is withdrawing?

- During opioid withdrawal the mother may experience tachycardia, hypertension, N/V which in turn may result in:
  - Miscarriage
  - Preterm labor
  - Premature rupture of membranes
  - IUGR
  - IUFD

- May be due to repeated fetal exposure to opioid withdrawal as well as withdrawal effects on placental function
Opioid Maintenance in Pregnancy

- Methadone or buprenorphine
- Improved prenatal care
- Decreased infection rates
- Fewer overdose fatalities
- Fewer premature births
- Fewer low birth-weight babies/less IUGR

- Will require dose increases as pregnancy progresses due to metabolic changes, volume shifts - may “split doses”
<table>
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<th>Methadone</th>
<th>Buprenorphine</th>
<th>p Value</th>
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<tbody>
<tr>
<td># Treated for NAS</td>
<td>41 (57%)</td>
<td>27 (47%)</td>
<td>0.26</td>
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<tr>
<td>Peak NAS Score</td>
<td>12.8</td>
<td>11</td>
<td>0.04</td>
</tr>
<tr>
<td>Total amount of morphine for NAS</td>
<td>10.4 mg</td>
<td>1.1 mg</td>
<td>&lt;0.0091*</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>17.5 days</td>
<td>10 days</td>
<td>&lt;0.0091*</td>
</tr>
<tr>
<td>Head circumference</td>
<td>33 cm</td>
<td>33.8 cm</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of NAS Treatment</td>
<td>9.9 days</td>
<td>4.1 days</td>
<td>&lt;.003125*</td>
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</table>
Naltrexone
Naltrexone

- Tablets approved for opioid dependence in 1984; IM gluteal injection (naltrexone-XR/Vivitrol) approved 2010 for opioid use disorder
- Long-acting opioid antagonist – no addictive potential
- High affinity for mu-opioid receptor: blocks opioids from binding, preventing euphoria
- Must first be opioid-free 7-10 days (to avoid precipitated withdrawal)
Naltrexone

• Cochrane review (Minozzi et al., 2006): oral naltrexone alone or with psychosocial therapy more effective in limiting heroin use than placebo alone or placebo with psychosocial therapy.

• “As a depot formulation, dosed monthly, Vivitrol obviates the daily need for patients to motivate themselves to stick to a treatment regimen - a formidable task, especially in the face of multiple triggers of craving and relapse.” -- Nora Volkow, MD, Director of NIDA.
Naltrexone

- Check liver function (AST, ALT, total bilirubin) prior to starting and periodically during treatment
- Most frequent adverse effects: nausea, vomiting, insomnia, headache
- Others: dizziness, fatigue, muscle cramps, rash, diaphoresis, diarrhea or constipation, delayed ejaculation, hepatitis, liver failure
- Warn patient: trying to overcome blockade may result in overdose
For example, in a cohort of 503 adults reporting current, nonmedical use of diverted prescription opioids in Appalachian Kentucky (and not presently in substance abuse treatment; study details are described elsewhere [8]), 15% of participants identified using gabapentin specifically “to get high” in the past 6 months. This represents a 165% increase in use compared with reports from 1 year prior and a 2,950% increase since 2008 within this cohort. Participants reported using gabapentin an average of 25 of the past 30 days and were more likely than nonusers to be abusing immediate-release oxycodone (64.8% compared with 46.5%; difference in percentages $d=18.3\%$; 95% Wald continuity corrected confidence interval [CI] = 3.1%–31.5%), buprenorphine (44.4% compared with 26.0%; $d=18.4\%$; 95% CI = 4.3%–33.1%), and benzodiazepines (42.6% compared with 21.6%; $d=21.0\%$; 95% CI = 7.1%–35.7%) in the prior 30 days “to get high.” There were no differences in past 30-day use of heroin, cocaine, and methamphetamine. Females (77.8%; $d=17.3\%$; 95% CI = 10.4%–24.6%) and participants reporting chronic medical conditions (48.2%; $d=16.3\%$; 95% CI = 1.8%–31.0%) were also significantly more likely to report gabapentin use. The two major sources of gabapentin were physicians (52%) and drug dealers (36%), and street costs were reported to be less than $1.00 per pill. Several volunteers reported use of dosages outside the range of standard medical care.
Abuse of Combinations of Gabapentint and Quetiapine

Roy R. Reeves, DO, PhD and Randy S. Burke, PhD

Case report. A 42-year-old man was admitted to a treatment program after his second arrest for driving under the influence of an unknown substance. He had used marijuana and cocaine but stopped after obtaining employment requiring drug testing. Afterward, he had negative drug screens but sometimes appeared “stoned.” He had prescriptions for quetiapine and gabapentin and misused these 2 medications together to replace the drugs he had taken. Taking up to 5 tablets of gabapentin 300 mg with 3 to 4 tablets of quetiapine 200 mg simultaneously produced a sensation of sedation and euphoria.

His girlfriend was prescribed and also misused gabapentin with quetiapine when she could not afford cocaine, taking 3 to 4 tablets of gabapentin 300 mg with 2 to 3 tablets of quetiapine 200 mg, sometimes with beer. She described similar, although weaker, effects. The couple was acquainted with 3 others who misused the same combination by taking 400–800 mg of quetiapine with 900–1,800 mg of gabapentin. Prescriptions were reportedly obtained by fabrication or exaggeration of symptoms. Tablets were sometimes sold or traded for illicit drugs.
Evidence exists for abuse of both gabapentin and quetiapine. Both have been removed from several prison formularies because of abuse by inmates. A woman substituted gabapentin 600–1,500 mg daily for cocaine.\textsuperscript{1} Florida inmates admitted snorting gabapentin powder for effects reminiscent of cocaine.\textsuperscript{2} Benzodiazepine-like withdrawal and dependence have been described.\textsuperscript{3,4} Gabapentin has been misused to potentiate the effect of methadone.\textsuperscript{5} About 20 cases of gabapentin addiction have been described in Europe.\textsuperscript{6} There are several reports of oral quetiapine abuse (800–1,200 mg at a time) for sedating and anxiolytic effects.\textsuperscript{7} Quetiapine powder is sometimes snorted intranasally; intravenous abuse has also occurred.\textsuperscript{9} Drug-seeking behavior, compulsive use, diversion, dependence, and withdrawal have been described.\textsuperscript{10,11} Quetiapine is sometimes called “quell” or “baby heroin” by inmates.
Resources

- PCSS-O (pcss-o.org) and PCSS-MAT (pcssmat.org)
- www.ASAMNationalGuideline.com
- SAMHSA’s Health Information Network
  www.samhsa.gov/shin
- SAMHSA Treatment Locator 800-662-HELP (also as an app)
References

4. Muhuri PK, Gfroerer JC, Davies MC; Substance Abuse and Mental Health Services Administration. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Review.
References