Objectives

- Describe the epidemiology of the current opioid epidemic
- Describe various evidence-based pharmacotherapeutic options to address the opioid epidemic
- Explain the differences between methadone, buprenorphine, and naltrexone mechanisms of action
- Identify the nurse’s role in assessment in induction and maintenance using opioid replacement therapies

Background

- Nurses working across settings have essential roles:
  - Assessment/screening
  - Inductions and maintenance
    - Inpatient and outpatient
  - Education and counseling
“…Not a Moral Failing”
-Surgeon General, 2016

Total US Drug Deaths 2016

Drug Deaths Involved in Overdose 2000-2016
Opioid Prescription Data

Evidence and Stats for Buprenorphine and Methadone

Rate of Past Year Opioid Abuse or Dependence* and Rate of Medication-Assisted Treatment Capacity with Methadone or Buprenorphine
### Why Opioid Replacement Therapy?

- **Route of administration**
  - Faster route has a greater abuse potential
  - Injecting IV > Injecting SQ > Oral
- **Drug Half life**
  - Briefer half-life has a greater reinforcing potential
  - Heroin > Methadone
- **Lipophilicity (faster across blood brain barrier)**
  - Higher lipophilicity has a greater reinforcing potential
  - Heroin > Morphine > Methadone

### Choosing an Opioid Replacement Pharmacotherapeutic Agent

### Opiate Receptors and Effect of Agonist

<table>
<thead>
<tr>
<th>Opiate Receptors</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu1 (μ1)</td>
<td>Analgesia, euphoria</td>
</tr>
<tr>
<td>Mu2 (μ2)</td>
<td>Constipation, respiratory depression</td>
</tr>
<tr>
<td>Kappa</td>
<td>Spinal analgesia, dysphoria</td>
</tr>
<tr>
<td>Delta</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

References: Grissinger, 2011; Ducharme, Fraser, & Gill, 2012; Ferrari, Coccia, Bertolini, & Sternieri, 2004.
### Opioid Replacement Therapy

- **Methadone**
- **Buprenorphine (Suboxone=Buprenorphine/Naloxone)**

### Full Versus Partial Opioid Agonist

- Work differently depending on:
  - Affinity, Intrinsic activity, Dissociation
- Methadone and buprenorphine
  - Ameliorate opioid withdrawal
  - Reduce opioid cravings
  - Treat pain (to varying degrees)
- Partial agonist vs. full agonist
  - Attenuated euphoria
  - Reduced side effects
  - "Ceiling effect" on respiratory depression
  - Potentially lower abuse/diversion potential
  - Less severe withdrawal

### Heroin versus Methadone versus Buprenorphine

<table>
<thead>
<tr>
<th>Route</th>
<th>Heroin</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruect</td>
<td>IV</td>
<td>PO</td>
<td>Sublingual; 5-20 mins to dissolve</td>
</tr>
<tr>
<td>Duration</td>
<td>3-6 hours</td>
<td>Half-life; Opioid-tolerant=24-36 hours</td>
<td>24-60 hours; Can bind on receptors for 24 hours</td>
</tr>
<tr>
<td>Euphoria</td>
<td>First 1-2 hours</td>
<td>None with correct dosage</td>
<td>None with correct dosage</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>After 3-4 hours</td>
<td>Usually after 24-36 hours</td>
<td>Usually after 24-36 hours</td>
</tr>
</tbody>
</table>

References: Grissinger, 2011; Ducharme, Fraser, & Gill, 2012; Ferrari, Coccia, Bertolini, & Sternieri, 2004.
Side Effects and Drug Interactions

**Methadone**
- Prolonged QTC
- Hypogonadism, Osteopenia
- Sedation, CNS depression
- Benzodiazepines, Alcohol, Other Sedatives
- Hyperhidrosis
- Lengthy List of Medication Interactions
- HIV medications
- Population-specific care
  - Liver, renal, respiratory complications
  - Pregnancy
  - Elderly

**Buprenorphine**
- Drug-to-drug interactions rare/less frequent vs methadone
- Headache, nausea, anxiety, insomnia, pain, respiratory depression, urinary retention (rare), allergic reactions (rare), rash (rare)
- CNS depression
- Benzodiazepines, Alcohol, Other Sedatives
- Less common vs. methadone
- Liver toxicity
- Less common vs. methadone
- Case reports of delayed hypogonadism, usually in those infected with HIV

References: Grissinger, 2011; Ducharme, Fraser, & Gill, 2012; Ferrari, Coccia, Bertolini, & Sternieri, 2004.

Interference with Serum Levels

**Methadone**
- Drugs that MAY reduce serum methadone level:
  - Ascorbic acid, barbiturates, carbamazepine, efavirenz, phenytoin, rifampin, efavirenz, nevirapine, other antiretrovirals with CYP3A4 activity
- Drugs that MAY increase serum methadone level:
  - Amitriptyline, atazanavir, atazanavir/ritonavir, cimetidine, delavirdine, diazepam, fluconazole, fluvoxamine, ketoconazole, voriconazole

**Buprenorphine**
- Drugs that MAY reduce serum buprenorphine level:
  - Ascorbic acid, barbiturates, carbamazepine, efavirenz, phenytoin, rifampin, efavirenz, nevirapine, other antiretrovirals with CYP3A4 activity
- Drugs that MAY increase serum buprenorphine level:
  - Amitriptyline, atazanavir, atazanavir/ritonavir, cimetidine, delavirdine, diazepam, fluconazole, fluvoxamine, ketoconazole, voriconazole


Baseline Nursing Assessment

**Interview Questions, Subjective**
- Patient's goal?
- Type: Drug and route
- Duration & quantity
- Side effects, effect on mood
- Withdrawal (dependence)
- Abnormal behavior, mood
- Per use (interviewed in detail?)
- Other references
- Barbiturates, withdrawal symptoms
- Psychiatric history
- Medical history & medications-RV meds, Hgb-C, sleep apnea or other respiratory, cardiac, falls, osteopenia, hypogonadism, pain etc.
- Other opioids or opioid antagonist
- Social Life stresses, job schedule, support

**Physical, Objective**
- COWS: Withdrawn
- Skin assessment: Track marks
- Ultrasound: Substances and synthetic
- Labs:
  - Hepatic, Renal, Coagulation
  - Hypogonadism or Hypothyroidism: Greater risk with methadone
  - Diabetes: Greater risk with methadone
  - Pregnancy: Greater risk with methadone
- History of prescriptions: Objective evidence of tolerance and/or aberrant behaviors
- Pregnancy, Elderly
Urine Toxicology

<table>
<thead>
<tr>
<th>Drug or Class</th>
<th>Expected Results</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid Naloxone</td>
<td>Ingestion, urine screen</td>
<td>Naloxone is an opioid antagonist.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Ingestion, urine screen</td>
<td>Benzodiazepines are sedative-hypnotic agents.</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Ingestion, urine screen</td>
<td>Barbiturates are hypnotic agents.</td>
</tr>
<tr>
<td>Codeine</td>
<td>Ingestion, urine screen</td>
<td>Codeine is a centrally-acting analgesic.</td>
</tr>
<tr>
<td>Tramadol (Uقوة)</td>
<td>Ingestion, urine screen</td>
<td>Tramadol is a centrally-acting analgesic.</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Ingestion, urine screen</td>
<td>Diazepam is a benzodiazepine tranquilizer.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ingestion, urine screen</td>
<td>Lorazepam is a benzodiazepine tranquilizer.</td>
</tr>
<tr>
<td>OxyContin</td>
<td>Ingestion, urine screen</td>
<td>OxyContin is a synthetic opioid analgesic.</td>
</tr>
<tr>
<td>Methadone</td>
<td>Ingestion, urine screen</td>
<td>Methadone is a synthetic opioid analgesic.</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Ingestion, urine screen</td>
<td>Fentanyl is a synthetic opioid analgesic.</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Ingestion, urine screen</td>
<td>Hydromorphone is a synthetic opioid analgesic.</td>
</tr>
</tbody>
</table>

More on Urine Drug Testing

**COWS-Clinical Opiate Withdrawal Scale**

- Any setting
- Initiation of medication
  - Implications vary depending on last use and type of ORT
- Detoxification from any opioid
- Taper from methadone or buprenorphine

**Methadone**

**Induction-Tolerance Level**

<table>
<thead>
<tr>
<th>Opioid-tolerant</th>
<th>Unknown tolerance or high risk for overdose</th>
</tr>
</thead>
</table>
| • Assessment findings  
  - UDS + opiates, withdrawal symptoms present, track marks  
  - Day 1: start 30 mg PO x 1 and may give additional 10 mg 1 hr later if no oversedation  
  - Day 2: 50 mg daily and increase to 90 mg daily in 10 mg increments every 3 days as tolerated  
  • Hold for sedation and side effects | • Methadone 10 mg daily x 3 days  
• Increase to 60 mg by 5 mg every 3-5 days as tolerated |
### Dosing

<table>
<thead>
<tr>
<th>Adjustments—During Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adjust dose 5-10 mg at a time</td>
<td>• Typically 60-120 mg, but research varies</td>
</tr>
<tr>
<td>• 5 days for full effect of dose change</td>
<td>• 35 inter-individual difference in methadone pharmacokinetics</td>
</tr>
<tr>
<td>• Has long half-life</td>
<td>• Holding dose</td>
</tr>
<tr>
<td>• May make adjustments faster if going down on dose or titrating toward previous dose</td>
<td>• Rapid Metabolizer test</td>
</tr>
<tr>
<td>• Helpful to remind patients “you don’t need a higher dose you need more time for current dose to build up”</td>
<td>• Consider checking peak/trough to see if rapid metabolizer of methadone</td>
</tr>
<tr>
<td>• Cumulative Effect</td>
<td>• Consider split dosing</td>
</tr>
</tbody>
</table>

### Methadone Maintenance

| • Regular UDS, Labs, Other substance use | • Always do EKG when considering increase in dosing |
| • Narcan Kit Dispensed | • EKG>500, check for prolonged QTc |
| • Stopping methadone | | |
| • Discussion: Prior overdoses, risks, benefits, switch to another ORT | | |
| • Tapering may take more than one year | | |
| • Lipophilicity | | |
| • Last 30 mg associated with worst cravings and withdrawal | | |
| • High risk for relapse | | |

### Buprenorphine
Precipitating Withdrawal

- Suboxone (buprenorphine with naloxone)
  - Developed to decrease abuse potential
  - Formulated with naloxone
  - Naloxone blocks opiate effect if injected
  - Naloxone has minimal oral bio-availability
- Precipitated Withdrawal
  - Due to buprenorphine activity if taken orally
  - Primarily due to naloxone activity if injected
- Treatment:
  - May give a benzodiazepine
  - May give another dose of buprenorphine

Induction-With Physical Dependence

<table>
<thead>
<tr>
<th>Long-Acting</th>
<th>Short-Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDS</td>
<td>UDS</td>
</tr>
<tr>
<td>Abstain about 24-48+ hours</td>
<td>Abstain 8-12+ hours</td>
</tr>
<tr>
<td>Assess for withdrawal: COWS</td>
<td>Assess for withdrawal: COWS</td>
</tr>
<tr>
<td>* Support and wait</td>
<td>* Support and wait</td>
</tr>
<tr>
<td>Methadone</td>
<td>Methadone</td>
</tr>
<tr>
<td>Verify dose with clinic (also illicit?)</td>
<td>Verify dose with clinic (also illicit?)</td>
</tr>
<tr>
<td>Lipophilicity a factor</td>
<td>Lipophilicity a factor</td>
</tr>
<tr>
<td>Decrease the daily dose until ≤30 mg of methadone</td>
<td>Decrease the daily dose until ≤30 mg of methadone</td>
</tr>
<tr>
<td><strong>Minimal score of 5 on COWS</strong></td>
<td><strong>Minimal score of 5 on COWS</strong></td>
</tr>
</tbody>
</table>

Long-Acting:
- Methadone
- Lipophilicity a factor
- Decrease the daily dose until ≤30 mg of methadone
- **Minimal score of 5 on COWS**

Short-Acting:
- Methadone
- Lipophilicity a factor
- Decrease the daily dose until ≤30 mg of methadone
- **Minimal score of 5 on COWS**

Induction

<table>
<thead>
<tr>
<th>Physical Dependence</th>
<th>Without or Unknown Physical Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWS scale shows opiate withdrawal</td>
<td>COWS scale shows non-opiate withdrawal</td>
</tr>
<tr>
<td>≥5-12</td>
<td>≥1-2 mg first day</td>
</tr>
<tr>
<td>Start with 2-4 mg</td>
<td>Start with 1-2 mg first day</td>
</tr>
<tr>
<td>Reassess approx. 1 hour after administration</td>
<td>Reassess approx. 1 hour after administration</td>
</tr>
<tr>
<td>Continue to titrate until symptoms resolve</td>
<td>Continue to titrate until symptoms resolve</td>
</tr>
<tr>
<td>Reassess patient 40 minutes to 1 hour after first dose</td>
<td>Reassess patient 40 minutes to 1 hour after first dose</td>
</tr>
<tr>
<td>Dose with 2mg sl</td>
<td>Dose with 2mg sl</td>
</tr>
<tr>
<td>Reassess over the next few hours</td>
<td>Reassess over the next few hours</td>
</tr>
<tr>
<td>First day usually about 8mg</td>
<td>First day usually about 8mg</td>
</tr>
</tbody>
</table>

Symptomatic Medication

- Diclofenac: Muscle aches
- Tylenol: Pain, headache
- Maalox: GI distress
- Immodium: Diarrhea
- Compazine: Nausea, vomiting
- Bentyl: Abdominal cramps
- Benadryl, Trazodone, Tylenol PM: Sleep
- Clonidine: Severe anxiety
### Typical Target Dose

- **First day:** Up to 8mg
- **Second day:** Up to 16 mg
- **Final dose usually 8-16 mg**
  - Receptor 95% occupied at 16mg-24 mg
- **Very few patients need up to 32mg (max)**

### Buprenorphine Maintenance

#### Clinical Staff
- Not all dosages and formulations are equal
- Monitoring of labs
- Not necessary to stop buprenorphine when having surgery
- Pregnancy

#### Patient Education
- Patients know how to adjust their dose!
- **Idea is to hold craving**
- Proper storage and handling
  - Date of expiry, labeled, Sharing pills is diversion-conscious/unsafe
- Sales
- Risk of Overdose
  - Other sedatives
  - Suboxone is dosed
- Precipitated Withdrawal
  - If on Methadone and Use Suboxone
- Harm Reduction
  - Clean needles, risk of HCV, HIV

### Special Populations

- Pregnant females
  - Consider Subutex, split dosing methadone
- Pain
  - Understanding of opioid-induced hyperalgesia
  - Split dosing of buprenorphine
- Hepatic dysfunction
  - Monitor for elevated liver enzymes
- Recent Detox (recently out of prison) or lack of dependence
  - High risk for overdose if return to full agonist use
Pregnancy

- Methadone "preferred" treatment
  - May breastfeed if not HIV +
  - May breastfeed if Hep C+ but must speak to clinician first
  - Neonatal Abstinence Syndrome (NAS)
- Buprenorphine category C-Risk cannot be ruled-out
  - NAS
    - Within 12 to 48 hours, peaks 72 to 96, lasts 120-168 hours (some seen 6 to 10 weeks)
    - Some research has found to be less intense than methadone

Reference: Substance Abuse Services and Mental Health Administration, 2014.

Naltrexone and Vivitrol

- Opioid antagonist, Completely blocks opioids for 4-6 week
  - PO and IM
- Has efficacy for treating alcohol use disorder
  - FDA Approved for OUD
- Pregnancy category C
- Special dosing in renal impairment

Key Concepts

- No opioid-containing medications, including over the counter preparations
- Major adverse effects: Eosinophilic pneumonia, depression, suicidality
- Labs: Liver transaminase levels, Bilirubin within normal limits, CrCl (estimated or measured) 50 mL/min or greater, Ensure patient has adequate muscle mass for injection, Urine beta-HCG for females
- Similar induction to buprenorphine
  - Similar to administering Narcan, except effects are less immediate and longer-acting, Oral-Peak plasma occurs within 1 hour; Injectable-Peak w/in 2 hours and again at 2-3 days
  - Precipitated withdrawal
    - Consider naloxone challenge, naltrexone tablet fast
    - Symptomatic Medication, monitor vital signs, hydration
- Maintenance:
  - Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter

General Education

- Dose adjustments
- Tolerance level
- Overdoses, other illicits
- Other Harm Reduction/Risks of Use
  - Clean needles
  - Safe sex
- Desire to discontinue or switch MAT
- Regular physicals
- Psychiatric treatment

Naloxone Distribution Laws-2016

Reference:
References


