OBJECTIVES

Participants will learn about:

1. The pharmacokinetics and pharmacodynamics of methadone and buprenorphine.

2. Therapeutic implications.

3. Why we dose the way we do.

METHADONE'S BACKGROUND

- 6-di-methylamine-4,4-diphenylheptanone
- Synthetic long-acting opioid
- Synthesized in 1938 by Bockmuhl and Ehrhart (they called it Hoechst 10820).
- Introduced in USA in 1974 as an analgesic under the trade name: Dolophine (from the Latin “dolor” (pain) and “fin” (end)).
- First used for the treatment of opioid addiction in Vancouver, Canada, by Dr. Robert Holiday in 1963.
- New York City: Prof. Vincent Dole and his wife, Marie Nyswander got all the glory in 1965, when they were awarded the Lasker Award for Medicine.

PHARMACOKINETICS (WHAT WE DO WITH METHADONE)

- Basic lipophilic drug
- With oral administration, completely absorbed within 30 min
- Peak plasma levels: 2.5 – 3 h
- High oral bioavailability: 41 – 99%
- Long half-life: ± 24 h with wide individual variability (7-65h, 8-90h)
- Large volume of distribution (brain, intestine, kidney, liver, muscle and lung)
- Protein binding: 85 – 90%
PHARMACOKINETICS

- Metabolized in the liver by Cytochrome P450 enzymes:
  - CYP 3A4, CYP 2B6, CYP 2D6
- Inactive metabolites:
  - 2 - ethyl - 1.5 dimethyl - 3.3 - diphenyl pyrrolidine (EDDP)
  - 2 - ethyl - 5 - methyl - 3.3 - diphenyl pyrrolidine (EMDP)

Side effects of Methadone:

1. Common to all opioids:
   - Sedation, vomiting, confusion, dizziness
   - Constipation (70%)

2. Largest risk: Respiratory depression
   - Clinicians and patients underestimate methadone
   - Most often in opioid naïve patients
   - Development of tolerance unpredictable
   - < 2 months of methadone: patients still show a decreased ventilatory response to carbon dioxide
   - > 5 months: tolerance to carbon dioxide, but incomplete tolerance to hypoxia

3. Cardiac:
   - Methadone is associated with Torsades de Pointes resulting from a prolonged QTc interval. Methadone blocks the hERG K channels (S-enantiomer)
   - Occurrence of TdP: 0.78% of patients with prolonged QTc
   - Median dose where these findings were present: 345 mg / day
   - 29% of TdP occur in the typical recommended range for MMT
   - 75% of cases: female gender, interacting medication, hypokalemia, hypomagnesemia, structural heart disease and other risk factors

QTc values by Age and Sex (ms)

<table>
<thead>
<tr>
<th>Age</th>
<th>1-15 years (ms)</th>
<th>Adult males (ms)</th>
<th>Adult females (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 440</td>
<td>&lt; 430</td>
<td>&lt; 430</td>
</tr>
<tr>
<td>Borderline</td>
<td>440 - 460</td>
<td>430 - 450</td>
<td>450 - 470</td>
</tr>
<tr>
<td>Prolonged</td>
<td>&gt; 460</td>
<td>&gt; 450</td>
<td>&gt; 470</td>
</tr>
</tbody>
</table>

Drug interactions due to cytochrome P450

1. Inducers could potentially decrease the effectiveness of methadone - could feel like withdrawal
2. Inhibitors could potentially increase the effect of methadone - dose will feel higher and the risk for toxicity is higher

Medications that may need hormone supplementation:
- Estrogen/progestin
- Testosterone

Avoid combination with drugs that mean the risk of QTc internal prolongation. Treat electrolyte disturbances and use diuretics that can cause with hypokalemia with care.
**PHARMACOKINETICS**

- Excreted in the feces and urine.
- In kidney failure – completely eliminated via feces.
- Found in breastmilk, but in concentrations that are harmless to the infant.
- Crosses the placenta and may induce Neonatal Abstinence Syndrome.
- Not associated with adverse obstetric outcomes: Normal birth weight and Apgar scores. No congenital birth defects.
- Versatile administration: Rectal, IV, IM, sub-cut, nasal, sublingual, spinal and epidural.

**WITI**

- Safe in renal failure.
- Encourage breastfeeding.
- Encourage pregnant women to switch from IV street drugs to maintenance therapy.

**BUPRENORPHINE'S BACKGROUND**

- Semi-synthetic long-acting opioid.
- Synthesized in 1969 by researchers Reckitt & Colman.
- Originally marketed in UK in 1978 as an analgesic.
- Sublingual form launched in UK in 1982.
- Approved in USA by Food and Drug Administration for the treatment of opioid addiction in 2002.
- Marketed as buprenorphine alone: Subutex, Butrans, Buprenex.
- In combination with naloxone: Suboxone.

**PHARMACODYNAMICS – WHAT METHADONE DOES TO US**

- Full MU opioid agonist. Binds to mu, delta & kappa.
  - Analgesia, miosis, euphoria.
  - Decreased GI motility.
  - Respiratory depression.
  - Dependence.
  - Tolerance.
- S-enantiomer (dextro-methadone). No opioid activity.
  - Moderate NMDA (N-Methyl-D-aspartate) antagonist (against glutamate).
  - Promotes serotonin + norepinephrine uptake inhibition in CNS.
  - Binds to the h ERG K+ receptor.

**WITI**

- Could be the reason for decreased development of tolerance to opioids, decrease in craving for opioids and the reason for efficacy in treatment of neuropathic pain.
- Responsible for serious arrhythmias at higher doses (>200mg).

**PHARMACOKINETICS: WHAT WE DO WITH BUPRENORPHINE**

- Fairly water soluble. Degrades in light.
- Poor oral bioavailability: <10% due to first pass metabolism.
- Fair sublingual bioavailability: 30-40%.
- Rapid onset of action: 30-60min.
- Protein binding: 96%.
- Long half-life: 37h (20 – 70).
- Peak effects: 1 – 4h.
- Durational action is dose dependent:
  - 2 – 4mg: 4 – 12h.
  - 4 – 24mg: 24h.
  - > 24mg: 2 – 3 days.
- Metabolism: Hepatic (glucoronic conjugation) and microsomal enzyme system: CYP 3A4, CYP 2CB.
- Excretion: Biliary (70%) and renal.

**WITI**

- If you swallow this drug, it loses 75% of its effect.
- Steady state in 3 – 7 days. Dose reductions should be made accordingly.
- Some patients can skip doses without feeling withdrawal.
- Metabolism: Hepatic (glucoronic conjugation) and microsomal enzyme system: CYP 3A4, CYP 2CB.
**PHARMACODYNAMICS: WHAT BUPRENORPHINE DOES TO US**

- **Semi-synthetic opioid**
  - Partial opioid agonist at the mu receptor, very high affinity for the receptor, low intrinsic activity
  - Antagonist at the kappa receptor
  - Partial agonist at the nociceptin/orphanin receptor
  - Partial agonist effect at the mu receptor
  - Blocker of the effect of other opioids prescribed for pain
  - Decreased risk of overdose. Ceiling effect – higher dose does not necessarily better effect.

**Side effects:**
- Headaches: In first week, 20-30% of patients
- Constipation
- Nausea
- Sedation, drowsiness, lethargy
- Sleep disturbances
- Sweating
- Sexual dysfunction – decreased libido, decreased performance

**Unique SE:** Precipitated withdrawal
- Occurs when buprenorphine “kids off” another opioid from the mu receptors
- 30-90 minutes after 1st dose
- Varies in severity: sweating, abdominal cramps diarrhea, nausea, craving, anxiety

**Drug Interactions:**
- Less than methadone
- Additive sedative effect with combinations of benzodiazepines, hypnotics, imidazopyridines – respiratory depression, heavy sedation, coma, death
- Higher affinity for the receptors than morphine
- Very high doses of naloxone required to cause withdrawal
- Blocks the effect of other opioids prescribed for pain

**Buprenorphine in Pregnancy:**
- Not associated with adverse neonatal or obstetric outcomes
- Birth weight and Apgar scores within normal range
- Not associated with congenital birth defects
- Nursing infant’s exposure to buprenorphine in breast milk is low and there is no clinical or pharmacokinetic reason to discourage breastfeeding.

**Notes:**
- For patients using other illicit opioids for maintenance, therapy with buprenorphine is a step up from methadone.
- If high doses of naloxone are needed to cause withdrawal, patients will drug-dose what they need over next drug of choice.

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### NALOXONE

- Pure opioid antagonist, high affinity for mu opioid receptors in the CNS, lower affinity for kappa and delta receptors.
- Oral bioavailability: 2% (90% absorption, but high first pass metabolism).
- IV: 100% bioavailability.
- Half life: 1 – 1.5 h.
- Onset of action: IV: 2 min, Duration of action: 30 – 60 min.
- Metabolized in the liver.
- Excretion: Urine and bile.
- WIT: Robust and immediate precipitated withdrawal with IV administration of crushed Suboxone tablets in patients using other opioids.
- Decreased street value.
- Decreased risk of diversion.

### COMPARISON

<table>
<thead>
<tr>
<th>METHADONE</th>
<th>BUPRENORPHINE</th>
</tr>
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<tbody>
<tr>
<td>Full mu agonist</td>
<td>Partial mu agonist</td>
</tr>
<tr>
<td>Classic opioid side-effects</td>
<td>Less sedating</td>
</tr>
<tr>
<td>Withdrawal severe</td>
<td>Decreased risk of overdose</td>
</tr>
<tr>
<td>Onset of action: 30 – 60 min</td>
<td>Withdrawal less severe</td>
</tr>
<tr>
<td>Peak effect: 1 – 4 h</td>
<td>Onset of action: 30 – 60 min</td>
</tr>
<tr>
<td>Titration lengthy process</td>
<td>Peak effect: 1 – 4 h</td>
</tr>
<tr>
<td>Oral</td>
<td>Onset of action</td>
</tr>
<tr>
<td>Affected by liver function</td>
<td>No adjustment needed in kidney failure</td>
</tr>
<tr>
<td>Safe in kidney failure</td>
<td>None</td>
</tr>
<tr>
<td>Stigma</td>
<td>Expensive</td>
</tr>
<tr>
<td>Cheap</td>
<td>Could stretch to alternate days in higher doses</td>
</tr>
<tr>
<td>Daily dosing</td>
<td>Lower retention in maintenance therapy</td>
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<tr>
<td>About 50% abstinence at one year</td>
<td>Weak active metabolite: nor-buprenorphine</td>
</tr>
<tr>
<td>No active metabolites</td>
<td></td>
</tr>
</tbody>
</table>

### QUESTIONS

- off the mark.com by Alex Parker