Learning Objectives

- Basic Clinical Pharmacology relevant to opioids and alcohol
- Pharmacology of co-administered alcohol and opioids
Alcohol consumption can be a contributing factor in opioid overdose due to additive or synergistic respiratory depression. (Kramer, 2003; Payte & Zweben, 1998)

Opiates and alcohol can interact in several ways
Two prerequisites for drug effects

1) The drug has to get to brain cells
   **Pharmacokinetics**

2) The drug has to affect brain physiology.
   **Pharmacodynamics**
Pharmacokinetics
- The processes by which drugs get to their site of action (movement of drugs through the body)
  - Includes absorption, distribution, elimination

Pharmacodynamics
- The processes by which drugs exert an effect at their site of action
  - Includes acute and chronic effects on brain receptors
Pharmacokinetics: Component Processes

- Liberation (most important for pills)*
- Absorption*
- Distribution
- Metabolism (primarily by the liver)
- Excretion (primarily by the kidneys)

* Bioavailability
Opiate Drug Concentration vs. Time

![Graph showing drug concentration over time for different substances.](image)
Two-compartment model

Dose, \( Q \) (oral)

Absorption

\( k_{\text{abs}} \)

Dose, \( Q \) (i.v.)

Central Compartment (1)

\( k_{\text{exc}} \)

Peripheral Compartment (2)

\( k_{\text{met}} \)

\( k_{12} \)

\( k_{21} \)

Excretion

Metabolism

Drug Concentration vs. Time

A

B

C
Blood Alcohol Concentration vs. Time
Zero-order kinetics
Factors Affecting Bioavailability

- Physical properties of the drug
  - (hydrophobicity, pKa, solubility)
- Formulation (excipients used, release methods)
- Relationship to food/meals
  - Interaction with foods – grapefruit juice (CYP3A4), acid/base
- Gastric emptying rate
- Circadian differences
- First-pass metabolism
- Gut (and brain) transporters (e.g. P-glycoprotein)
- Individual differences – Age, Gender, GI tract disease
# Half-lives of Commonly Prescribed Opiates

<table>
<thead>
<tr>
<th>Opiate Drug</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (morphine-6-glucuronide)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>3.7</td>
</tr>
<tr>
<td>Codeine</td>
<td>3 - 4</td>
</tr>
<tr>
<td>Meperidine (Normeperidine)</td>
<td>3 - 4 (14 - 21)</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>5</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>2.5 – 3.5</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Methadone</td>
<td>24</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>12 - 15</td>
</tr>
<tr>
<td>Propoxyphene (Norpropoxyphene)</td>
<td>30 - 40</td>
</tr>
</tbody>
</table>
Oral Modified-Release Opioid Products

Representation of (A) an extended-release bead formulation (B) a sustained-release matrix tablet prepared using a hydrophilic polymer.
## Alcohol affects bioavailability of Oral Modified-Release Opioid Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage Form</th>
<th>Strength</th>
<th>Dosing Frequency</th>
<th>Bioavailability (%)</th>
<th>Time to Steady-State (days)</th>
<th>Interaction with Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>immediate+ extended- release capsules</td>
<td>Immediate and extended release beads</td>
<td>24 h</td>
<td>&lt;40</td>
<td>2–3</td>
<td>Yes</td>
</tr>
<tr>
<td>Avinza</td>
<td>sustained-release capsules</td>
<td>Polymer coated pellets</td>
<td>12–24 h</td>
<td>20–40</td>
<td>~2</td>
<td>Yes</td>
</tr>
<tr>
<td>Kadian</td>
<td>sustained-release capsules</td>
<td>Matrix</td>
<td>8–12 h</td>
<td>~40</td>
<td>1–2</td>
<td>?</td>
</tr>
<tr>
<td>Oramorph</td>
<td>sustained-release tablets</td>
<td>Matrix</td>
<td>8–12 h</td>
<td>~40</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>MS Contin</td>
<td>controlled-release tablets</td>
<td>hydrophilic/ hydrophobic matrix</td>
<td>8–12 h</td>
<td>~40</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
<td>controlled-release tablets</td>
<td>immediate and extended hydrophobic matrix</td>
<td>12 h</td>
<td>60–87</td>
<td>1–1.5</td>
<td>?</td>
</tr>
<tr>
<td>OxyContin</td>
<td>extended-release tablets</td>
<td>matrix pellet formulation</td>
<td>24 h</td>
<td>~30</td>
<td>1–1.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>extended-release tablets</td>
<td>matrix pellet formulation</td>
<td>24 h</td>
<td>~30</td>
<td>1–1.5</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Morphine Metabolism

- Glucuronidation – renal elimination
  - Morphine-6-glucuronide (potent analgesic)
  - Morphine-3-glucuronide (excitatory side-effect)

- Demethylation
  - Normorphine (excitatory side effects)
    - CYP3A4 (grapefruit juice), CYP2C8 (quercetin)
Pharmacokinetics of alcohol

- Alcohol is converted by alcohol dehydrogenase (ADH) to acetaldehyde: $\text{CH}_3\text{CH}_2\text{OH} + \text{NAD} \rightarrow \text{CH}_3\text{CHO} + \text{NADH}$

- Acetaldehyde is converted by aldehyde dehydrogenase (ALDH) to acetic acid, then to CO2 and water in the Krebs cycle: $\text{CH}_3\text{CHO} + \text{NAD} \rightarrow \text{CH}_3\text{COOH} + \text{NADH}$

- The rate of metabolism is Zero order – i.e. it is not concentration dependent (about 7 g/hr) at BACs > 0.02 g/L

- Cytochrome P450 Ethanol Oxidation by CYP2E1, CYP3A4: CYP2E1 is inducible and greater in chronic heavy drinkers, accounting for an increased rate of metabolism at high BACs
Alcohol Morphine Metabolic Interactions

- **Glucuronidation**
  - Ethanol metabolism produces reduced NAD (NADH)
  - NADH reduces ability of liver to produce UDP-glucuronic acid, necessary for glucuronidation of morphine and other drugs

- **Demethylation**
  - Acute ethanol can inhibit CYP3A4, potentiating morphine
  - Chronic ethanol induces CYP3A4, increasing morphine metabolism and reducing effects
Pharmacokinetic interactions between methadone and alcohol

- Chronic ethanol induces cytochromes P450 2E1, 3A4 and 1A2. CYP3A4 and CYP1A2 can contribute to an increased rate of methadone metabolism in alcoholics (Meskar et al. 2001), leading to reduced methadone efficacy.

- Alcoholics can also develop severe liver disease and chronic liver disease may alter methadone disposition (Kreek, 1988).
Pharmacodynamics

- The processes by which drugs exert an effect at their site of action
- Includes acute and chronic effects on brain cells, including receptors and other cellular components
Mu-opioid receptor and bound opiate
Pharmacodynamics of Opiates

- Depends on drug-receptor interactions
  - Binding of ligands to receptor complexes
  - Signal transduction across the cell membrane due to changes in the receptor complex
  - Change is proportional to % receptors occupied or by rate of reversible binding (attachment) of ligand
  - Effects are agonistic or antagonistic
# Opioid Receptors and Ligands

<table>
<thead>
<tr>
<th>Receptor subtypes</th>
<th>Agonists</th>
<th>Antagonists</th>
<th>Second messengers</th>
</tr>
</thead>
<tbody>
<tr>
<td>mu-opioid</td>
<td>Morphine, Beta-Endorphin</td>
<td>Naloxone, Naltrexone</td>
<td>(-)cAMP, (+)gK+</td>
</tr>
<tr>
<td>delta-opioid</td>
<td>DPDPE enkephalins</td>
<td>Naltrindol</td>
<td>(-)cAMP, (+)gK+</td>
</tr>
<tr>
<td>kappa-opioid</td>
<td>ketocyclasocin dynorphinA 1-32</td>
<td>Norbinaltorphimine</td>
<td>(-)gCa²⁺</td>
</tr>
</tbody>
</table>
Antagonists have no effect on activity by themselves, but block the activity of agonists and partial agonists
Distribution of Brain Opioid Receptors
Ethanol is a Drug With Complex Pharmacodynamics

- Ethanol has no single mechanism of action (ie, no one active site)
- High doses nonspecifically disrupt membrane functioning (“fluidization”)
- Low doses act on membrane proteins (receptors, transporters, etc), binding to hydrophobic pockets or displacing water
- Individuals differ in their sensitivity to alcohol effects based on genetic differences

Neurochemical Systems and Drugs of Abuse

- Enkephalin Inhibitory Neuron
- Acetylcholine Neuron
- Glutamate Excitatory Input
- Nicotinic Receptors
- Enkephalin Inhibitory Neuron
- GABA Inhibitory Feedback
- Dopamine Neuron
- GABA-A Receptors
- Presynaptic Opioid Receptors (μ, δ?)
- GABA Inhibitory Feedback
- Dopamine Receptors
- REWARD

- Opioid Receptors
- Nicotinic Receptors

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- Opioid Receptors
- Nicotinic Receptors
Pharmacodynamic interactions between methadone and alcohol

- Alcohol consumption results in the release of the body’s naturally occurring opiates, endorphins both in the brain and in the periphery.
  - If opiates are consumed simultaneously with alcohol the exogenous and endogenous opioid effects can be additive.

- All opiate receptors are G-protein linked receptors. Ethanol facilitates receptor-G-protein coupling, potentiating the effects of opiates.
Pharmacodynamic interactions between methadone and alcohol

- Both alcohol and opioids can sensitize ventral tegmental dopamine neurons and facilitate use of the other agent (Brodie 2002; Leite-Morris et al 2004).

- Recent in vivo PET neuroimaging studies find that abstinent alcoholics show significantly elevated μ-opioid receptor availability in the ventral striatum and prefrontal cortex (Heinz et al 2005), suggesting that alcohol can increase opioid receptors.
Alcohol Increases the Activity of Endogenous Opioids (endorphins)

Release of β-endorphins

Reduction in inhibitory GABAergic output and increased dopamine release

Adapted from Kenna et al., *Am J Health Sys Pharm* 2004;61:2272.
Pharmacodynamic interactions between opiates and alcohol

- Synthetic opioids, including methadone have nonopioid actions, including inhibition of N-methyl-D-aspartate (NMDA) receptors (Callahan et al. 2004).

- One of alcohol’s major effects is inhibition of NMDA receptors, as well.

- Acutely, alcohol and opiates can enhance each other’s inhibitory effects on NMDA receptors, leading to increased sedation.

- Chronically, alcohol and opiates can upregulate NMDA receptors potentially leading to increased withdrawal symptoms of both alcohol and opiates.
The NMDA-Glutamate Receptor inhibited by acute alcohol and up-regulated (supersensitive) during alcohol withdrawal.
Opioids as NMDA Antagonists

Active at NMDA receptors

Inactive at NMDA receptors $K_i > 100 \mu M$
Summary of Opiate Alcohol Interactions

Pharmacokinetic Interactions
- Liberation of modified release oral formulations
- Metabolism – Acute and chronic effects
  Glucuronidation, CYP3A4, liver disease

Pharmacodynamic Interactions
- Acute release of endorphins by alcohol
- Changes in opiate receptors with chronic alcohol
- Ethanol facilitation of opiate effects at the receptor by actions on G-protein coupling
- NMDA receptor inhibition by alcohol and opiates