Opioid Pharmacology

F. Michael Ferrante, MD
Director, Pain Management Center
Professor of Clinical Anesthesiology and Medicine
David Geffen School of Medicine at UCLA
Nomenclature

- **Opium** is the dried powdered mixture of 20 alkaloids obtained from the unripe seed capsules of the poppy.
- **Opiate** refers to any agent derived from opium.
- **Opioid** refers to all substances (exogenous or endogenous) with morphine-like properties.
- *The generic term for the class of agents is “opioid”*
Opium Poppy
Structure-Activity

- **Alkaloid:** derived from the poppy
  - morphine
  - codeine

- **Semisynthetic:** modification of morphine functional groups:
  - diacetylmorphine (heroin)
  - hydrocodone
  - hydromorphone
  - oxycodone
  - oxymorphone
Morphine (Phenanthrene Ring)
Semisynthetic Opioids

- Diacetylmorphine (Heroin)
- Morphine
- Hydrocodone
- Oxycodone
- Hydromorphone
- Oxymorphone
Structure-Activity

- **Synthetic:** progressive reduction in the number of fused rings in phenanthrene moiety:

  **Morphinan**
  - levorphanol

  **Phenylpiperidine**
  - meperidine
  - fentanyl
  - sufentanil
  - alfentanil

  **Propioanilide**
  - methadone
  - propoxyphene
Synthetic Opioids

5-ring Phenanthrene  
edg. Morphine

4-ring Morphinan  
edg. Levorphanol

3-ring Benzomorphan  
edg. Pentazocine

2-ring Phenylpiperidine  
edg. Fentanyl

“Common Core”
Pharmacodynamics
Opioid Receptors

Opioid receptors serve two functions:

- **Recognition**: only L-isomers exhibit analgesic activity

- **Biologic action**: The strength of attachment (binding affinity) correlates with analgesic potency

\[
\text{\(\downarrow\) adenylate cyclase} \quad \text{\(\uparrow\) presynaptic Ca}\]
**µ-Receptor Binding Affinities**

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Binding Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>0.1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.6</td>
</tr>
<tr>
<td>Morphine</td>
<td>5.7</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>19.0</td>
</tr>
<tr>
<td>Meperdine</td>
<td>193.0</td>
</tr>
</tbody>
</table>

*Binding Affinity is measured by the equilibrium inhibition constant (Ki) for [H*] sufentanil (nM). The lower the value of (Ki), the Higher the binding affinity for the µ-receptor.*
# Opioid Receptor Classification

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Prototypic drug</th>
<th>Proposed actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ₁</td>
<td>Most endogenous, naturally-occurring or synthetic opioids</td>
<td>Supraspinal analgesia</td>
</tr>
<tr>
<td>µ₂</td>
<td>Morphine</td>
<td>Respiratory depression, Cardiovascular effects</td>
</tr>
<tr>
<td>δ</td>
<td>Enkephalins</td>
<td>Spinal analgesia</td>
</tr>
<tr>
<td>κ</td>
<td>Ketocyclazocine and dynorphin</td>
<td>Spinal analgesia, Sedation, miosis</td>
</tr>
<tr>
<td>σ</td>
<td>N-allylnormetazocine</td>
<td>Psycotomimetic effects</td>
</tr>
</tbody>
</table>
### Major Groups of Endogenous Opioids

<table>
<thead>
<tr>
<th>Name</th>
<th>Amino acid sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine-enkephalin</td>
<td>Tyr-Gly-Gly-Phe-Leu-OH</td>
</tr>
<tr>
<td>Methionine-enkephalin</td>
<td>Tyr-Gly-Gly-Phe-Met-OH</td>
</tr>
<tr>
<td>α-Neoendorphin</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys</td>
</tr>
</tbody>
</table>
Secretion as Prohormones

Diagram showing the structure of POMC, Pro-enk, and Pro-dyn peptides and their respective active components such as ACTH, β-lipotropin, γ3MSH, αMSH, CLIP, γ-lipotropin, β-endo (1-31), F, E, B, ME, ME-RGL, ME, LE, ME-RF, α-neo-endo, and dyno (1-17).
Localization in CNS
Intrinsic Activity

The relationship between receptor binding and response

- **Agonists** produce a maximum biologic effect
- **Antagonists** have no intrinsic activity and prevent the access of agonists to the receptors
- **Partial agonists** have a submaximal response
Intrinsic Activity

Graph showing the relationship between dose and maximal effect for full agonists, partial agonists, and antagonists.
Partial Agonists

- Less steep dose-response curve than agonists
- Ceiling effect
- Concomitant administration of a partial and full agonist reduces (antagonizes) the effect of the full agonist
Mixed Agonist-Antagonists

- **Partial antagonism**: interaction at a single receptor type

- **Agonist-antagonists**: have divergent activities at different receptors, acting simultaneously as an agonist at one and an antagonist at another
Mixed Agonist-Antagonists

PENTAZOCINE

BUTORPHANOL

NALBUPHINE

BUPRENORPHINE
### Mixed Agonist-Antagonists

<table>
<thead>
<tr>
<th>Opioid</th>
<th>µ</th>
<th>κ</th>
<th>σ</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>partial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butorphanol</td>
<td>antagonist</td>
<td>agonist</td>
<td>agonist</td>
<td>-</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>antagonist</td>
<td>partial</td>
<td>agonist</td>
<td>-</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>antagonist</td>
<td>agonist</td>
<td>agonist</td>
<td>-</td>
</tr>
</tbody>
</table>
Mixed Agonist-Antagonists

- Less steep dose-response curve than agonists
- Ceiling effect
- Concomitant administration of a partial and full agonist reduces (antagonizes) the effect of the full agonist
- Addictive potential
Mixed Agonist/Antagonists

- Butorphanol (Stadol):
  - Potency: 5X Morphine (parenteral)
  - Nasal spray: 1mg per spray
    - Headache
  - 50% less nausea/vomiting than Morphine
  - Sedating

- Nalbuphine (Nubain): equipotent to Morphine
Buprenorphine

- Semisynthetic derivative of thebaine.
- Highly lipophilic.
- Prolonged and avid binding to $\mu$-receptor
- 20-30X potency of MS (0.2-0.3mg = 10mg MS)
- Formerly, most common route: parenteral
- Well absorbed sublingually
  - Opioid detoxification
  - Maintenance programs
Pharmacologic Considerations: Opiates
Morphine

- Routes: PO, IM, IV, SQ, nebulized & rectal
- Sustained release preparations:
  - MS Contin
  - Oramorph
  - Kadian
  - Avinza (true qd dosing)
Morphine Metabolites

- Morphine: conjugated in the liver
- Metabolites include:
  - Morphine-3-glucuronide (M3G)
  - Morphine-6-glucuronide (M6G)
- Metabolites are cleared in kidneys
- M6G:
  - Active metabolite,
  - Accumulates in CNS
- M3G
  - May affect tolerance
Dextromethorphan

- d-isomer of morphine
- No classic analgesic effects (only L-isomer)
- NMDA antagonist (neuropathic pain)
  - Need “industrial” doses: impractical
Codeine

- Opiate (naturally occurring in poppy)
- Low affinity for opioid receptors
- 10% of dose demethylated to morphine
  - Fraction responsible for analgesia?
- Schedule II
- Most prescribed opioid in the world.
- Probably the most widely used analgesic
  - (Excluding aspirin)
- Limited by:
  - Low potency (do not use for severe pain)
  - Perceived frequency of nausea/vomiting
Pharmacologic Considerations: Semisynthetics
Hydrocodone Combinations

- With acetaminophen
  - Norco (5,7.5,10/325)
  - Anexia (5/500;7.5/650)
  - Lortab (2.5,5,7.5,10/500)
  - Vicoden (5/500)
  - Vicoden-ES (7.5/750)
  - Lorcet (7.5, 10/650)

- Vicoprofen (ibuprofen 200/7.5 mg hydrocodone)
Oxycodone Combinations

- Percocet/ Tylox:
  - oxycodone 5/acetaminophen 500
- Percodan:
  - oxycodone 5/ASA 325
- Roxycodone/ Oxy IR
- OxyContin
Oxymorphone (Opana)

- Opana ER: 5, 10, 20, 40 mg tabs
- Opana (IR): 5 and 10 mg
- Oral: 3x potency of morphine
- Old N/A IV: 10X potency of morphine
- “Tamper-proof” gum
- RF: OK in mild-mod (CC > 30 mL/min)
- Dose 1h before or 2hr s/p eating
Pharmacologic Considerations: Synthetics
Methadone

- Dolophine: incorrectly attributed to Hitler
- 10 mg tabs & 40 mg wafers
- Half-life:
  - Acute: $1^\circ t_{1/2} = 14\ h;\ 2^\circ t_{1/2} = 55h$
  - Chronic: $t_{1/2} = 23h$
- Analgesic duration $<< t_{1/2}$ (slow terminal elimination)
  - Sequestered & unavailable for analgesia
  - Dose q6-q8
- Beware accumulation
Methadone

- Stigma of heroin maintenance
- Must write: “for pain” in some states
  - Special license for methadone maintenance
- Inexpensive
- d-isomer = NMDA antagonist (neuropathic pain)
  - Available as racemic mixture in US
  - Available as l-enantiomer in Europe
Meperidine and Congeners

- Meperidine (Demerol/Mepergan)
  - Structurally similar to atropine
    - Tachycardia (unlike most opioids: bradycardia)
  - Problems with MAO inhibitors
  - Normeperidine metabolite (CNS excitation)
    - Renally cleared
    - “Slow excretors”: normal creatinine clearances
  - Very short duration of action $\cong 3$ h

- Diphenoxylate (Lomotil, with atropine): 20mg/ d $\div$ doses
- Loperamide (Imodium): 4-8mg/ d, max 16mg
Propoxyphene

- Unique:
  - d-isomer has analgesic properties
- Darvocet/ Darvon/ Darvon Compound
- Potency $\approx 2\times$ codeine
- More effective in combination
Tramadol

- Dual mechanism of action
  - μ-opioid activity (30%)
  - inhibition of serotonin/NE re-uptake (70%)

- Nonscheduled opioid
  - Less abuse potential
## Tramadol-IR and –ER Dosing

<table>
<thead>
<tr>
<th></th>
<th>Usual Dosing</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tramadol IR</strong></td>
<td>Start at 25 mg once daily; titrate up by 25-mg increments every 3 days to 100 mg/d (25 mg qid); thereafter titrate up as necessary every 3 days to 200 mg/d (50 mg qid); do not exceed 400 mg/d</td>
<td>Dizziness/vertigo, nausea, constipation, headache, somnolence</td>
</tr>
<tr>
<td><strong>Tramadol ER</strong></td>
<td>Start at 100 mg qd, titrate up as necessary by 100-mg increments every 5 d–not to exceed 300 mg daily</td>
<td>Dizziness, nausea, and constipation</td>
</tr>
</tbody>
</table>

Concept: Equianalgesic Dosing

“All opioids can be made equipotent or equianalgesic by adjusting for physicochemical and pharmacokinetic differences among individual opioids by correcting for dose and route of administration.”
<table>
<thead>
<tr>
<th>Opioid</th>
<th>Route</th>
<th>Equianalgesic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Parenteral</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Parenteral</td>
<td>2 mg</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td>4 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Parenteral</td>
<td>75 mg</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td>300 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>Parenteral</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td>20 mg</td>
</tr>
</tbody>
</table>
Equianalgesia: Route of Administration

- **ORAL**
  - **ACUTE**
    - 600:
  - **CHRONIC**
    - 300:

- **PARENTERAL**
  - 100 : 10

- **EPIDURAL**
  - 1

- **SUBARACHNOID**
  - 0.1

- **ICV**
Controlled Substances Act 1970

- Concept of balance
- Intro of scheduling
- "Narcotic drugs" defined, not by pharmacology
- Defined by law enforcement needs
Schedule I

- No accepted medical use in the US
  - Heroin
  - LSD
  - Peyote
  - Mescaline
  - Marihuana (except for refractory nausea)
Schedule II

- High abuse potential:
  - Morphine
  - Codeine
    - Add ASA or acetaminophen = Schedule III
    - Add expectorant = Schedule V
  - Hydromorphone
  - Methadone
  - Oxycodone
Schedule III

- Hydrocodone + acetaminophen
  - Norco (5/325, 10/325)
  - Anexia (10/660)
  - Lortab (2.5, 5, 7.5, 10/500)
  - Lorcet (7.5, 10/660)
  - Vicoden (5/500, 7.5/750, 10/660)
  - Vicoprofen (ibuprofen 200/7.5 hydrocododone)

- Tylenol #x (codeine)
Abuse Potential

- Actual abuse not directly tied to schedule
- Schedule II abuse < Schedule III or IV
- In past, Schedule II monitored closely:
  - Couldn’t be refilled
  - Couldn’t be prescribed by telephone
  - Why Vicodin (III) popularity c/w Percocet (II)
Schedule IV and V

- **Schedule IV**: Benzodiazepines
- **Schedule V**:
  - Antitussive
  - Antidiarrheal
  - Analgesic
    - e.g., Buprenorphine
Codeine:

- Schedule II
- + Acetaminophen or ASA = Schedule III
- + Cough syrup = Schedule V
Tolerance, Physical Dependence, Addiction

Definitions & Concepts
Tolerance

- With continued use, progressively more and more opioid is necessary to produce the same effect

- *Pharmacologic property* of a class of agents

- Incomplete cross tolerance
Physical Dependence

- A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

- *Not synonymous with tolerance or addiction*
“Cold Turkey”: Opioid Withdrawal

- Symptoms of opioid withdrawal:
  - Diaphoresis
  - Lacrimation
  - Coryza
  - Tachycardia
  - Abdominal cramps
  - Nausea
  - Vomiting
Other Withdrawal Syndromes

- Rebound hypertension
- Exacerbations of asthma after stopping steroids in steroid-dependent patients
- Rebound insomnia
- Discontinuation syndrome with SSRIs
- Rebound anxiety
- Seizures after D/C benzodiazepines
Addiction

- A psychic and physical state characterized by compulsive behavior to obtain a drug in order to experience its psychic effects, despite full knowledge of its harmful effects.

- Not a pharmacologic property.

- Not synonymous with tolerance or physical dependence.
Physical Dependence & Addiction

Physical Dependence

Addiction
Addiction

- Compulsive desire to obtain drugs for their euphoric effect despite full knowledge of the action

- Behavioral
Addiction: 5“Cs”

- Chronic
- Compulsive *use*
- Control *impaired*
- Craving
- Continued *use despite harm*