Pharmacology for **PAIN:** Prescribing Controlled Substances

Judith A. Kaufmann, Dr PH, FNP-BC
Robert Morris University

The Impact of Pain
- The National Center for Health Statistics estimates that 32.8% of the U.S. population has persistent pain
  - ~94 million U.S. residents have episodic or persistent pain (1 in every 5 adults)
- Treatment for chronic pain rarely results in complete relief and full functional recovery
  - Of patients diagnosed with chronic pain and treated by a PCP, 64 percent report persistent pain two years after treatment initiation

Impact of Pain
- Pain ranks low on medical tx priority
  - only 15% of primary care physicians report that they “enjoy” treating patients with chronic pain
  - Dahl et al., and Redford (2002) found that patients said they fear dying in pain more than they fear death
- Pain over the past 10 years has been designated the 5th vital sign
- Pain is 3rd leading cause of absence from work

- Americans constitute 4.6% of world’s population—but consume ~ 80% of world’s opioid supply
- Americans consume 99% of world supply of hydrocodone
- Between 1999 and 2006, the number of people >age 12 using illicit prescription pain relievers doubled from 2.6 to 5.2 million
  - 2006 National Survey on Drug Use and Health (NSDUH)

Are we the Pushers?
- 55.7% of users obtained drugs from a friend or relative who had been prescribed the drugs from 1 provider
- 19.1% of users obtained their drug directly from 1 provider
- 1.6% reported doctor shopping
- 3.9% reported purchasing drugs from a dealer

Can we be found guilty?
- Since 1999, opioid analgesic poisonings on death certificates increased 91%
  - During same period, fatal heroin and cocaine poisonings increased 12.4% and 22.8% respectively
- In 2008, 36,450 opioid deaths were reported
  - CDC, 2011
- Male:female ratio = 1.5:1 but death rate for females is 20x higher than males
Is opioid abuse a recent phenomenon?

- Pain relief and euphoric effects of opioids were well known to Sumerians and Egyptians (4000-2000 BC)
- Ancient Greeks first identified and used the latex of immature seed capsules of the poppy flower derived from opium — (Papaver somniferum).

Classifications of Pain

- Acute V. Chronic
  - Acute pain has easily defined onset and is transient
    - Occurs only between the time of tissue injury and tissue recovery
  - Chronic pain persists or recurs over extended period of time and interferes with patient’s functioning
    - Associated with depression and dysfunction and diminished quality of life
    - Much more complex and difficult to treat

Classifications of Pain

- Nociceptive V. Neuropathic
  - Nociceptive: Primary sensory neurons
    - Stimulation of pain receptors (nociceptors) located throughout the body
    - Respond to noxious stimuli - thermal, mechanical, chemical
  - Can be further subdivided into somatic and visceral pain

Nociceptive pain

- Somatic nociceptive: originates in skin or skin structures
  - Well localized to specific area in the body
    - e.g., tendinitis, post surgical pain
- Visceral nociceptive: originates in the internal organs as a result of infiltration, compression, stretching
  - Difficult to localize and often referred to distant sites
    - e.g., MI pain, pancreatic pain, GB pain
- Both types of nociceptive pain respond to both non steroidal anti-inflammatories and opioids

Chemical Mediators of Pain

- Initiate or perpetuate continuing stimulation of small pain conducting fibers
- Neurotransmitters:
  - Acetylcholine and histamines
  - Serotonin
    - Influences pain perception
- Polypeptides:
  - Bradykins, prostaglandins (PG), and substance P
- Blocking any of these substances minimizes pain signals and the perception of pain
- Targets for pharmacologic agents to control pain
Pain-Modulating receptors

- Tolerance for pain varies person-to-person
- May be due to individual production of endogenous pain relieving substances
  - **Enkephalins and Endorphins**
    - Enkephalin is the most important endogenous analgesic identified to date
    - Released by the pituitary in response to painful stimulus or stressor
    - Found in bloodstream and in specific neurons
    - Once released, β-endorphin stimulates inhibitory neuronal receptors (opioid receptors)
    - The **μ receptor** (an opioid receptor) inhibits the transmission of pain signals to and from the higher brain centers
    - These same μ receptors are stimulated by morphine-like drugs (opioids)

“just don’t inhale…”: Cannabinoid receptors and endogenous cannabinoids have become a focus for research on pain regulation

- **Two cannabinoid receptors**:
  - CB1-expressed in the brain, SC, and sensory neurons
  - CB1 receptors appear to be responsible for the euphoric and anticonvulsive effects of cannabis
  - CB2-expressed in non-neural tissue and immune cells, including microglia
    - Microglial cells that acts as first line of active immune defense in the CNS
  - CB2 receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic effects of cannabis

Blocking the endocannabinoid system: Lesson from Rimonabant

- Was in Phase III clinical trials for treatment of obesity
- Trials discontinued due to unexplained suicides in treatment group
- Found that drug also blocked pleasure center in the brain

Pain receptors and Their Biologic Effects

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Biologic response to Stimulation</th>
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<tbody>
<tr>
<td>MU (μ)</td>
<td>Respiratory depression, physical depression, tolerance, constipation, euphoria, miosis</td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>Spinal level analgesia and sedation without respiratory depression, pupil constriction (miosis)</td>
</tr>
<tr>
<td>Sigma (σ)</td>
<td>Vasomotor stimulation, psychomimetic effects, + miosis</td>
</tr>
</tbody>
</table>

Neuropathic Pain

- Originates from compression or injury to peripheral nerve fibers or to the central nervous system
  - Describes as burning, shooting, electrical
    - Can be dermatomal or non-dermatomal in distribution
  - E.g., post herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy
- Less responsive to analgesics or anti-inflammatories
- May require antidepressants, anticonvulsants

Pain Perception

- There are two ways for nociceptive information to reach the CNS
  - the neospinothalamic tract for “fast spontaneous pain”
    - Fast pain is felt within a 0.10 second of application of the pain stimulus
    - Sharp, acute, prickling pain felt in response to mechanical and thermal stimulation
    - Aδ fiber (A delta-fibers) terminate on the dorsal horn of the spinal cord where they synapse with the dendrites of the neospinothalamic tract
  - paleospinothalamic tract for “slow increasing pain”
    - Slow pain is transmitted via slower type C-fibers
    - Neurons terminate throughout the brain stem (thalamus, medulla pons and midbrain)
    - Slow pain is stimulated by chemical stimulation
      - poorly localized
      - described as aching, throbbing or burning pain
When nociceptors become sensitized (i.e., more responsive), their thresholds are reduced, thus causing hyperalgesia (i.e., hypersensitivity to pain).

- Bradykinin, histamine, leukotrienes, prostaglandins, serotonin, and K+ that are often released near damaged or dying cells sensitize nociceptors.
- K+ activates the nociceptors.
- Substance P is also released from nociceptors through an axon reflex causing hyperalgesia, vasodilatation and increased capillary permeability.
- Glutamate may be co-released with substance P from C-fibre terminals.

The CNS discards more than 99% of all incoming signals as irrelevant.

**The gate-control hypothesis of pain**

- Pain transmission is suppressed by signals in thick myelinated afferents.
- Pain sensation is enhanced by signals in thin afferents.
- Inhibitory interneurons (in dorsal horn of the SC) perform the gate-control through a special type of pre-synaptic inhibition called primary afferent depolarization (PAD), and the receptors on the cell body of the secondary neuron is the gate.

**Recommended Order of Treatment for Pain**

<table>
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<tr>
<th>Severity of Pain</th>
<th>Agents</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Mild to Moderate</td>
<td>Acetaminophen, ASA, NSAIDs</td>
<td>Maximum doses should be used before proceeding to opioids</td>
</tr>
<tr>
<td>Moderate to Severe</td>
<td>Codeine, hydrocodone, oxycodone, propoxyphene</td>
<td>Usually prepared in combination with non-opioid analgesics, side effects limit dosing</td>
</tr>
<tr>
<td>Severe</td>
<td>Morphine, oxycodone, hydromorphone, fentanyl, meperidine</td>
<td>MSOs is the gold standard in all patients – including the elderly</td>
</tr>
</tbody>
</table>

**Structural Brain Changes**

- Short term opioid use has been associated with gray matter changes in patients with chronic pain.
- LONG TERM gray matter changes correlated with the dose of morphine after only one month of use.
  - Changes persisted an average of 4.7 months after drug stopped.
  - *Younger, et al., 2011*

**Opioid Analgesics**

BLACK BOX WARNING: Use Cautiously. Can lead to “pain in the …” for the provider.
General Overview

- Opioid analgesics are:
  - Associated with unexplained loss, misplacement
  - Frequently the drug of choice for dogs
  - Drugs most often flushed down the toilet
  - Difficult names for patients to recall
    - Kaufmann, et al., 1988-2012

Analgesic Effects

- Bind with one of four opioid receptors
  - Analgesic effects associated with binding to μ and κ receptors
    - Full agonists = morphine, hydrocodone, hydromorphone, fentanyl, methadone, codeine, oxycodone
    - Partial agonist-antagonist = pentazocine (Talwin)
      - Can precipitate withdrawal
    - Weak agonists = tramadol (Ultram)
  - Activation of a opioid receptor is associated with analgesia and undesired effects
    - Respiratory depression, euphoria, mydriasis, sedation, nausea, tolerance
    - Agonist activity at the opiate μ- or κ-receptor can result in analgesia, initial miosis followed by mydriasis, and/or decreased body temperature

Opioids are classified by their ability to stimulate (agonist) or block (antagonist) opioid receptors

- Kappa receptor stimulation produces analgesia, dysphoria and respiratory distress
- Stimulation of delta opioid receptors produces analgesia without respiratory distress

Opioid Action

- Opiate agonists alter perception of and emotional response to pain
- Precise mechanism of action has not been fully elucidated
- Opiate agonists act at several CNS sites, involving several neurotransmitter systems to produce analgesia
- Pain perception is altered in the spinal cord and higher CNS levels

Opioid Action

- Opiate agonists do not alter the threshold or responsiveness of afferent nerve endings to noxious stimuli, nor peripheral nerve impulse conduction
- Opiate agonists act at specific receptor binding sites in the CNS and other tissues; opiate receptors are concentrated in the limbic system, thalamus, striatum, hypothalamus, midbrain, and spinal cord

General Pharmacokinetic Precepts of Opioids

- Hepatically metabolized to active and inactive metabolites
- Active metabolites differ with each drug
  - E.g., meperidine is metabolized to active metabolite, normeperidine, that accumulates and causes seizures
- Analgesic effects begin 30-60 minutes and reach peak effect in 1-2 hrs
- Duration of action varies with each drug
  - Unlike NSAIDs, pure opioid agonists do NOT have a ceiling effect
    - Increased dosage produces increased analgesia
- Eliminated in the urine
November 19, 2010

- FDA removed propoxyphene (Darvon/Darvocet and generic) from the US market
- Decision was made based on new clinical data showing that the drug puts patients at risk for potentially serious or even fatal heart rhythm abnormalities
- An estimated 10 million patients have used these products
- Changes to the heart's electrical activity are not cumulative
  - once drug is d/c'd, the risk is gone

Cellular Mechanism of Action

- Binding of opioid to receptor:
  - Decreases calcium entry into cells allowing increased time for channels to remain closed
- Activation of opioid receptors leads to:
  - K+ efflux and increases the negative charge of the cell membrane →
  - failure of calcium channels to activate with net result of decrease in release of dopamine, serotonin and nociceptive peptides (Substance P) →
  - Blockage of nociceptive transmission

Morphine: Prototype of Opioids

- Low cost, well studied
- Distributed throughout the body
- Crosses BBB in small amounts
  - Least lipophilic of all opioids
- Plasma T1/2 ~ 3 hrs due to nearly complete metabolism in the liver
- Multiple routes of administration and duration of effect (short acting, immediate release, sustained release)
- Indicated for severe pain
  - Best for dull, chronic pain regardless of anatomic source

Additional Actions

- Depression of cough reflex
  - Receptors for antitussive action appear to differ from analgesia receptors
- Treatment of intractable diarrhea
- Treatment of acute pulmonary edema
  - ?d/t vasodilatory effect

Adverse reactions

- Emesis without unpleasant sensations
- Hypotension and bradycardia
- Histamine release → urticaria, sweating, flushing
- Hormonal effects:
  - Lowers testosterone and cortisol levels
  - Increases prolactin and growth hormone release
  - Increases antidiuretic hormone → urinary retention

Contraindications/ Precautions

- Respiratory depression
- Acute or severe bronchial asthma or hypercarbia
  - Use with extreme caution in patients with COPD or cor pulmonale
- Known or suspected paralytic ileus
- Head Injury and Increased Intracranial Pressure:
  - The respiratory depressant effects of morphine (with CO2 retention and secondary elevation of CSF pressure) may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure
**Codeine and Derivatives**

- Indicated for tx of mild-moderate pain
- Excellent oral bioavailability but only 1/10 as potent as MSO4
  - Much less addictive and produces little euphoria
  - Less intense adverse effects except in children
    - Can cause respiratory depression
- Partially metabolized into morphine
  - Accounts for analgesic effect
  - Often used in combination with ASA
    - Increased pain relief dit inhibition of prostaglandins & inhibition of nociceptive transmission

**Notes on Other Opioids**

- Meperidine (Demerol) is a potent anticholinergic agent
  - Causes dry mouth, blurred vision and tachycardia, ectopic beats
  - Active metabolite is proconvulsant and hallucinogenic
  - Unlike MSO4, not associated with prolongation of labor
    - Increases uterine contractions

**Oxycodone hcl**

- **Pharmacokinetics**
  - **Absorption**
    - High oral availability due to low presystemic or first-pass metabolism.
    - The immediate-release oral bioavailability is 100%.
    - The oral bioavailability is 60% to 87%
    - Peak plasma concentration increased by 25% with a high fat meal
  - **Metabolism**
    - Extensively metabolized in the liver to noroxycodone (a major metabolite) and oxymorphone.

**Hydrocodone**

- Always compounded with acetaminophen
  - Toxicity related to high doses of acetaminophen
    - Adults should not take more than 4000 mg/day
    - Liver disease < 2000mg/day
  - Overdose of acetaminophen is due to toxic metabolite that can cause acute liver necrosis
  - Consider when single ingestion exceeds 140 to 200 mg/kg or chronic use exceeds 10 days at usual doses.

**Notes on Other Opioids**

- Hydromorphone is 8x more potent than MSO4
  - Indicated for severe pain and in high doses for pain relief in opioid addicted patients
- Fentanyl is 80-100x more potent than MSO4
  - Excellent for post op pain after the immediate post op period d/t respiratory depression
    - In lozenge form (to induce anesthesia) and transdermal (cancer pain, chronic pain)
      - Far more intense SEs than with MSO4
      - Potentially teratogenic and possibly implicated in SIDS

**Opiate Dependence**

- Repeated opioid use results in adaptations of noradrenergic locus ceruleus (located in the pons) that are associated with physical dependence and withdrawal, based on study in mice and rats (J Neuroscience 2005; 25(25): 6005)
- Repeated opiate use may alter neurotransmitter and neuropeptide systems that regulate stress response and drug seeking behavior (J Neuroscience 2002, 22(9): 332)
- Physical dependence usually occurs 1-4 weeks after continuous opioid use
Chromosome 17 Harbors Opioid Dependence Genes

- An estimated 898,000 adults in the United States are opioid dependent (AAFP, 2006)
- Methadone has been the treatment of choice in the United States
- Methadone maintenance programs typically have stringent entrance criteria, long waiting lists, and primarily are located in urban areas
- Only 14% of patients who are addicted to opioids are treated in traditional methadone clinics.

Opioid Addiction

- Twin studies also suggest that certain genes may increase the risk of opioid addiction without affecting the likelihood of addiction to other drugs.
- Candidate genes impact in a variety of ways, including statistical studies to determine the effects of eliminating, activating, or inactivating the genes on animals’ responses to drugs.

Treatment Options for Opioid Abuse

- Methadone
  - Mu receptor agonist with delayed onset of action and longer half life
  - Analgesic profile and potency and SE's similar to MSO4
    - Longer duration of action and better oral bioavailability
    - Useful in treatment of addiction
  - Once tolerance develops, has little impact on mood, judgment, and psychomotor skills

Methadone

- In pregnant heroin-addicted women, substitution with methadone associated with fewer LBW newborns and fewer learning/cognition problems in children
- Methadone has similar addiction potential to opioids and heroin

Methadone Side Effects

- Common:
  - Insomnia, restlessness, nervousness, drowsiness, weakness, vomiting/nausea, diarrhea, constipation, dry mouth, changes in appetite, decreased libido, male impotence and anorgasmia
- Sudden withdrawal:
  - anxiety, irritability, insomnia, hypertension, increased perspiration, rigors, abdominal pain, myalgias and arthralgias, muscle spasms and an overall "sick" feeling.
    - w/d occurs 24 and 48 hours after stopping methadone and increase in intensity over the next 6 days

Buprenorphine (Suboxone)

- The Drug Addiction Treatment Act of 2000 enabled physicians to provide office-based treatment for opioid addiction using buprenorphine, a partial mu-opioid receptor agonist
- Clinical studies indicate buprenorphine effectively manages opioid addiction
- Buprenorphine is more effective than placebo for managing opioid addiction but may not be superior to methadone
- Family physicians are required to complete eight hours of training before they can prescribe buprenorphine for opioid addiction.
Mechanism of Buprenorphine Action

- Partial agonist at the mu receptor
  - Limits the intense high of other opioids (ceiling effect)
  - Alters mood but with less intensity
- Tightly binds to mu receptor
  - Prevents other opioids from accessing the receptor site
  - Displaces other opioids from mu receptors

Message to Providers: It may be time to...