Control of Pain & Inflammation

Narcotics and Non-narcotics

Opiates and NSAIDs

2 lectures

PHRM 203

Allison Beale
Pain

- Differentiating pain
  - Sensation linked to neuron type
  - Location
    - Somatic - skin, muscle, easiest to pinpoint
    - Visceral (often referred) – thoracic, abdominal, pelvic
    - Neuropathic - nerve “damage”
  - Nociceptive vs Non-nociceptive
    - Nociceptive: somatic or visceral
    - Non-nociceptive: neuropathic, sympathetic or psychogenic

According to the Society for Neuroscience, in 2008, 97M Americans suffered from chronic pain

Headache, alone, is classified into 13 different pain categories by the International Association for the Study of Pain

OPTIONAL
Listen to an 8 minute TED Talk by Elliot Krane, MD, called, “The mystery of pain as a disease.”
https://www.ted.com/talks/elliot_krane_the_mystery_of_chronic_pain

Remember: PGs sensitize neurons (nociceptors) to pain input!
Pain Medications

• Opioids
• NSAIDs/Acetaminophen
• Corticosteroids
• Muscle relaxants
• Anxiolytics
• Anti-depressants (TCAs, SNRIs, etc.)
• Anti-epileptic drugs (AEDs)
• Alpha-2 agonists
• NMDA antagonists
• Bisphosphonates (bone pain only)
• For migraine: Beta blockers, triptans, anti-depressants, etc.

Neurotransmitters

• Glutamate
• GABA/Glycine
• Endorphins
• Dopamine (D or DA)
• Serotonin (5-HT)
• Substance P
• Prostaglandins (PGs)
• Histamine
• ATP
• Bradykinin
• Hydrogen (H^+)
Pain Pharmacology

WE ARE COVERING: Nociceptive pain treatment

• Somatic
  – Opioids (today)
  – NSAIDs and Acetaminophen (Paracetamol) (Next Lecture)

• Visceral
  – Opioids
  – NSAIDs (menstrual pain)

**Opioid versus non-opioid (NSAID)**
• Opioids \( \Theta \) neurotransmission of pain
• NSAIDS \( \Theta \) autocoids (e.g., prostaglandins) that modulate pain

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Non-nociceptive

• Neuropathic
  – TCAs
    • Doxepin, Amitriptyline
  – SNRIs
    • Duloxetine, Milnacipran
  – AEDs
    • Gabapentin, Carbamazepine, Pregabalin
  – Anti-arrhythmics
    • Mexiletine (Mexitil®)
  – NMDA antagonists
    • Memantine? Off label?
  – Topical capsaicin (Qutenza®)

• Sympathetic
  – As above
  – \( \beta \)-blockers, triptans, etc.
Pain

- Nociception can cause autonomic effects apart from conscious pain
  - Pallor
  - Diaphoresis
  - Tachycardia, ↑ BP
  - Syncope
  - Nausea, vomiting

- Neuropathic pain
  - When nerves become electrically unstable, firing randomly or inappropriately – is often coupled with nociceptive pain
  - Common after burns, trauma, tumors
  - Types of neuropathic pain
    - Degenerative (nerve damaged)
    - Pressure (trapped/pinched)
    - Inflammation (slipped disc)
    - Infection (viruses, e.g., herpes)

- Other non-nociceptive pain
  - Sympathetic
    - Common after fractures/soft tissue injuries
  - Psychogenic

How to classify fibromyalgia, a disorder in which the hallmark feature is pain?
- Often best treated with antidepressants!
## Sampling of Nociceptors

<table>
<thead>
<tr>
<th>Function</th>
<th>Type</th>
<th>Axon type</th>
<th>Axon diameter (µm)</th>
<th>Conduction Velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proprioception</td>
<td>Muscle spindle</td>
<td>Ia, II - myelinated</td>
<td>13-20</td>
<td>80-120</td>
</tr>
<tr>
<td>Touch</td>
<td>Merkel, Meissner, Pacinian, Ruffini</td>
<td>Aβ - myelinated</td>
<td>6-12</td>
<td>35-75</td>
</tr>
<tr>
<td>Pain, T°</td>
<td>Free nerve endings</td>
<td>Aδ - thin myelinated</td>
<td>1-5</td>
<td>5-30</td>
</tr>
<tr>
<td>Pain, T°, itch</td>
<td>Free nerve endings</td>
<td>C - unmyelinated</td>
<td>0.2-1.5</td>
<td>0.5-2</td>
</tr>
</tbody>
</table>

A Beale

PHRM 203: narcotic & non-narcotics
Referred Pain

• Ice Cream Headache
  – Vagus cooled
• Right shoulder pain
  – Liver, gall bladder or stomach, pericarditis
• Left shoulder pain
  – Lung or diaphragm
• Heart attack
  – Arm, neck pain
• Phantom limb pain and sensations

Nerve fibers from high sensory input locations (e.g., skin) enter the spinal cord at the same level as nerves from low sensory input areas (internal organs).

The brain is not used to getting high input readings from low input neurons, so it ASSUMES it is coming from High Input Neurons.
Gate Control Hypothesis

Why massage and acupuncture work

Other non-traditional pain control methods that work:

- Visualization
- Journaling
- Meditation
- Distraction alleviates pain
Opioid Peptides

- **Plant-derived = opiates**
  - Opium - from *Papaver somniferum*
    - Morphine, codeine and thebaine - from opium
- **Semisynthetic (thebaine-derived)**
  - Hydrocodone, oxycodone, oxymorphone, etc.
- **Synthetic**
  - Fentanyl, methadone, tramadol
- **Endogenous opioids**
  - Enkephalins (Met-enkephalin & Leu-enkephalin), endorphins, endomorphins, dynorphins
Opioid Receptors

- All are GPCR
  - They depress activity of various neurons
    - Sensory (substance P) and sensory modulating neurons (GABA_B)
    - Hypothalamus and Pituitary (decrease hormone release)
    - Cortex
    - Autonomic effectors
  - Three types
    - μ - mu - morphine
    - δ - delta - deltorphin
    - κ - kappa - ketocyclazocine

Narcotics = opioids, but, not all opioids are narcotic…

Remember, GABA_B is EXCITATORY!
The opposite of GABA_A

Opioids ↓ pain perception and ↑ pain threshold.
The presence of pain changes the net effects of opioids.

BZD and Barbiturates act directly on GABA_A receptors

Most opioid receptors in GIT and CNS
Opioid Receptors have MANY Physiological Functions

- In addition to pain modulation and addiction
  - Regulation of membrane ionic homeostasis
  - Cell proliferation
  - Emotional response
  - Epileptic seizures
  - Immune function
  - Feeding/obesity
  - Respiration
  - Cardiovascular control

- The δ opioid receptor
  - Protection against hypoxic and/or ischemic stress
    - Neuroprotection
    - Cardioprotection

Pharmacodynamics of Opioid Meds

Opioids are used for their analgesic, sedative, anti-diarrheal & antitussive effects

- **CNS effects**
  - Analgesia
  - Sedation/narcosis (T*)
  - Euphoria or dysphoria (T)
  - Miosis \((\text{pin point pupils})\)
  - Nausea/vomiting (T*)
  - Respiratory depression (T*)
  - \(\Theta\) of cough reflex (cough suppressant)

* \(T = \text{tolerance develops w/in } \sim 1 \text{ week to effect}\)

**Sedation, nausea & euphoria** most problematic with changes in serum \([\_]\); thus, sustained release formulations of short \(t \frac{1}{2}\) drugs are popular (morphine, hydrocodone, fentanyl and oxycodone)

**Vomiting = both CNS & GI effect** – control with a weak CNS active antiemetic \((\text{Haloperidol})\) or a stronger one \((\text{Ondansetron})\), or a prokinetic \((\text{Metoclopramide or Domperidone})\)
Pharmacodynamics of Opioids

- **CV effects**
  - ↑ histamine release from peripheral mast cells
    - Itch!
    - **VASODILATION** (indirect effect)
      - Flushing of face and neck
  - ↓ Peripheral resistance
    - **ORTHOSTATIC HYPOTENSION**
  - ↓ Baroreceptor activity
    - **ORTHOSTATIC HYPOTENSION**
  - ↑ Intracranial pressure

*Use antihistamine like fexofenadine (Allegra) to control histamine*

Reflex tachycardia a result
Pharmacodynamics of Opioids

• GI effects
  – ↑ Smooth muscle tone
    • CONSTIPATION!!! *(No Tolerance develops!)*
  – ↑ tone of biliary sphincter
    • PAIN, “GALL BLADDER ATTACK”
  – ↑ tone of bladder sphincter
    • URINARY RETENTION *(T)*
  – ↓ GIT secretions
    • Dry mouth

*Constipation a BIG problem – laxatives almost ALWAYS given along with fiber and lots of water*
Pharmacodynamics of Opioids

• Other effects
  – ✆ Hypothalamus & Pituitary gland
    • ✆ ADH (posterior pituitary) = SIADH
    • ✆ PRL (anterior pituitary)
    • ✅ LH (anterior pituitary)
  – ✅ Natural killer (T) cell activity
    • IMMUNOSUPPRESSION

• Super-additive effect
  – Co-administration with an antidepressant (MAOI, TCA) or anti-psychotic (phenothiazine type) results in ✆ potency of the narcotic. Poorly understood.

Remember, XS prolactin results in: impotence, amenorrhea, breast growth and breast cancer
Pharmacodynamics of Opioids

• Adverse effects
  – **Respiratory depression**
    • ↑ Intracranial pressure as a result
  – ⊕ chemoreceptor trigger zone (CTZ) in medulla
    • Nausea, vomiting
  – **Tolerance** - down regulation of receptors (Δ sensitivity)
    • *No “upper” limit for dosage as person gains tolerance*
  – **Physical dependence** - cells require continued stimulus
  – ↑ **histamine release** from mast cells
    • Itching (puritus), flushing
    • Allergic reactions fairly common - contact dermatitis in nurses = occupational hazard
### Poppy-derived Opioid Analgesics

Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karch. Lippincott, Williams and Wilkins, 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Mild to moderate pain; coughing induced by mechanical or chemical irritation of the respiratory tract</td>
</tr>
<tr>
<td>Morphine</td>
<td>Moderate to severe acute &amp; chronic pain; pre- &amp; post-op, &amp; during labor. Commonly used in <em>Patient-controlled analgesia (PCA) devices</em> suitable for children &amp; adults - especially the elderly.</td>
</tr>
<tr>
<td>C-II</td>
<td>PO, PR, IM/IV, epidural, intrathecal</td>
</tr>
<tr>
<td>Roxanol, MS-Contin, KMS, Duramorph</td>
<td></td>
</tr>
<tr>
<td>Opium</td>
<td>Treatment of diarrhea, relief of moderate pain</td>
</tr>
<tr>
<td>Thebaine</td>
<td>Not used clinically, but is the major synthetic precursor for the semi-synthetic narcotics. It actually has ⊕ effects and can <em>cause strychnine-like convulsions at toxic levels</em></td>
</tr>
</tbody>
</table>
Morphine  C-II

- Pharmacokinetics & dynamics
  - So-so GI absorption ~ 25% is bioavailable - it’s polar
    - Lots of 1st pass metabolism - mostly conjugation with glucuronic acid
    - Active and inactive metabolites
  - Most excreted in urine, some in bile that enterohepatically recycles
  - Tolerance
    - Attenuated by Ca\(^{++}\) channel blockers and NMDA antagonists (e.g., ketamine)
    - Enhanced by Mg\(^{++}\) &/or Zn\(^{++}\) deficiency (diuretic use, alcoholics…)

- Indications
  - Used to treat severe trauma pain, MI and cancer
    - Patient Controlled Analgesia (PCA) devices
      - Usually intrathecal and require 1/300th the dose of morphine vs PO

Chronic pain often controlled with a long t ½ drug (e.g., methadone), while BREAK-THROUGH pain is controlled by a short t ½ drug administered using a PCA device
### Semi-synthetic Opioid Analgesics

Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karch. Lippincott, Williams and Wilkins, 2008

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Hydrocodone C-II (alone or compounded)</td>
<td>Cough suppressant, moderate pain relief in combo products Compounded with Acetaminophen (APAP) (Vicodin), with aspirin (Lortab), with ibuprofen (Vicoprofen), with chlorpheniramine (Tussionex) PO</td>
</tr>
<tr>
<td>Diphenoxylate (Lomotil)</td>
<td><em>Not narcotic</em>, an opioid agonist used to treat diarrhea Compounded with Atropine C-V (w/o atropine C-II) PO</td>
</tr>
<tr>
<td>Naloxone (Narcan)</td>
<td>Opioid antagonist used to Dx narcotic overdose and reverse opioid effects (<em>not a controlled substance</em>) IV/IM, SC</td>
</tr>
<tr>
<td>Naltrexone (Revia, Vivitrol)</td>
<td>Opioid antagonist used to treat alcohol or narcotic dependence in adults (<em>not a controlled substance</em>) PO, IM</td>
</tr>
</tbody>
</table>
Semi-synthetic Moderate Opioid Agonists

Hydrocodone C-II (usually co-compounded e.g., with APAP = Vicodin) *from* codiene & thebaine

- P450 metabolism via CYP2D6 to morphine, so if you don’t have isozyme, *no pain relief*
- Renal excretion, $t_{1/2} \sim 4$ hrs.
- Used for *mild to moderate pain, anti-tussive*

Other combos: ibuprofen (Vicoprofen), chlorpheniramine (Tussinex), atropine (Tussigon, Hycodan)

PO

Codeine C-II *from* opium poppy

Tylenol #2,3,4 = codeine + APAP
Other Opioid Agonists

Diphenoxylate - \( \text{Rx C-II or C-V if compounded} \)

\( \text{with atropine (Lomotil)} \)

- Similar to Loperamide (Imodium) and a congener of Meperidine (Demerol)
- \( t_{1/2} = 12-14 \) hours
- Used to \text{stop diarrhea}
  - At low doses it is constipating
  - At high doses – other opioid effects (hence compounded with atropine for toxicity)
Opioid Antagonists

Naloxone (Narcan)

- Synthetic derivative of thebaine, potent $\mu$- antagonist, less potent at $\kappa$- & $\delta$- receptors
- $t_{1/2}$ 1-1.5 hours
- P450 & Phase II
- Urine, bile
- Used to counter opioid overdose

- *Given before $O_2$ to any ER patient admitting with respiratory depression. Respiratory depression (along with coma and miosis) is pathognomonic for opioid OD.*
- *Giving $O_2$ 1st will further depress respiration in an opioid OD patient*

Ohio has Project DAWN (Deaths Avoided with Naloxone)
Opioid Antagonists

Naltrexone (ReVia, Vivitrol)

- Synthetic, inverse agonist at $\mu$- & $\kappa$- receptors, less potent at $\delta$- receptors.
- $t_{1/2} = 4\text{-}13$ hours
- Liver (other enzyme + P450)
- Urine
- Used to treat alcohol or opioid addiction
- Not controlled

Routes: PO, IV/IM

Boxed warning: liver damage

Inverse agonists bind to same site as ligand, but exert opposite effect
# Synthetic Opioid Analgesics

*Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karch. Lippincott, Williams and Wilkins, 2008*

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<tr>
<td><strong>Fentanyl</strong> (<em>Duragesic</em>)</td>
<td>Pre- peri- and post-op analgesia; transdermal patch for chronic pain - 100X more potent than morphine <strong>C-II</strong></td>
</tr>
</tbody>
</table>
| **Meperidine** (*Demerol*)  | Moderate to severe pain, pre- and peri-op analgesia and anesthesia support, obstetrical analgesia. Toxic metabolites limit long term use. **C-II**  
*In Europe, the generic name is, “Pethidine”* |
| **Methadone** (*Dolophine*) | Severe pain, treatment of narcotic addiction in adults **C-II**              |
| **Sufentanil** (*Sufenda*)  | Analgesic during general anesthesia, epidural in labor and delivery - requires anesthesia practitioner to administer. 1000X more potent than morphine. **C-II** |
Fentanyl (Duragesic) **C-II**

- **Kinetics**
  - Potent opioid agonist
  - \(100 \, \mu g \text{ fentanyl} \approx 10 \, g \text{ morphine or } 75 \, mg \text{ meperidine}\)
  - High lipid solubility
  - P450 metabolism by CYP3A4
  - Excreted in urine, \(t_{1/2} = 7 \, \text{hrs}\)
    - Short \(t_{1/2}\) allows rapid titration to stable serum levels
    - TD SLOW onset: 12-22 hours to start working
    - Transmucosal FAST onset: 20 minutes to start working

- **Indications:** chronic pain, MI & cancer, including breakthrough pain associated with injuries & cancer. It is also used as a surgical anesthetic & analgesic

**NUMEROUS Boxed Warnings!**

Routes: PO, TD, IM, IV, sublingual, buccal

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**A Beale**

PHRM 203: narcotic & non-narcotics
Meperidine (Demerol) 🚒 C-II

- **Kinetics & dynamics**
  - Synthetic
  - No antitussive or pupil effects. Less GI etc.
  - Heavy 1st pass metabolism - P450 metabolism to a **toxic** metabolite (seizures), Phase II metabolism follows; t½ 3-4 hours

- **Indications:** **acute pain & obstetric or post-surgical analgesia**
  - Severe Drug-drug interactions include “serotonin syndrome”

- **ADRs**
  - Altered mental state
    - Agitation, hallucinations, etc
  - RESPIRATORY depression
  - Fetal respiratory/CNS depression
  - ↑ intracranial pressure
  - Urinary retention
  - Mast cell degranulation
  - ↑ effects of NMJ blockers
  - Hypotension
  - ↓ seizure threshold

Routes: PO, IV/IM (SC is irritating)
Methadone (Dolophine, Methadose) C-II

- **Kinetics**
  
  - Synthetic (an analog of codeine)
  - $t_{1/2} = 24-36$ hours (up to 60 hrs!)
  - P450 (CYP3A4, CYP2B6 & CYP2D6) metabolism with lots of individual variation
  - Renal excretion

- **Indications:** analgesic (chronic pain), anti-tussive and anti-addictive for opioid addicts

**Routes:** PO, IV/IM, SC

Methadone sounds like Metadate (methylphenidate); both are C-II, PO, multidose 10 mg formulations!

Long $t_{1/2}$ makes rapid titration impossible – not indicated for rapidly changing pain

Boxed warnings: 1. death possible at initiation; 2. fatal respiratory depression; 3. long QT interval; 4. dispensing regs.
Narcotic Agonists-agonists

Adapted from: Focus on Nursing Pharmacology, 4th Ed., by AM Karch. Lippincott, Williams and Wilkins, 2008

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<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Buprenorphine (Buprenex)</td>
<td>Mild to moderate pain, CIII, analgesic potency 20-30X morphine</td>
</tr>
<tr>
<td>Butorphanol (Stadol)</td>
<td>Pre-op analgesic, moderate to severe pain, migraine, CIV</td>
</tr>
<tr>
<td>Nalbuphine (Nubain)</td>
<td>Labor and delivery, adjunct to general anesthesia, moderate to severe pain in adults. Analgesia similar to morphine. Not scheduled.</td>
</tr>
<tr>
<td>Pentazocine (Talwin)</td>
<td>Moderate to severe pain, labor and delivery, postpartum pain, adjunct to general anesthesia C-IV</td>
</tr>
</tbody>
</table>
Buprenorphine (Buprenex, Suboxone) C-III

- Semisynthetic thebaine derivative
  - agonist at \( \mu \)- \( \kappa \)- and \( \delta \)- receptors
- \( T_{1/2} = \sim 37 \) hours (20-70 hours)
- P450 CYP3A4 (*high 1st pass*), Phase II
- Indications: *moderate to severe chronic pain or peri-op analgesia & opioid drug dependence.*

Routes: Sublingual, IV/IM, TD, PO

Lots of individual variation!!
Pentazocine (Talwin) C-IV

Talwin NC = pentazocine + naloxone

• Kinetics
  – Synthetic, \(\kappa\)-\(\sigma\)-agonists
  – \(T_{1/2} = 2-3\) hours

• Indications
  – Mild to moderately severe pain, pre-anesthesia, or supplement to surgical anesthetic

• Issue
  – May precipitate withdrawal in patient using chronic opioid such as methadone

Routes: IV/IM, SC (may cause severe tissue damage), PO (contains naloxone)

\[T’s \text{ & Blues = Heroin substitute.} \]
\[IV \text{ of crushed pentazocine tablets with an antihistamine}\]
Mixed Opioid Agonists-Antagonists & Partial Agonists

Butorphanol (Stadol) C-IV

- Synthetic, ⊕ & ⊖ μ- and ⊕ κ- receptors
- IV, intranasal spray
- $T_{1/2} = 4-7$ hours
- P450 & Phase II
- Used for migraine, moderate to severe pain

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In veterinary medicine, super potent opioids may be used, including, etorphine (M99) at 1K X morphine and carfentanil (Wildnil) at 10K X morphine
Mixed Opioid Agonists-Antagonists & Partial Agonists

Nalbuphine (Nubain)

- Synthetic, works better in women, than men and may ↑ pain in men. Analgesia similar to morphine.
- IV, SubQ, IM
- $T_{1/2} = 3$-$6$ hours
- P450 & Phase II
- Used for moderate to severe pain, surgical anesthesia or analgesia
Other Opioid Agonists

Oxycodone (OxyContin) C-II
- Semisynthetic from thebaine
- P450 metabolism
- Renal excretion
- Used PO as an analgesic for moderate to severe pain

Percodan = oxycodone + aspirin
Percocet = oxycodone + APAP
Other Opioid Agonists

Tramadol (Ultram) C-IV

- Synthetic, atypical with multiple MOA
  - 13-50% of patients experience seizures
  - Increased risk of suicide
- $T_{1/2} = 5-7$ hours (parent, longer for metabolites)
  - P450 CYP2D6 → stronger active metabolites
- Used as an analgesic for moderate to severe pain

It ⊗ NE & 5-HT reuptake - Serotonin syndrome Alert

May induce seizures at therapeutic doses, especially if taken with: MAOIs, TCAs, SSRIs, other opioids, neuroleptics, AEDs, or drugs that lower seizure threshold
Other Opioid Agonists

• Dextromethorphan (DXM or DM, Robitussin, Vicks 44, Percussin, etc.)

  – OTC, derived from opioid, but **not a narcotic.**
    
    It may trigger histamine release

  – Available PO

  – $T_{1/2} = 1.5\text{-}4$ hours

  – P450 CYP2D6 mostly, some 3A4 & 3A5

  – Used as a **cough suppressant**, it interacts with the NMDA and $\sigma$ receptors (It acts centrally to suppress cough)
That’s it for opioids… now on to the non-narcotic analgesics and gout medications.

This next section covers musculoskeletal pain, such as arthritis.
Part 2: Non-Narcotic Pain Relief

• Introduction to NSAIDs
  – Antiinflammatory, analgesic, antipyretic and anticoagulant agents

  • Nonsteroidal antiinflammatory drugs, or NSAIDs
    » Most are organic acids
    » Usually chemically unrelated
    » Share certain therapeutic actions and side effects
    » The prototype is aspirin
Shared Therapeutic Activities of NSAIDs

• Antipyretic, analgesic, anticoagulant & anti-inflammatory
  – *Except for acetaminophen (which is NOT an NSAID)*

• Effective against pain of low-to-moderate intensity
  – Better for *musculoskeletal* than *visceral* pain
    • *Except for dysmenorrhea where XS PGs cause pain*

• No Δ in the perception of sensory modalities other than pain.

*May cause SIADH*
Antipyretic effect

- NSAIDs control Fever caused by:
  - Tissue damage
  - Inflammation with or without infection, graft rejection or malignancy

- Body temperature controlled by the hypothalamus
  - Insult causes the release of Cytokines (Interleukins and Tissue Necrosis Factor-α)
    - ↑ synthesis of PGE₂ in hypothalamic area
    - PGE₂, via ↑ in cyclic AMP → the hypothalamus to ↑ Bₜ° by ↑ heat generation and ↓ heat loss.

- NSAIDs ↓ fever by ⊗ the synthesis of PGE₂
Pain Relieving effects

• NSAIDs usually are **mild** analgesics
  
  – Analgesic efficacy determined by type of pain and intensity.
  
  – Particularly effective **BEFORE** inflammation has caused **sensitization of pain receptors** to **normally painless** mechanical or chemical stimuli.

• Pain that accompanies inflammation and tissue injury
  
  – results from local stimulation of pain fibers **especially by Bradykinin and Histamine**

  – *Analgesic effects due to inhibition of prostaglandin synthesis.*
Anticoagulant effect

- **NSAIDs** \(\Theta\) synthesis of thromboxane (TXA\(_2\))
  - TXA\(_2\) promotes **platelet adhesion**

**Basic mechanism for clot formation**

- **Blood vessel damaged and releases collagen**
- **Platelets are attracted and bind to collagen forming a plug**
  - and are stimulated to release autacoids including TXA\(_2\)
- **Fibrin stimulated to form and covalently bind**
- **RBCs become stuck in matrix with more platelets**
Anti-Inflammatory effect

- Inflammatory responses
  - three distinct phases
  - mediated by different mechanisms
- Acute transient phase
  - characterized by local vasodilatation and increased capillary permeability
- Delayed, subacute phase
  - most prominently characterized by infiltration of leukocytes and phagocytic cells
- Chronic proliferative phase
  - tissue degeneration and fibrosis occurs.

Dominated by autocoids - complement proteins (e.g., anaphylatoxins), PGs, LTs, NO, cytokines, bradykinin, histamine, serotonin, etc.
# Shared NSAID Side Effects

*Adapted from Goodman and Gilman’s 11th Ed., p 683*

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Abdominal pain, nausea, anorexia, gastric erosions, perforations, hemorrhage or ulcers, anemia, diarrhea (all less with selective COX-2 drugs), worsening of inflammatory bowel disease</td>
</tr>
<tr>
<td>Renal</td>
<td>Salt &amp; H2O retention leading to edema, hyperkalemia, ↓ in the effectiveness of antihypertensives &amp; diuretics</td>
</tr>
<tr>
<td>CNS</td>
<td>Headache, vertigo, dizziness, confusion, depression, lowering of seizure threshold, hyperventilation (salicylates)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Platelet activation, ↑ bruising &amp; hemorrhage (with long term or high dose use)</td>
</tr>
<tr>
<td>Uterus</td>
<td>Prolongation of gestation, Θ labor</td>
</tr>
<tr>
<td>Immune</td>
<td>Vasomotor rhinitis, angioneurotic edema, asthma, urticaria, flushing, hypotension, shock</td>
</tr>
<tr>
<td>Vascular</td>
<td>Closure of the ductus arteriosus in the fetus, hypertension, congestive heart failure</td>
</tr>
</tbody>
</table>
Mechanism of Action of NSAIDs

• The principal therapeutic effects of NSAIDs
  – Related to \( \Theta \) prostaglandin production
    • \( \Theta \) the enzymes involved in prostaglandin synthesis.
      – Prostaglandin endoperoxide synthase, or fatty acid cyclooxygenase (COX)
      – The first enzyme in the prostaglandin synthetic pathway
      – This enzyme converts arachidonic acid to the unstable intermediates PGG2 and PGH2.

• There are two forms of cyclooxygenase
  – cyclooxygenase-1 (COX-1)
  – cyclooxygenase-2 (COX-2)
Mechanism of Action

• Aspirin
  – Covalently binds to both COX-1 and COX-2
  – Resulting in an irreversible $\otimes$ of all COX activity.

10% of people develop bronchospasm
• Due to shift from PG synthesis to LTs
• LTC$_4$, and metabolites, 1,000’s X more potent than histamine at triggering bronchospasm
• COX$_2$ inhibitors don’t do this

Aspirin-induced Exacerbated Respiratory Distress (AERD) and NSAID-induced rash are due to a shift from PG to LT synthesis. LTs also cause Mast cell degranulation.
Function of COX

• COX-1
  • Expressed in all tissues
  • Has a variety of homeostatic physiologic functions. Produces:
    • Protective prostaglandins in the kidney and stomach, proinflammatory PGs everywhere
    • Thromboxane in platelets.

• COX-2
  • Not normally found in most tissues
  • Expressed under conditions of tissue damage
    • Plays an active role in the inflammatory response.
Insult

Corticosteroids

Arachidonic Acid

Dietary Ω3 FA substitution

Phospholipase

Insult

COX

NSAIDs

Leukotrienes

Lipoxygenase

Prostaglandins

Prostacyclin

Thromboxane

Zileuton (LOX inhibitors)

Receptor level antagonists Montelukast (Singulair)

Leaky vessels Bronchoconstriction ↑mucous production (congestion…)

WBC attraction and activation

WBC aggregation

Etanercept (Enbrel)

Cytokines

Inflammation, fever
Functions of Prostaglandins

- Stimulate smooth muscle
  - Vasodilation or vasoconstriction
  - *Bronchospasm*

- Platelet effects
  - *Aggregate*, or not

- Sensitize nociceptors to *pain*

- Regulate inflammation: pro- vs anti-inflammatory roles

- Stimulate *fever*

- Modulate Ca\(^{++}\) movement

- Control hormones, cell growth, WBC function
Aspirin Pharmacokinetics

• *Absorption.*
  – PO - Bioavail ~100%

• *Distribution.*
  – Throughout most body tissues and fluids
  – Readily crosses the placental barrier.
  – PPB is as much as 90+% 

• *Biotransformation and Excretion.*
  – The biotransformation occurs in many tissues, but mostly in the liver via Phase II processes.
  – Excretion: kidneys. $T_{1/2} \sim 3$ hrs.
Aspirin Actions

• Platelets
  – Are especially susceptible to aspirin-mediated irreversible inactivation of COX
  – Little or no capacity for protein biosynthesis and cannot regenerate COX.
  – In practical terms, this means that a single dose of aspirin will \( \times \) COX for the life of the platelet (8 to 11 days)
    • In humans, a daily dose of aspirin as small as 40 mg is sufficient to produce this anticoagulant effect.
Analgesic effects of Aspirin

• Low intensity pain
  – From integumental structures rather than from viscera
    • Especially headache, myalgia, and arthralgia.
  – Aspirin is more widely used for pain relief than any other type of drug - up to 20 tons/yr in US.

• Long-term use does not lead to tolerance or addiction

• Toxicity is lower than that of opioid analgesics.
  – Aspirin overdose is a medical emergency
    • Metabolic acidosis
    • Pulmonary edema
Toxicity

• Symptoms and Signs.
  – Mild chronic aspirin intoxication = salicylism.
  – Headache, dizziness, tinnitus, deafness, dimness of vision, mental confusion, stupor, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting, and occasionally, diarrhea.
  – More severe aspirin intoxication is characterized by more pronounced CNS disturbances (including generalized convulsions and coma), skin eruptions, and marked alterations in acid-base balance. Fever is usually prominent.

• Treatment.
  – An acute medical emergency
  – Death may occur despite treatment
Figure 36-4. Approximate relationships of plasma salicylate levels to pharmacodynamics and complications. (Modified and reproduced, with permission, from Hollander J, McCarty D Jr: Arthritis and Allied Conditions. Lea & Febiger, 1972.)
Hepatic Effects of Aspirin

- **Dose-dependent Hepatotoxicity**
  - Typically when plasma concentrations are maintained above 150 mg/ml.

- **Reye's syndrome (not dose-dependant)**
  - Severe hepatic injury and encephalopathy
    - 30% mortality rate
  - This syndrome is a rare but often fatal consequence of infection with varicella and other viruses, especially the influenza virus, and aspirin.
  - Unknown mechanism, but aspirin and the viral illness may act to damage mitochondria

*The use of aspirin in children or adolescents with chickenpox or influenza is contraindicated.*
### Salicylates

*Adapted from: Focus on Nursing Pharmacology, 4th ed., by AM Karch. Lippincott, Williams and Wilkins*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Fever, pain, inflammation; at low doses to prevent MI and transient ischemic events</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>Mild to moderate acute ulcerative colitis</td>
</tr>
<tr>
<td>Choline salicylate</td>
<td>Mild pain, fever, arthritis</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>Ulcerative colitis and other inflammatory bowel disease</td>
</tr>
<tr>
<td>Sodium thiosalicylate</td>
<td>Gout, muscle pain, rheumatic fever</td>
</tr>
</tbody>
</table>
### Other NSAIDs

*Adapted from: Focus on Nursing Pharmacology, 4th ed., by AM Karch. Lippincott, Williams and Wilkins*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Celecoxib (Celebrex)</strong> 🚒 -C</td>
<td>Acute arthritis, pain, dysmenorrhea, colorectal polyps</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Acute and chronic inflammation-related pain</td>
</tr>
<tr>
<td><strong>Ibuprofen (Advil)</strong> 🚒 -B/D</td>
<td>Pain, arthritis, dysmenorrhea</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Short-term pain management, arthritis, ophthalmic formulation for ocular itch</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Acute and chronic arthritis</td>
</tr>
</tbody>
</table>
Nonacetylated Salicylates - Celecoxib (Celebrex)

- **Celebrex** relieves the pain and inflammation of osteoarthritis and rheumatoid arthritis. Also used for ankylosing spondylitis and menstrual pain.
  - *Used off-label as adjuvant in schizophrenia treatment*

- It is a "COX-2 inhibitor"
  - It does not interfere with COX-1
  - Celecoxib is highly selective for COX-2 (375X more than COX-1)
  - Less likely to cause the bleeding and ulcers that sometimes accompany sustained use of the older NSAIDs.
  - It does not affect platelet aggregation.

*Robecoxib (Vioxx) withdrawn in 2004*
Nonacetylated Salicylates-

Celecoxib (Celebrex)

- Reduces colorectal polyps (growths in the wall of the lower intestine and rectum) in people who suffer from the condition called familial adenomatous polyposis (FAP),
  - An inherited tendency (autosomal dominant) to develop large numbers of colorectal polyps that eventually become cancerous.
  - 1,000s of polyps start growing at puberty
  - Cancer by 20-30 years old
Celebrex Toxicity

• Serious liver damage
  – Warning signs of liver damage are nausea, vomiting, tiredness, loss of appetite, itching, yellow coloring of skin or eyes (jaundice), “flu-like” symptoms and dark urine.

• Effects on vision
  – Blurred vision
  – Ocular pain
  – Conjunctivitis

• Serious kidney effects
  – Includes sudden kidney failure
  – Worsening of pre-existing kidney problems

• Edema
  – Fluid retention can be a serious problem if high blood pressure or heart failure is also present

NSAIDs as a class share these effects
Celebrex toxicity

• Celebrex contains a sulfonamide derivative
  – Stevens-Johnson syndrome.
  – Symptoms usually start within 1-4 weeks from the onset of starting drug therapy.
    • They can start within hours or days
  – Symptoms:
    • Mild rash, or mucosal lesions or fever of an unexplained origin. Mucosal lesions include lesions of the mouth, eyes, GI and respiratory tract, anus and vagina
    • Skin rash that may progress to epidermal sloughing
    • May cause permanent vision loss

Boxed warnings: CV risk, GI bleeding risk
Propionic acid derivatives

- *Ibuprofen (Advil), naproxen, fenoprofen, ketoprofen, and oxaprozin*
  - Pharmacodynamics pretty much the same for the class
  - Effective reversible COX inhibitors
    - Considerable variation in their potency. For example, naproxen is approximately 20 times more potent than aspirin, while ibuprofen, fenoprofen, and aspirin are roughly equipotent as COX inhibitors.
  - Alter platelet function
    - Prolong bleeding time
  - Assume - any patient who is intolerant of aspirin also may suffer a severe reaction after taking of one of these drugs.
Ibuprofen ADRs

• GI - 5-15% of patients
  – Epigastric pain, nausea, heartburn, and sensations of "fullness" in the gastrointestinal tract.

• Other
  – thrombocytopenia, skin rashes, headache, dizziness and blurred vision, and, in a few cases, toxic amblyopia, fluid retention, and edema. *Patients who develop ocular disturbances should discontinue the use of ibuprofen.*

• Ibuprofen is not recommended for use by pregnant women, or by those who are breast-feeding their infants
Other

Adapted from: Focus on Nursing Pharmacology, 4th ed., by AM Karch. Lippincott, Williams and Wilkins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Acetaminophen (Tylenol) **️  🍯 -B</td>
<td>OTC Pain and fever reduction</td>
</tr>
<tr>
<td><strong>Aurothioglucose</strong></td>
<td>Rheumatic disorders</td>
</tr>
<tr>
<td><strong>Etanercept (Enbrel) 🎈 -B</strong></td>
<td>Severe rheumatoid arthritis, ankylosing spondylosis, psoriatic arthritis. Disease Modifying Anti-Rheumatic Drug (DMARD). Route: SC only</td>
</tr>
<tr>
<td><strong>Penicillamine</strong></td>
<td>Severe rheumatoid arthritis</td>
</tr>
<tr>
<td><strong>Hyaluronic acid (Hyalgan) 🎈  🍯 -C</strong></td>
<td>Injected into the knee to relieve arthritis pain Routes: Topical, SC, intra articular injections</td>
</tr>
</tbody>
</table>
Acetaminophen

**OTC**

APAP added to >950 OTCs!!

- Effective alternative to aspirin as a non-narcotic analgesic-antipyretic agent
  - *Not an NSAID*!!
  - *Not an anticoagulant*

- Anti-inflammatory activity is poor.
  - *Okay for osteo-, not for rheumatoid arthritis*
  - Acetaminophen is a weak (reversible) inhibitor of COX in the presence of the high peroxide concentrations found in inflammatory lesions

*Actual mechanism not understood, APAP may Θ a 3rd form of COX in CNS*

AKA Paracetamol

PO, PR, IV
APAP Pharmacokinetics

APAP = N-acetyl-para-aminophenol = Acetaminophen

• Absorption
  – PO - bioavailability almost 100%
  – Cholestyramine ↓ absorption

• Distribution
  – Uniform tissue distribution

• Metabolism
  – Liver conjugation, T_{1/2} ~ 2 hours

• Excretion
  – Renal

Toxicity Warning
>1,000 mg/dose,
>4,000 mg/day (adults)
or
>2,000mg/day if consuming alcohol, can saturate metabolic pathways leading to toxicity

Institute for Safe Medication Practices (ISMP) reports
~1 hospitalized patient/day exceeding 4 gram/day limit
Toxicity of Acetaminophen

• Metabolism has a rate limiting step
  – APAP is *metabolized to a highly reactive intermediate* (N-acetyl-p-benzoquinoneiminem, NAPQI).
  – Large doses can *deplete hepatic glutathione*, the next conjugating step.
  – NAPQI then reacts with (sulfhydryl groups in) hepatic proteins causing *irreversible, potentially fatal, hepatotoxicity*.
  – #1 cause of acute liver failure in the US & Europe
    • In US - 140K poisonings/yr; >100 deaths
  – N-acetylcysteine (Mucomyst) acts to detox NAPQI
Etanercept (Enbrel)

- Recombinant DNA drug
  - \( \ominus \) TNF-\( \alpha \) (*tissue necrosis factor alpha*)
    - Immunosuppressant (Disease-modifying anti-rheumatic drug, or DMARD)
    - Must be injected (SC), once or twice per week
  - \( T_{1/2} \) 70-130 hours

- Wide usage in rheumatology
  - Rebound “flare” = relapse that can’t be controlled
  - Potential *indications* for Alzheimer’s, influenza

Other anti-TNF drugs: Infliximab (Remicade), Golimumab (Simponi) & Adalimumab (Humira)

Part of an \( IG_{(1)} \) it mimics the receptor that inactivates TNF

Refrigerate

Boxed warning: potential for serious infections
Hyaluronic acid or Hyaluronan (Hyalgan)

- Glucosaminoglycan found in connective tissue
  - Major component of synovial fluid and skin
    - Lubrication
    - Repair

- Indications
  - Wound dressing (Bionect)
  - Osteoarthritis & eye surgery (Shellgel, Hyalgan, Synvisc)
  - Smooth out facial wrinkles (Juvederm, etc.)
  - Dry, scaly skin treatment (Hylira)
Gout

• Undersecretion of uric acid *(metabolic arthritis)*
  – Causes urate crystals to precipitate in tissues
• Drugs
  – NSAIDs
    - Colchicine
      • Mitotic spindle poison, Unk. Mech., in use since 6\textsuperscript{th} century
    - Allopurinol (Zyloprim)
      • Blocks urate synthesis by \(\Theta\)’ing xanthine oxidase
    - Rasburicase (Elitek)
      • Recombinant urate oxidase makes uric acid water soluble
    - Probenecid (Benuryl)
      • ↑ uric acid excretion by \(\Theta\)’ing organic acid reabsorption
      • *Also indicated to ↓ excretion of penicillin antibiotics*