PAIN

Pain consists of the sensation of pain (nociception) and the emotion of perceiving pain (suffering). **To stop pain** you can either (broadly speaking): blunt or **reduce the cause of the pain (anti-inflammatories), reduce the transmission of pain (local anesthetics) or reduce the perception of pain (opiates & Tylenol)**. Numerous neurotransmitters and signaling molecules are involved in the response, transmission and perception of pain.

Analgesia = reduction of pain **Anesthesia** = loss of sensation

NARCOTICS/ENDORPHINS (Opiates/Opioids)

Endorphins are the "natural opiates" found in the brain
responsible for the **"natural high**" as experienced by runners and thrill seekers)

Bind three types of opiate receptors (called **Mu**, Delta and Kappa.)
Found in gray matter of the cerebral cortex (and throughout the body, including GI tract!)

*Note on terminology: The term "**opiate"** originally referred to a naturally occurring drug derived from opium like morphine, heroin or codeine, whereas "**opioid"** meant a synthesized drug such as oxycodone. Nowadays, almost everyone uses the terms interchangeably.* ☺

This is a good drug class to introduce the term: "**partial agonist"** & "**agonist-antagonist**"
a **partial agonist** drug has only partial efficacy compared to the natural ligand
example: buprenorphine
agonist-antagonist drugs stimulate one subtype of receptor but block another.
example: pentazocine: blocks Mu but stimulates Kappa

Some Agonist drugs: **morphine**
codeine,
hydrocodone (in *Vicodin*® & *Norco*® with acetaminophen),
fentanyl,
meperidine *(Demerol),* heroin, methadone, oxycodone *(Oxycontin)***,** others

Antagonists: **naloxone** *(Narcan):* direct-acting antagonist. blocks opiate mu receptors **naloxone** is used for **opiate overdose** and **is available OTC** (ask pharmacist)

Therapeutic Effects:

1. **Block pain mostly centrally** (in the brain)
   by changing whether your brain decides the pain is mild or severe.

2. ***stop*** **coughing** (**dextromethorphan**) – **DM** in cough medicine
   commonly abused by misinformed teenagers "robotrippin'"
   cross-reacts with NMDA receptors to cause **dissociative state** much like ketamine

3. ***stop*** **diarrhea (by causing constipation**): block Mu receptors in gut
   examples: diphenoxylate *(Lomotil),* **loperamide** *(Imodium)*)
   Do not cause euphoria or relieve pain
   To combat **opiate-caused constipation,** newer **opiate antagonists that do not cross the BBB** bind mu receptors in the GI tract to reverse constipation caused by opiate pain medications. Example: methylnaltrexone (*Relistor)*

Side effects: miosis (small pupils), urinary retention, vomiting, euphoria
orthostatic hypotension (induces histamine release which dilates blood vessels)

Current opioid epidemic (prescription, heroin and designer fentanyl derivatives) has led to a political and federal mandates reduction in opioid production in US, leading to shortages in hospitals and pharmacies, as well as prosecution of doctors who prescribe opiates to patients. Meanwhile, opioid abuse is now the **leading** cause of injury-related death in the US.

See also reading: Srivastava B Beyond Supply: How We Must Tackle the Opioid Epidemic (2018) *Mayo Clin Proc.* 93(3):269-272 n https://doi.org/10.1016/j.mayocp.2018.01.018 https://www.mayoclinicproceedings.org/article/S0025-6196(18)30067-3/fulltext

Opioids, continued: Usual cause of overdose death: **<u>Respiratory (Medullary) Depression</u>**:
This is why **you pay attention to respiratory rate (RR) while giving IV opioids!**

Prescription opioids (often obtained illegally) cause more deaths than car accidents

Outpatients MUST NOT take opiates with other respiratory depressants
(like alcohol, benzodiazepines, barbiturates, anesthetics)

mechanism of respiratory depression: **via inhibition of the medulla oblongata**
1) **limits the amount you can give** a patient to control pain, and
2) **causes death** when patients **abuse** the drug (i.e. do not use it as directed)

Some abusers crush PO opiate medications to inject or inhale in an attempt to get a rush of euphoria but get a fast very high blood level, which can lead to death via respiratory depression.

Newer formulations to deter patients from crushing pills to get high: Newly approved 2016: *Troxyca* is a combination of the opiate oxycodone with beads containing the antagonist naltrexone that is released if the pill is crushed, making the oxycodone ineffective and saving the patient's life!

Because of euphoria, morphine and other **fast-acting** opioids have high abuse potential

Tolerance (loss of effect over time) develops quickly to euphoria, pain, sedation (and luckily respiratory depression), so patients require **higher and higher doses,** leading to patients requiring high doses that prescribers are reluctant to give (because of prosecution of prescribers seen to be prescribing too much opioids). Patients acquire illegal sources that are not regulated, and take unknown doses, leading to tragedy.

Tolerance and dependence occurs in almost all **chronic** pain patients. (It's a myth that you won't get dependent if you take the drugs for pain.) Remember dependence is NOT addiction.

Opioids have fairly **high first-pass metabolism,** so PO doses are higher than by other routes

Critical thinking: An Italian study in the late1990s showed that most people who died from opioid overdose had abstained from opioid use for the four months preceding their deaths. Why did that happen?

Pharmacokinetics are variable as different opiates are broken down by different P450 enzymes e.g. **codeine**, a prodrug, is biotransformed by CYP2D6 into **morphine**

Question: CYP2D6 absent in some people, and superfast in other people…*How will that affect those patients' response to the drug?*

"Neonatal Abstinence Syndrome" occurs in babies born to mothers addicted to opiates, amphetamine, cocaine, marijuana, barbiturates or benzodiazepines. In the case of opiates the symptoms show up 24-48 hours after birth. **Unlike opiate withdrawal in adults, withdrawal in an infant can be fatal.** The infants sometimes have to be given methadone (a opioid agonist) and weaned off over the course of a *month*.

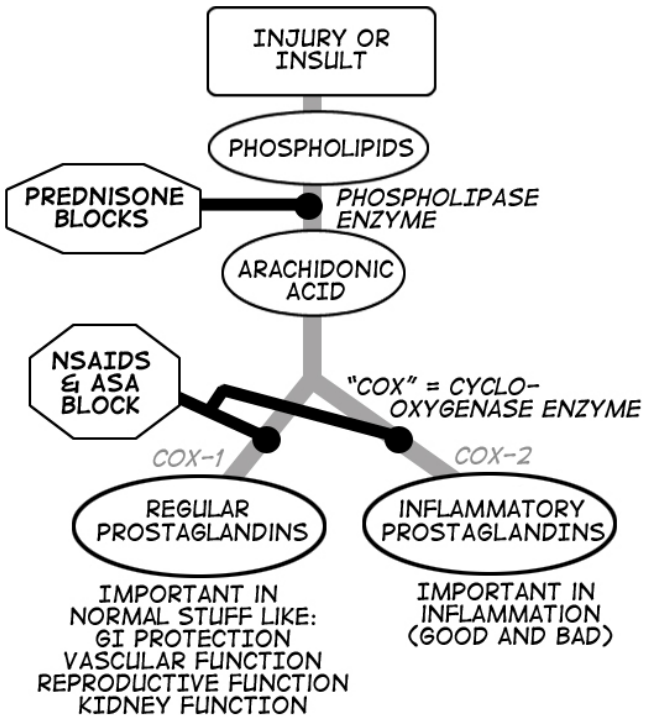
***Robotrippin'** is the term for people trying to get "high" from cough syrups like Robotussin. Although **dextromethorphan** is an opiate derivative, in moderate overdose it causes very unpleasant **ketamine-like dissociative anesthesia symptoms** *(see anesthesia section later),* and not the morphine high the users were hoping for.

NON-OPIOID ANALGESICS

ASA and NSAIDs
How do anti-inflammatory drugs work? Let's look at aspirin (ASA). **Aspirin can reduce inflammation, but it also reduces fever, relieves mild pain and prevents clotting**. How can one drug do so many things?

Whether we talk about the allergic response, or the more generalized inflammatory reaction of cells due to insult or injury (or infection), there are some common events that take place: redness, swelling, heat production and pain. *(In Latin:"rubor, tumor, calor, dolor")* This is regulated via immune cells, enzymes and other chemical mediators produced via multiple pathways.

One such pathway is the arachidonic acid pathway, which, through the action of the enzyme cycloxygenase (**COX-1, COX-2**), produces **prostaglandins** as well as other inflammatory factors. There are a wide variety of prostaglandins, and they are very useful in normal tissues in processes having nothing to do with pain or inflammation (such as protective mucus production in the stomach). In theory, the "normal" "good" prostaglandins are made by the COX-1 enzyme. The inflammatory pain-inducing prostaglandins are made mostly by COX-2.



The drug **aspirin (ASA) inhibits *both* the COX-1 and COX-2 enzymes**.
(They are "COX Blockers", although no one calls them that)

We usually use aspirin (and NSAIDS) to treat unwanted symptoms like pain and inflammation due to actions of COX-2.

Side effects of (like reduction of stomach mucus production) are usually due to the drug also blocking the actions of COX-1.

Additionally, it is critical that you understand that the **normal actions of the prostaglandins** (and related molecules like thromboxanes and leukotrienes) **have many actions** in the body, **some of which oppose each other,** which explains why **aspirin** vs **other NSAIDs** do not have the same effects.

For example: **aspirin reduces** the chance of heart attack, **but naproxen increases** the chance of heart attack. **Aspirin** and the **other NSAIDS** are **not interchangeable**.

By the way: **NSAID stands for *Non Steroidal* Anti-Inflammatory Drug.** .
Technically, Aspirin is considered an NSAID since it isn't a steroid, but because it is SO different in its effects on cardiovascular health and clotting, as well as its indications, you should think of it as a different drug.

Aspirin's effects are ***irreversible***. NSAIDS like ibuprofen ***reversibly*** inhibit COX synthesis.

A *steroidal* anti-inflammatory drug refers to cortisol agonists like **prednisone**. Glucocorticoids reduce inflammation by inhibiting phospholipase production as shown in the figure on page 1. A topical steroid you may be familiar with is **hydrocortisone**.

Also note: Unlike some opioids, pain relievers like aspirin, NSAIDS and acetaminophen have a ceiling to the pain relief they can provide, **so more is NOT better**.

ASPIRIN (ASA)

DO NOT confuse aspirin with other salicylates like:
methyl salicylate (*BenGay, Oil of Wintergreen*) – poisonous PO, used topically only
trolamine salicylate *(Aspercreme)*
para-amino-salicylic acid : bacteriostatic against tuberculosis
salicylic acid: topical acne drug that burns off top layers of skin
bismuth subsalicylate (*Pepto Bismol):* prevents bacterial adherence to GI mucosa

stands for Acetyl Salicylic Acid**)**

chemical class is "**salicylates**"
because there is a salicylate structure in the molecule.

Indications: **pain:** at usual 325mg dose
fever: at usual 325mg dose
inflammation: usually requires *very high* doses
stable **angina** *(see unit 3)*
some types of acute MI
a history of MI, angina, CVA, TIA
-ASA is an "antiplatelet" drug
-for anticoagulation, a **low dose 81mg/day** is as effective as the higher doses but does **NOT** increase risk of GI ulcer.
low dose ASA may also reduce risk of colon and prostate cancer!

NOTE: concomitant chronic use of other NSAIDS will negate the beneficial effect of low-dose aspirin therapy to prevent <u>recurrent</u> MI and stroke

Contraindications for Aspirin:
Stomach Ulcers
Children under 18, esp. those with **flu/fever** symptoms: **Reye's Syndrome!**
Pregnant women (esp. third trimester) Pregnancy Category D
concern is premature closure of **ductus arteriosis** (see below)
Bleeding or bleeding disorders
One low dose ASA can prolong bleeding time for up to two weeks!
Be especially careful about possible bleeding into the brain or spinal cord
"**Samter's Triad**": 1. **nasal polyps**
2. **asthma**
3. **allergy-*like* reactions to ASA/NSAIDS**
Note: Patients can also be truly allergic to ASA & NSAIDs

Side Effects: Bleeding, GI disturbances (**GI bleeding**, stomach upset, diarrhea, nausea etc)
Only at higher doses!
ASA Toxicity aka **"Salicylism"**: **tinnitus**, **tingling in fingers**
High levels of ASA in bloodstream lowers pH (this is called metabolic acidosis)
In response, rapid breathing/panting increases the blood pH!
(that effect called respiratory alkalosis it's so cool!)
Severe poisoning: seizures, coma

Beware aspirin disguised in other OTC and prescription products such as
Anacin, Excedrin, percodan, Alka-Seltzer, Pamprin, OTC migraine drugs

NSAIDS like ibuprofen

ibuprofen (*Advil*, *Motrin*)
<u>Indications:</u> **pain**
fever
inflammation (can take 3-10 days to get maximum effect)
very high dose NSAIDs are used for some types of arthritis

patent ductus arteriosus in babies born premature (used in IV form)

Contraindications:

Cardiovascular or cerebrovascular disease

BLACK BOX WARNING 1: increased risk of MI or CVA with increased dose and duration of use.

BLACK BOX WARNING 2: causes GI disease (ulcer, etc)

Bleeding: ibuprofen prolongs bleeding time mildly, but not in a useful way.

Kidney disease, heart failure,

Pregnant women (esp. third trimester) Pregnancy Category D

Ibuprofen can close the ductus arteriosus, right? You don't want that to happen until after the baby is born and can breathe air!

Allergy and/or **Samter's Triad**

Side effects: **GI ulcers, GI bleeding**

Toxicity: (GI injury can be prevented with the **prostaglandin agonist misoprostol**)

Blurred vision, tinnitus similar to salicylism

Kidney failure :-(

Also, different NSAIDs seem to act preferentially on different areas of the body.
Ex. **ibuprofen** is particularly good for **menstrual cramps** as compared to some other NSAIDS.

LONG-TERM use of NSAIDs like ibuprofen **negate the beneficial actions of antiplatelet drugs like ASA** or *Plavix*. An ibuprofen now and then is fine, don't panic.

Drug interactions: anticoagulants, lithium, SSRIs, loop diuretics, beta-blockers, ACE inhibitors, (high protein binding)

Other NSAIDS that are like ibuprofen: All carry the same black box warnings

1. naproxen (*Aleve*): PO

Naproxen also comes in combination with a proton pump inhibitor lansoprazole in OTC formulation called *Prevacid*.

Note: Some recent correlative studies suggest that naproxen may not be as likely to cause MI or stroke as ibuprofen.

2. ketorolac (*Toradol*): Used PO, **IV, IM** and as eye drops for post-surgical pain

(Eye drops don't carry a black box warning)

3. celecoxib (*Celebrex*): A COX-2- specific NSAID

Indications: severe **arthritis** (various forms)
juvenile arthritis
ankylosing spondylitis (severe back arthritis seen usu. in young men)
familial adenomatous polyposis (FAP) colon polyps -*weird!)*

Celecoxib *theoretically* was not going to cause the COX-1 side effects of other NSAIDS. It *does* reduce GI side effects but reduction of GI toxicity is lost if *any* other NSAID is added, including low-dose aspirin. Also, it still **increases risk of MI** (by four-fold!!)

Tylenol®

acetaminophen (*Tylenol*) is chemically a para-aminophenol derivative:

Mechanism of action: Acts **centrally** in the brain to reduce pain and fever.

Lab evidence shows that acetaminophen also acts on prostaglandin synthesis, but only centrally (in the brain). Perhaps there is a brain-specific COX-3 enzyme? Still not clear.

Indications: **pain, fever** (no action on inflammation)

Contraindications: **liver disease**, **alcoholism**, some anemias

Pharmacodynamics: **Metabolized in the liver to a very toxic metabolite that is normally immediately neutralized by glutathione**. In liver disease or overdose, this toxic metabolite kills liver cells.
The metabolite is neutralized also by **N-acetylcysteine.** ⇐ the antidote for poisoning

Side effects/toxicity: Acutely: **hepatotoxicity**
Increased lifetime dose increases chance of kidney failure later in life

VERY LOW TI
Acetaminophen poisoning: Single dose: **>7.5-10g** (liver changes seen as low as **4g** if fasting)
toxicity with chronic use is ~ 4-6g/day
(kids 0-5y: 200 mg/kg over 8 hours, over 6y 200 mg/kg over 24 hours)

Toxic **chronic** dose: 4 g/d in adults, 75 - 150mg/kg in children)

Horribly, **it takes up to two weeks to die from a toxic dose.**

Toxicity timeline: Stage 1: GI symptoms (nausea), may not start for 12 hours after dose
Stage 2 (24-72 h): increased LFTs (liver function enzymes)
Stage 3 (72-96 h): liver failure
Stage 4 (**up to 14 days later**): death or recovery with liver transplant

N-acetylcysteine (the "antidote" to acetaminophen) **must be administered in the first 24 hours**

Beware acetaminophen in other OTC and prescription drugs: Tylenol with codeine, Nyquil, Percocet, Vicodin,Alka-Seltzer Aspirin-free, Benedryl Allergy Sinus, Dimetapp, Theraflu

Several drug interactions: **alcohol**, warfarin, carbamazepine, phenytoin, others

New labeling intended to make dosing easier to understand and reduce risk of overdose

Example: Extra-strength 500mg Tylenol (and generic clones)
Take 2 caplets (1,000 mg) every 6 hours while symptoms last (revised from 2 caplets every 4 to 6 hours).
Do not take more than 6 caplets (3,000 mg) in 24 hours (revised from 8 caplets in 24 hours).
"Severe liver damage may occur if more than 4,000 mg of acetaminophen is taken"

Fun Fact! In Europe acetaminophen has the generic name "paracetamol" or "APAP" because a different guy in the UK discovered it at the same time as an American guy and they stubbornly named it two different names!
(APAP because the chemical name N-Acetyl-P-AminoPhenol)

Headache and Migraine Drugs

According to my neurologist Tim Hain, there are over >100 types of headaches. So not every drug works for every patient's achy head

Major classes used to treat "headache" or "migraine" are:
OTC Pain relievers: **ASA, NSAIDs, Acetaminophen**
Caffeine (for caffeine-withdrawal headaches that are very commonly misconstrued by patients to be migraines)
Triptans (constrict blood vessels and block pain awareness in the brain)
These drug names end in **-triptan**

ex. sumatriptan

Ergots

Used at the onset of a migraine
Can make vomiting worse
Drug names end in **-ergot**

Opioids

Glucocorticoids

Anti-nausea drugs (see GI Lecture)

American Headache Society Guidelines for Newer Migraine Treatments just released Oct 2018

In general: Use preventative meds when there is very frequent migraine and/or there is significant patient disability

Proven Preventative Migraine drugs:

Beta-blockers like **propranolol,** metoptolol, timolol
Antiepileptic drugs like valproate/**valproic acid** *(Depakote),* **topiramate** *(Topamax)*
Botox
injected into muscles of neck and head every 3 months
monoclonal antibodies to CGRP or CGRP receptor
like erenumab, fremanezumab, galcanezumab
frovatriptan

Probably effective prevention drugs but not yet proven (Oct 2018)

venlafaxine *(Effexor),* amitriptyline *(Elavil),* atenolol, nadolol

Other things people try:

Magnesium, Vitamin B2, calcium channel blockers (CCBs), ACE Inhibitors, ARBs, alpha-agonists, clonidine, pindolol, antihistamines, dietary changes, derp derp derp...

...and of course, like all brain problems, poor sleep hygiene makes migraines worse...

LOCAL ANESTHETICS

Used **locally**:
Topically (creams/ gels) or Injected (infiltrative, intradermal, nerve block, epidural, etc.)

Many available OTC (over the counter): potential for overdose

Mechanism of action: affects permeability of voltage-gated sodium
(Na+) channels by binding receptors on the channels themselves

LAs first block small fibers with smaller myelin sheaths, so:
Order of loss of nerve function: Pain ⇒Temperature ⇒Touch

They recover from LAs in reverse order.
Why does your dentist tell you not to eat for an hour after dental work?

Adjuncts:
Bicarbonate: LAs are weak bases, so bicarbonate is added to solution to allow the drug to penetrate myelin and get to nerves.

Epinephrine: Local vasoconstriction of blood vessels (⇓blood flow)
Increases duration of action (slows loss of the LA)
Usually ***very*** diluted (i.e. 1:200,000)

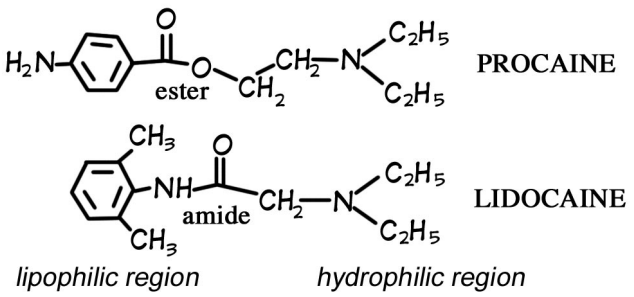
Overdose: **First complains of weird taste in mouth.**
Then, hypotension (↓BP) , ↓heart rate and arrhythmias
CNS effects direct neural toxicity at very high doses
(dizziness ⇒agitation ⇒ tremor⇒ seizure ⇒coma ⇒ death)

Black box warning for some drugs for heart patients, pregnancy

<u>TWO MAIN CLASSES of Local Anesthetics</u>

ESTERS
Metabolized by plasma cholinesterases
allergy more common than for amides
-patients are allergic to a metabolite of the drug

Examples: **procaine** *(Novocain),* benzocaine *(Solarcaine)*
because of **allergy issues**, rarely used by dentists



AMIDES
Longer acting than esters
Metabolized by liver with some active metabolites
Excreted by kidney in urine

Examples: **lidocaine** *(Xylocaine, Soalarcaine, Lidoderm)*: indicated for local anesthesia and heart arrhythmias, contraindicated in patients with sulfite allergies
other amides: bupivacaine (*Marcaine*), prilocaine (*Citanest*), articaine *(Septocaine)*

Popular OTC TOPICAL Pain Killers:

Many of these compounds have been used for hundreds of years, but even now their mechanisms of action are poorly understood or attributed to placebo effect

menthol (various throat lozenges, *Icy Hot*® cream)
- inhibits pain nerves by interfering with calcium movement
  - lozenges inhibit cough only if it is caused by irritation of the throat
- "cooling effect" is due to action on cold and heat receptors (also via calcium channels)
- also shown to bind kappa opioid receptors in the lab (see opioids on next page!)
- extracted from mint plants (peppermint odor)
  - Sept 2012 FDA warning of cases of burns after topical use

methyl salicylate (*BenGay*, Oil of Wintergreen) – poisonous PO, used topically only
- inhibits prostaglandins similar to aspirin
- absorption through skin adds to this action (but **do NOT EVER take internally**!!!!)

trolamine salicylate (*Aspercreme)*- no convincing proof OTC is better than placebo

capsacin - the hot molecule that makes chili peppers hot
- low doses found in over-the-counter medications are only modestly better than placebo
- high doses given in clinic setting (can cause burns) helpful in some pain types
- binds its own receptor (TRPV1) and changes pain receptors and nerves in several ways
  - including changes in calcium movement
- may have role in coughing
- does increase blood flow in area applied

camphor - also binds a variety of receptors involved in pain and cough
- binds TRPV1, TRPV3 and TRPA1

Counter-irritants: Menthol, camphor, capsacin, and methyl salicylate are often cited by all-natural enthusiasts as example of "counter-irritants", compounds that cause superficial pain to relieve deeper pain
- There is very little evidence that these are better than placebo to relieve pain
- Previous theories about substance P depletion as a basis for the idea disproved
- Other promoted counter irritants include: turpentine, iodine, mustard

Also consider the placebo effects of rubbing, moisturizing, odors or the sensation of hot or cold when evaluating the actions of many OTC and all-natural topicals.