# PAIN

## prescription
- $300 billion per year (US)
- requires doctors prescription

take these more but as you get older you need more prescription as your body wares out

## Over the counter (OTC)
- $25 billion per year (US)
- no prescription required
- some are "behind the counter"

## TOP OCT drugs
- Cough & cold $8.2 bil
- pain reliever $4.1 bil
- Antacid $2.7 bil
- tooth paste $1.5 bil
- laxative $1.3 bil

## to consider when buying
very safe, dangerous drugs need prescriptions
- safety
- Indications
- Counter-indication

## DOSE MAKES THE DRUG
- dose doesn't have to do with how bad the pain is rather how large your body is (but 2 isn't going to harm a smaller body)

## DOSE MAKES THE POISON
- If you go alittle over it won't hurt you as they put a rather larger margin for error

side effects → working
- All useful drugs have side effects

need both to evaluate the risk
- Effect - what is it
  - Info is easy to find
  - label or box
  - google
- Incidence - how common is it?
  - info is difficult to find (best found on FDA)

## Indications (easier to treat if you know the cause)
- What to use for?
- many people take the wrong drug
- many people take drugs unnecessarily

## Counter Indications

- when you should NOT use
  - Conditions (ex, pregnancy and many drugs)
  - drug combinations
  - foods
  - "Natural" remedies/supplements (some have ingredients that interfer with medication)

## Willow Leaves

- Sumerians used for pain in 2,200 BC
- Egyptians used for inflammation

## The dark ages

- Knowledge of herbs was lost in dark ages
- Church was the only place for medical information and if the church didn't agree it was discarded

### Reverend Edward Stone (1702 - 1768)

- rector in Church of England
- Described treatment for ague (or fever) in 1763
  - went for a walk and tasted the willow bark randomly and realized it was bitter an knew a medicine was like that so it could possibly treat ague

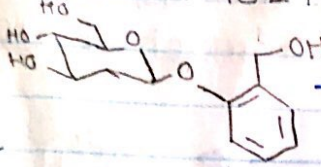
#### Doctrine of signature

- Association between disease and cure
  - people how live near swamps get malaria
  - people w malaria get fevers
  - treat malaria w quinine
  - quinine is bitter
  - willow bark is bitter
  - willow grows in swamps
  - willow bark will cure fever!
    - dried bark, ground into powder, given for fever (it works)

Down sides to willow

- Expensive (only rich people could afford to have it formed)
- limited supply (only found in swampy areas)
- variable effectiveness (no indecator of how much active ingredient is in each piece)

Salicin → turns into salicyclic acid in body
→ Active ingedient in willow
→ isolated in 1829



Chemical structures (really look like drawing)
- represent shape & function of molecule
- match shapes to match function

* very important to see how molecule will work in the body

you get alittle salicin from alot of bark
→ Salicin was converted to salicyclic acid in 1838
→ occurs in meadowsweet flowers

manufactured from (waste product in 1800s) ← Coal Tar (using Kolbe-schmitt reaction)
- lowers price
- avalible in large quantities

→ better in smaller doses
→ helps · Analgesic (pain)
· Antipyretic (fever)
· Antiflammatory (swelling)

## Synthetic Vs. Natural

Natural
- directly from plant or animal (natural source)
  - ex; 2 millon tonnes willow bar produces 58 billon tablets
  - has smaller supply

Synthetic (meaning manufacture from oil)
- man made material
  - ex; 62,000 tonnes of oil produces 58 billion tablets
  - usually made in mass quantities and are cheaper and takes less time

product you get is exactly the same product

salicylic acid was made and sold by them

DYE companies speacialized in coal/tar chemistry
↳ all opened up oppurtunity for all families to be able to afford drugs

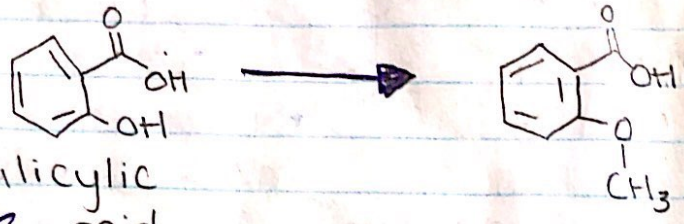
However...

Salicylic Acid had side effects

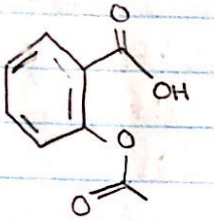
- Bitter taste
- stomach irritation (could be strong enough to kill you)

## Felix Hoffman

- father had arthritis and took salicylic acid but suffered from stomach issues
  - ↳ thought stucture may be able to be modified to avoid stomach issues



salicylic acid → added group to make less bitter; No stomach issues BUT got rid of pain relief



Acetasalicylic Acid

ON Aug 10 1897

first Artifical drug

modified by humans (purely synthetic)

→ ASPIRIN (initially sold as powder

→ tablets were made to get rid of th bitter side effect; ensure exact dos

→ also known as ASA but asprin was easy to remember and wasn't scary

→ only bayer can call ASA by the name asprin, but if you look 4 scientific name you have a wider choice

A.S.A → good for muscle pain, Not for organ/viscero pain

**Benefits**

- pain
- fever
- Inflammation
- reduces heart attack risk

**side effects**

- tinnitus
- stomach irritation
- blood clotting

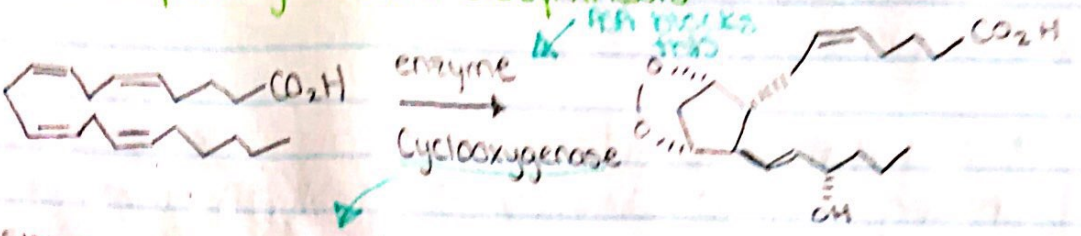
## Postaglandins are local hormones

- produced and "used" in same cell
- Carry very short messages and are only in the body for a very short time

→ ASA interferes with postaglandins

### postaglandins biosynthesis

if turned into Thromboxanes cause blood clotting




shape of enzyme is what gives its ability to do what it does in the body

postaglandin → pain, fever, inflammation

### Enzymes are machines

- works like a machine or, it has a physical movement that occurs, this is how it carries out the action

### Other Benefits

→ taking aspirin over a long period of time can reduce your risk of heart attack

→ do only under prescription of doctor

→ side effects of taking aspirin everyday that out weigh risk of heart attack unless you are high risk

→ very small reduce risk of cancer, if you take for 10 yrs

Anders Breivik → used aspirin to make home made explosives

### Side effects of ASA

- death
  - more than 60 tablets at once is lethal dose (only possible on purpose)
- Ringing in the ears (tinnitus)
  - more than 10 tablets (stop consuming to stop ringing)
  - warning of salicylism (aspirin poisoning)
    - ↳ go to hospital or call poison control

- Stomach irritation
  - Causes damage to stomach because of excess HCl
    - mucus protects/insulates stomach
    - Prostaglandins help protect stomach
      - decrease acid production
      - increase mucus production

ASA block this function (taking can corrode the stomach lining)

→ long term aspirin use can cause damage (hole in linning - kill 10-20 thousand in North America a year)

Prevention

**Bufferin**
- Contains an antacid
  - $MgSO_4$ (gypsum) - counter acts the stomach acid
- Pill dissolve quickly

**Plastic Coating on ASA**
- special coating prevents it from dissolving in the stomach - popular when used for arthritus

**Drink lots of Water**

**MIGHT be connected to Reye syndrome & influenza**
→ Brain swelling in children
- Childrens aspirin was taken of market as precautio even though it was never proven
- not worth testing as there were other options like childrens advil

→ An association between 2 things does not mean that one thing influenced (caused) the other
* like winner of LSU vs Alabama football game and US presidental election (coincidence)

↳ An cause requires a body
- Association between 2 things
- Control experiments
  - eliminate other possibilities
- experiments with animals
- biochemical explanation of the effect
- deliberately change one factor to look for changes in the other

ex;

→ Aspirin & stomach ulcers

large amount of data shows this
- ulcers common in ppl who take Aspirin (long term)
- ulcers less common in ppl we don't use aspirin (control)
- Aspirin dosing in rats results in more ulcers (animal)
- prostaglandin production in stomach lowers stomach acid and increases mucus production (biochemical)
- Aspirin use raises stomach acid & decreases mucus production - ASA inhibits prostaglandin productio
- Stomach irritation reduction if stop taking ASA (change, animals)

## different types

- regular and extra strength
- Tablets and caplets and gelcaps → doesn't work any faster
- some forms add caffeine for headaches
  - ASA - 325 mg
  - Caffeine - 32 mg

## Brand Name Vs Generic → quality costs more

→ ppl associate name brands w quality
→ generic drugs are the same quality as name brands
- same chemical substance
- same dosage
- equivalent bioavalibility → how much drug gets into body
  - same amount of drug enters the body

* By law a scientist must make sure that the generic get approx. the same amount into the body as name brand

Use name brand to find generic
→ products w/ same words/numbers are the same product

price per 100 tablets

| | | |
|---|---|---|
| Bayer aspirin | 9.49 | > basically the same b/c they sell less regular (price is higher to compensate |
| extra strength | 9.99 | |
| low dose | 17.99 | > covered by insurrance plans |
| generic | 2.50-7.99 | |

A. Cahn & P. Hepp 1886
- experimenting to find a vermifuge
- noticed fever reduction in person who was given acetanilide

Antikamnia (antifebrin)
→ made from coal tar

Carl Duisberg
- Chemist @ bayer
- needed to dispose of 50 tonnes of aminophenol
  → noticed that excess was identical to another product

Phenacetin
- APC tablet
  - aspirin
  - phenacetin } each can treat headaches
  - caffine

→ Both this and ASA convert to acetaminophen in body (1947) → this is Acetaminophen (tylenol)
pain relief
(because it raises pain threshold)

→ used for muscle pain & visceral pain
→ is an antipyretic
→ not for inflammation (does not inhibit prostaglandin synthesis)

Used for Arthritis ~~tissue~~
- Osteoarthritus (more effective) } better for some types
- Rheumatoid arthritus

→ Stomach irritation
- ASA
  - Strong irritation (chronic)
- Acetaminophen
  - weak irritation - hard to find

→ death
- more than 60 tablets (have to do it on purpose)
- # 1 suicide drug in england

→ liver toxicity
  * look up

→ never take for hangover
- alchol stimulates liver function
- liver tries to detox the body from the alconol - does it in toxic way when mixed with tylenol

Acetaminophen poisoning is common

→ Have to watch using multiple meds because Acetaminophen is considered safe and used in lots of meds (many OTC)

No risk of Rye Syndrom
- no association for acetaminophen

Chidren's tylenol = small bottles (safety)
- very expensive
- packaged in small bottles as safety precautions (not enough to harm child) ↑ 1 or 2 doses
- taste like cherries

tylenol regular
- acetaminophen 325 mg

tylenol extra stength
- acetaminophen 500mg (50% more approx)

tylenol arthritus/muscle & body
- Acetaminophen 650 mg

tylenol migrain
- Acetaminophen 500 mg
- Caffine 65 mg - could just take tylenol & coffee

Tylenol & cyanide (1982)
- drugs in tylenol were replaced w cyanide - and bottles put back on shelf and many people died.
- recalled all tylenol before mystery solved
- recalled by J & J
- Tylenol caplets replace capsules (tamper proof)
- safety seal added to all OTC meds

price per 100 tablets

| | |
|---|---|
| tylenol | 1049 |
| extra strength | 900 |
| muscle/body | 1874 |
| arthritis | 2298 |
| Childrens | 3299 |
| generic | 320-799 |

Ibuprofen
- Developed in 1961
- originally by prescription only
- OTC use approved 1984
- blocks active site of cyclooxygenase

Advil = Mortin

migrian vs. headache meds
- read back of box they are the exact same b/c ppl think migrian meds are stronger

# Naproxen

- Aleve
- very good for inflammation
- generic now avalible
- relatively expensive

Top pain relievers (North America)

- Acetaminophen - 43%
- ASA - 28%
- Ibuprofen - 26%
- Naproxen - 3%

## COX-1 (innibition)

- Stomach
  - HCl production increases
  - mucus production decreases
- Platelets
  - clotting is inhibited
- long term COX-1 inhibition
  - ulcers in stomach can bleed severely

* Harmful

## COX-2 (inhibition)

- reduces pain
- reduces inflammation } distributed around muscles
- reduces fever

* Beneficial in Arthritus treatment

### Selective COX-2 inhibitor 4 arthritus

- drug with COX-2 skip stomach irritation to stomach
- vioxx is a canadian drug - safe alternative

### Canadian trials

- Appoximatly 60 studies done
  - more than 5000 patients
  - no serious side effects
  - no difference in cardiovascular disease vs placebo
- Drug approved in 1999
  - sales average $25 billion/year

because clinical trail came out after drug was on market they got in trouble

## VIGOR

- illustrate reduced risk of ulcer
  - 18 month study
  - use naproxen as a placebo
    - used VIOXX @ twice the normal dose
    - naproxen was given @ the normal amount
  - study showed 54% reduction in serious GI side effects with VIOXX
    - 56 out of 4047 for vioxx
    - 121 out of 4029 for naproxen
- Increased risk of heart attack
  - 0.4% for VIOXX (45 out of 4047 patients)
  - 0.1% for naproxen (19 out of 4029 patients)
  - no difference in mortality
- paper in NEJM reported no adverse effects
  - only data from first 10 month included
    - ↳ no problems in 1st 10 months but after there was 4x chance of heart attack (covering up)

**FDA analysis of 1.4 mil patients**

- estimated that VIOXX caused 88,000 - 139,000 heart attacks during 1999-2004
- In 2004, Merck voluntarily removed drug from market
  - Cut 7000 jobs
  - 10,000 lawsuits

but too expensive to put back on market

↳ should be put back on market as benefits out weigh risks

→ heart attack over death