

## Drugs 101 Mid-Term Review

### INTRO AND HISTORY

#### Most Reliable Information on Web

- Pharmaceutical company websites
- Government websites
- University websites
- Scientific journals

#### Science vs Magic

- Science
  - Collect facts
  - Draw conclusions based on those facts
  - Test your conclusions in several ways
- Magic, superstition
  - Draw the conclusions you want
  - Find some facts to fit those conclusions
  - Avoid testing or challenging your conclusions
- Human brain's default mode is "magic"
  - We create our own reality
  - Draw the conclusions
  - Find some facts to fit those conclusions
  - Avoid testing or challenging your conclusions
  - Ignore or explain away contradictory evidence
- Concept of science is new
  - Developed in last 150 years
    - Collect facts
    - Draw conclusions based on those facts
    - Test your conclusions in several ways
    - Include all evidence

#### Life expectancy through history

- Approx 30 to 35 years for most of recorded history and stone age
- 82 years in 2009
  - Most improvements over the last 150 years

#### Life in History

- Disease was common and dangerous
- Lice and fleas on humans
- Life with worms

#### Main Causes of Death

1900	2004
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<ul style="list-style-type: none"> <li>- Pneumonia</li> <li>- Tuberculosis</li> <li>- Influenza</li> </ul>	<ul style="list-style-type: none"> <li>- Heart disease</li> <li>- Cancer</li> <li>- Stroke</li> <li>- Lower respiratory infection</li> <li>- Diabete</li> </ul>
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#### Main reasons for improved health

- Improved sanitation
  - Outhouses were common in cities
  - Chamber pot was used when cesspits were available
  - Open sewers before closed
  - Populations exposed to dead and dying
- Clean drinking water
  - Nature does not create pure water
    - Guinea worm - dracunculiasis
  - Major improvement is chlorination
- Refrigeration
  - Food spoilage was common before refrigeration
  - Seasonal availability was depended on
  - Modern food storage stores all year round
- Vaccination
  - Pharmaceuticals improve health
  - Greatest achievement in medicine
    - Immunization
    - Very successful for viral diseases
    - Smallpox eliminated in 1977 (only exists in labs and biological weapons)
    - Polio eradicated from North America in 1991
- Antibiotics
  - For bacterial infections

#### Modern Drugs

- Each starts with a scientific idea, optimized using scientific methods, tested scientifically
- North American drug market (2009)
  - Prescription drugs
    - \$30 billion
  - Over the counter (OTC) drugs
    - \$25 billion
- Modern Pharmaceutical industry
  - Started in 1856
  - Uses scientific methods (Chemistry, biology, molecular biology, epidemiology)
  - Regulated by the government

#### Ancient Drugs

- Feel better just by getting treatment
- Most from plants
- Sola dosis facit venenum
  - Poison - kill
  - Potion - cure
  - Later found out only the dose makes the poison
- Papyrus Ebers
  - Egyptian medical document (1500 BC)

Drugs: Produce desired (beneficial) biological effect

Poisons: Produce undesired (harmful) biological effect

ONLY THE DOSE MAKES THE POISON

How were drugs discovered before 1900?

- Observation (rare)
  - People observed the effect of the drug
  - Strong poisons
  - Strong poisons (common)
    - Easily identified
    - Low dose makes it into a drug
      - Opium, digitalis, nicotine, cocaine
    - Drugs observed:
      - Opium is the basis of modern painkillers
        - Analgesics, Codeine, Oxycodone, Fentanyl, Methadone, Demerol
      - Cocaine as a stimulant
        - Anesthetics, Novocaine, Procaine, Lidocaine, Benzocaine
  - Problems with observation
    - Human brain searches for patterns
      - Apophenia: Seeing patterns or connections in random or meaningless data
      - Pareidolia: Perceiving sounds or images as something else
    - Ancients did not use experiments or statistics
      - Anecdotal evidence (stories)
      - Drug and effect may be coincidence
      - Perceptions subject to placebo effects
      - People lie
    - Once evidence is available, hard to contradict
      - Poor control over dose
      - Preparation changes chemical composition
      - No standardization
      - Difficult to correct information
- Weak poisons (uncommon)

- Large quantity for effect
  - Caffeine, salicin
- Philosophy (very common)
  - Based on belief
  - Cure arrived at by reasoning (make it up)
  - Search for “proof” afterward
  - Healing often connected with superstition, magic, religion
  - Hippocrates develop doctrine of humors
    - Body is made up of for humors
      - Blood
      - Phlegm
      - Yellow bile
      - Black bile
    - 4 humors are normally in balance
    - Too much or not enough of a humor causes disease
    - Cure by rebalancing the humors
    - Fever associated with hot and dry, cure using cold and wet
    - Treatment developed: bloodletting, purges, fasting, and special foods
  - Doctrine of Signatures
    - Jakob Bohme, shoemaker and philosopher (1575-1624)
      - God left clues to tell us how to use things
      - Disease and cure were linked
      - This approach is/was used by almost all cultures
    - Ex) Walnuts look like brains which means walnuts are good for brain health, Boneset stems grow through the leaves, sharks don't get cancer, breath mints have chlorophyll, mandrake roots look like people so used for demonic possession, rhino horn as an aphrodisiac, and mercury as a purgative because it is a heavy liquid
    - Based on appearance or location and required imagination to see connections

#### Drug discoveries throughout history

- Surgery without anesthetic
- Amputation learned by trial and error
- Sir Humphry Davy discovered nitrous oxide
  - Nitrous oxide as a propellant
- William TG Morton and ether 1846
- Anesthetics make modern surgery possible
- Less than 30% survived surgical treatment
- Joseph Lister used phenol as antiseptic 1867
  - Toxic effect of phenol on doctors
  - Washing and glove use was safe
- Carbolic acid sprayer during surgery
- Antiseptics brought to Canada by Thomas Roddick in 1877

- Listerine becomes a household product
  - For dandruff
  - Listerine no longer contains phenol
- William Perkin first synthetic dye 1856
- Dye companies become pharmaceutical companies
- The first artificial drug in 1897 - Aspirin
  - Artificial drugs were better and cheaper
- Most modern drugs are artificial
  - Designed for optimal activity, safety
  - Provide convenience
  - Manufactured in large quantities
    - Lower cost?
- Most pharmaceuticals are made from oil
- Genetically engineered drugs
- Rise of patent medicine late 1800's
  - Included the word patented on the label which made the public think patented = quality
  - You could sell anything
- Alcohol was the most common "active ingredient"
  - Alcohol, Opium, and Cocaine due to the "feel good" component
- William J.A. Bailey makes Radithor which is radioactive water
- Thalidomide
  - Developed as a sedative - 1957
    - Very few side effects
  - By 1962, thalidomide recognized as a teratogen
    - Phocomelia
    - Attenuated limbs
    - Teratogen causes birth defects
      - From Greek word "teratos" for "monster"
      - Thalidomide was tested in rats
        - Rats do not often give birth to deformed pups
        - In humans, problems with fetus result in miscarriage, stillbirth or birth defects

## Rules

- Regulation of drugs
- Regulation of medical devices and procedures
- Before 1907 there were no rules
  - Anybody could make and sell drugs
    - No proof that anything worked
    - No safety testing
    - No testing of any kind
  - Most drugs were "made-up"
    - Put some leaves in a bottle with water or alcohol

- Start selling it
- Board of Food and Drug Inspection
  - Formed in 1907
    - First government regulations for medicines
    - Labeling only
    - No regulation of therapeutic claims
    - No safety testing
- Food and Drug Administration (FDA) created
  - Food, drug, and cosmetic act 1938
  - Ensure the safety of drugs
  - Animal testing was now required (safety only)
  - Clinical trials were done to follow safety in humans
  - Directions for proper use were required on the label
- Modern safety standards
  - Safety testing done in at least 2 species
  - At least one must be a primate
  - Must show that the drug is bioavailable
    - Gets into body
  - Must use relevant doses
- Industry regulation is important as it
  - Ensures safe products
  - Ensures products work
  - Ensures good manufacturing quality
  - But regulation increases cost

#### How modern drugs work

- Each starts with a scientific idea
- Each is optimized using scientific methods
- Each is tested scientifically
- Manufacturing is standardized
- Drug industry is tightly regulated
  - Must provide scientific proof

## **PAIN**

#### Over the counter meds

- Top OTC meds
  1. Cough and cold
  2. Pain reliever
  3. Antacid
  4. Toothpaste
  5. Laxative
- Important considerations when buying
  - Safety

- Indications
- Counter-indications
- Safety
  - Dose makes the drug
  - Dose makes the poison
- Side effects
  - ALL drugs have side effects
  - Effect: what is it?
    - Info is easy to find
    - Label or box
    - Google
  - Incidence: how common is it?
    - Info is difficult to find
  - Need both to evaluate risk
- Counter indications
  - When you should NOT use
    - Conditions
    - Drug combinations
    - Foods
    - "Natural" remedies
- Pain relievers are the most common OTC drug
- Aspirin
  - One of the world's most popular drugs
  - Salix
    - Genus (family)
      - Willow
      - Poplar
      - Beech
      - Wintergreen
  - Salicylates
  - Willow
    - Sumerians used willow leaves for pain
    - Egyptians used willow for inflammation
    - Reverend Edward Stone 1702-1768
      - Rector in Church of England
      - Described treatment for ague in 1763
  - Doctrine of signatures
    - Associate between disease and cure
      - Ex) people who live near swamps get malaria, people with malaria have a fever, treat malaria with quinine, quinine is bitter, willow bark is bitter, willows grow in swamps.... Willow bark with cure fever
  - Willow bark for fever

- Dried bark
- Ground to a powder
- Given for fever
- Expensive
- Limited supply
- Variable effectiveness
- Active ingredient in willow is salicin, and that was isolated in 1829
- Salicin converted to salicylic acid in 1838
  - Better drug than salicin (lower dosages)
  - Occurs in meadowsweet flowers (very small amounts)
    - Analgesic
    - Antipyretic
    - Anti Inflammatory
- Synthetic vs Natural
  - Natural: 58 billion tablets require 2 million tonnes of bark
  - Synthetic: 58 billion tablets requires 62,000 tons of oil
- Salicylic acid made and sold by dye companies
- Felix Hoffmann 1868-1946
  - Father had arthritis
    - Took salicylic acid for pain
    - Suffered from stomach problems
- Aspirin initially sold as a powder
- Aspirin tablets became more popular
- Aspirin and Acetylsalicylic acid (ASA)
  - ASA effective for muscle pain but not effective for visceral pain
- How aspirin works
  - Prostaglandins are local hormones
    - Produced and used in same cell
    - Exist for short times
  - Prostaglandin biosynthesis
    - Cyclooxygenase
    - Enzymes are machines, drugs block machine action, and aspirin blocks the cyclooxygenase machine
- Aspirin can cause acid damage in the stomach because of the increase in acid production and decrease in mucus production
  - Bufferin contains an antacid
  - Children's aspirin removed as a precaution
- Some forms add caffeine for fast relief of headaches

#### Acetaminophen

- A. Cahn and 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 at Bayer
  - Needed to dispose of 50 tons of aminophenol
- Phenacetin
  - APC tablet
    - Aspirin
    - Phenacetin
    - Caffeine
- Both drugs (antikamnia and phenacetin) converted to acetaminophen in body in 1947
- Acetaminophen for pain relief
  - Raises pain threshold
  - Muscle and visceral pain
- Antipyretic
- Not for inflammation
  - Does not inhibit prostaglandin synthesis
- Arthritis use
  - Osteoarthritis
  - Rheumatoid arthritis
- Acetaminophen liver toxicity
- NEVER TAKE FOR HANGOVER
  - Alcohol stimulates liver function

#### Ibuprofen

- Developed in 1961
- Originally by prescription only
- OTC approved in 1984
- Inhibits cyclooxygenase
  - Blocks the active site
- Naproxen
  - Very good for inflammation

#### Top Pain Relievers (North America)

- 1) Acetaminophen 43%
- 2) A.S.A 28%
- 3) Ibuprofen 26%
- 4) Naproxen 3%

#### Chemical Structures

- Represent the shape and function of molecules
- Match shapes to match function

#### COX-1 and COX-2

- Effect of COX-1 inhibition
  - Stomach
    - HCl production increases

- Mucus production decrease
- Platelets
  - Clotting is inhibited
- Long term COX-1 inhibition
  - Ulcers in stomach can bleed severely
- Harmful effects
- Effect of COX-2 inhibition
  - Reduces pain
  - Reduces inflammation
  - Reduces fever
  - Beneficial effects
- Current arthritis treatments inhibit both COX-1 and COX-2

### Cause and Association

- An association between two things does not mean that one thing influenced the other
- Cause
  - Requires a body of evidence

Effect	A.S.A.	Acetaminophen	Ibuprofen	Naproxen
Pain	yes	yes	yes	yes
Fever	yes	yes	yes	yes
Inflammation	yes	no	yes	yes
Prevent heart attack	yes	no	no	no
Reduced blood clotting	yes	no	yes	yes
Stomach irritation	yes	no	yes	yes
Rye syndrome	maybe	no	no	no
Liver toxicity	no	yes	no	no

## HEADACHE

### History

- Once believed headaches were caused by demons
- Lose the demon to lose the headache
- Magic pulls out the pain
- Surgical cure for headaches
- Trepanation as a cure for headache
  - Speciality tools
  - There are modern practitioners of trepanation
- Ergot
  - Rye bread common in medieval Europe
    - Ergot is a fungus that grows on rye
    - Midwives used ergot to induce labour

- Ergot is a powerful hallucinogen
- Ergot poisoning seen as demonic possession
- Extracts of ergot for migraine in 1862
  - Dangerous due to poor control of dosage
  - Extracts tend to give variable amounts
- Arthur Stoll isolates ergotamine in 1918
  - Easy to control dose using purified substances
- Cafergot still available today
- Ergotamine
  - Prevents migraine
  - Poison in high doses: hallucinations, muscular contractions, vasoconstriction, gangrene, and death
  - Drug-like substance: effective, safe, convenient for the user, and cheap
- Albert Hoffman discovered LSD by accident
  - LSD was used by the CIA at McGill in 1950s
  - Hallucinations from part of ergotamine

#### Headaches:

- Brain itself does not feel pain
- Pain in the thin tissue surrounding skull
- Understand the headache before treating it
  - 12 types of headaches
    - 60 sub type
  - Headaches grouped into 2 classes
    - Muscular
      - Muscular band around the skull
      - Caused by stress
      - Treatment: ASA, Acetaminophen, Ibuprofen, Naproxen
    - Vascular
      - Involves blood circulation
      - 3 Major types
        - Toxic: caused by poison and the pain is caused by vasodilation.
          - Most common type of toxic headache is the hangover.
          - Alcohol activates CYP450 making acetaminophen toxic
          - Caffeine gives rebound vasodilation, causes vasoconstriction
          - Treatment: ASA, Ibuprofen, Naproxen
        - Migraine
          - Starts with serotonin

- Serotonin levels change during migraine
  - Amounts drop during aura
  - Prevent migraine by replacing missing serotonin with a drug
    - Poor drug because it does not easily pass from blood to brain.
- Affects smaller % of population. 18% of women get migraines, 6% of men get migraines
- Two phases
  - Phase 1: Vasoconstriction
  - Phase 2: Vasodilation
- Initiated by a trigger: tension, lack of sleep, menstruation, food, relaxation, too much sleep, pregnancy, drugs, strong smells
- Follow a progression:
  - Prodrome phase
    - 30-40% of sufferers
    - Mood swings
  - Aura
    - 20 to 30% of sufferers
    - One or two hours before pain phase
    - Scotomas: visual disturbances, flashes of light
    - Olfactory hallucinations
    - Auditory hallucinations
    - Vertigo
    - Reduced sensation
    - Hypersensitivity
  - Pain
    - Involves half of the head
      - Hemicrania
      - Hemicrania
      - Lasts 1 to 72 hours
      - Nausea is common
      - GI disturbances
      - Movement makes it worse
  - Postdrome
    - May take hours or days
      - "Hung over"
      - Exhaustion
      - Poor concentration
      - Depression or euphoria

- Treatment: ASA, Acetaminophen, Ibuprofen, Naproxen, Prescription pain meds

- Cluster

## **COLDS**

- Colds are the most common infection
  - Outnumber all others by 25 to 1
  - More than 200 viruses cause colds
- Virus destroys tissue, immune system makes symptoms
- No cure for the common cold
  - Average cold lasts a week
  - Some cold medications relieve symptoms
  - Many remedies do nothing
  - No medication will prevent colds
- Myth busts:
  - Sneezing does not spread colds well
  - Being cold does not cause colds
  - Wet hair does not cause colds
  - Direct exposure to virus does not always cause cold
- Cold virus is in nasal secretions and can be spread easily
- Cold viruses are transferred by touching
- Colds are more common in crowds
  - School season is cold season
- As you age you acquire immunity by being infected
  - Exposure to virus causes illness
    - Immune response is too slow and weak to prevent
  - Body makes large amounts of antibodies only during infection
  - After each infection you build up “memory” cells
  - Later exposure to the same virus does not make you sick
    - Rapid and strong immune response