REFERENCING GUIDLINE

BY

MAHMOOD SALIH

Referencing Importance

- Reliable
- Credible
- Robustness of Research

Referencing styles

- MLA (Modern Language Association)
- APA (American Psychology Association)
- Chicago
- Harvard
- Vancouver

In text citation

- Human exposure to different types of substance, some of these substances are cytotoxic like antineoplastic medication in which cytotoxicity is a major pharmacological action against cancerous cells[1]
- Metronidazole is antiprotozoal medication. It used to treat many pathological conditions like endocarditis, bacterial vaginosis, giardiasis, trichomoniasis, and amebiasis[7,8]

Reference List (Bibliography)

- Article with 1 to 6 authors
- Author AA, Author BB, Author CC, Author DD. Title of article. Abbreviated title of journal. Date of
- publication YYYY Mon DD; volume number(issue number):page numbers.
- Example:

Petitti DB, Crooks VC, Buckwalter JG, Chiu V. Blood pressure levels before dementia. Arch Neurol. 2005 Jan;62(1):112-6.

Reference list (Bibliography)

- Article with more than 6 authors (list 6 authors only and use et al for the remaining):
- Author AA, Author BB, Author CC, Author DD, Author EE, Author FF, et al. Title of article.
- Abbreviated title of journal. Date of publication YYYY Mon DD;volume number(issue number):page numbers.
- Example:

Hallal AH, Amortegui JD, Jeroukhimov IM, Casillas J, Schulman CI, Manning RJ, et al. Magnetic resonance cholangiopancreatography accurately detects common bile duct stones in resolving gallstone pancreatitis. J Am Coll Surg. 2005 Jun;200(6):869-75.

Reference list (Bibliography)

- Electronic journal article:
- Author AA, Author BB. Title of article. Abbreviated title of Journal [Internet]. Date of publication YYYY MM [cited YYYY Mon DD];volume number(issue number):page numbers. Available from: URL
- Example:

Stockhausen L, Turale S. An explorative study of Australian nursing scholars and contemporary scholarship. J Nurs Scholarsh [Internet]. 2011 Mar [cited 2013 Feb 19]; 43(1):89-96. Available from: http://search.proquest.com.ezproxy.lib.monash.edu.au/docview/858241255?accountid=12528

Reference List (Bibliography)

- Print book:
- Author AA. Title of book. # edition [if not first]. Place of Publication: Publisher; Year of publication. Pagination.
- Example:

Carlson BM. Human embryology and developmental biology. 4th ed. St. Louis: Mosby; 2009. 541 p.

Reference List (Bibliography)

- Chapter in a book:
- Author AA, Author BB. Title of book. # edition. Place of Publication: Publisher; Year of publication. Chapter number, Chapter title; p. [page numbers of chapter].
- Example:

Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia: Lippincott Williams & Wilkins; c2005. Chapter 29, Endometriosis; p. 1103-33.

Reference List (Bibliography)

- Electronic book:
- Author AA. Title of web page [Internet]. Place of Publication: Sponsor of Website/Publisher; Year published [cited YYYY Mon DD]. Number of pages. Available from: URL DOI: (if available).
- Example:

Shreeve DF. Reactive attachment disorder: a case-based approach [Internet]. New York: Springer; 2012 [cited 2012 Nov 2]. 85 p. Available from: http://ezproxy.lib.monash.edu.au/login?url=http://dx.doi.org/10.1007/978-1-4614-1647-0

Reference List (Bibliography)

- Edited Book:
- Editor AA, Editor BB, editors. Title of book. # edition [if not first]. Place of Publication: Publisher; Year. Pagination.
- Example:

O'Campo P, Dunn JR, editors. Rethinking social epidemiology: towards a science of change. Dordrecht: Springer; 2012. 348 p.

Reference List (Bibliography)

- Website (trusted)
- Website name, name of topic[format] year [cited date] available online from URL.
- Example

World Health Organization. Drinking water [Internet]. Geneva: World Health Organization; 2015 Jun [cited 2015 Jul 20]. Available from: http://www.who.int/mediacentre/factsheets/fs391/en/

Further information

- Trusted references
- https://guides.library.uwa.edu.au/vancouver

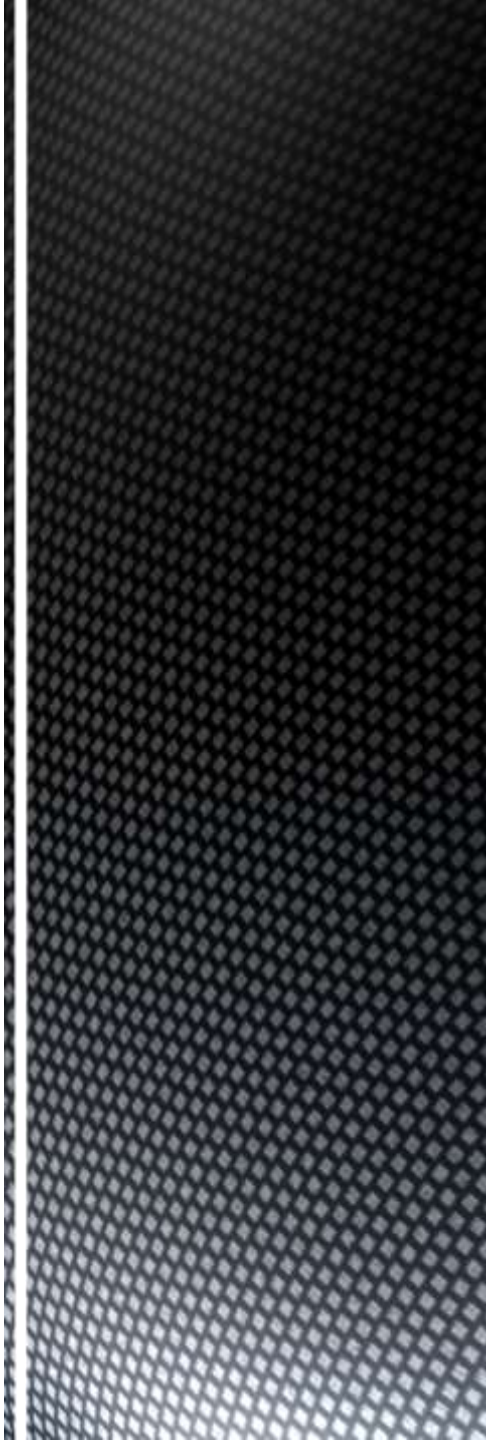
Any questions

Thanks for Listening

Analgesics

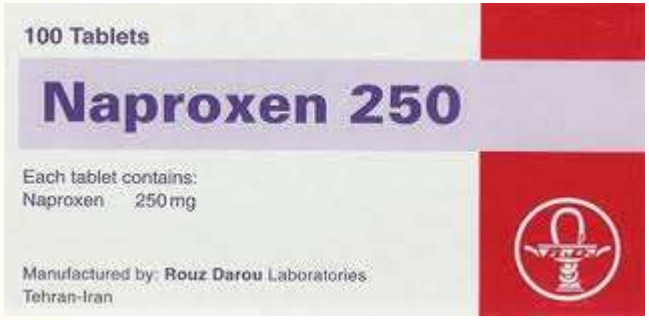
Acetaminophen & Salicylates

Hasan Alhaddad, MSc
Department of Pharmacology and Toxicology
College of Pharmacy/ University of Baghdad
2014



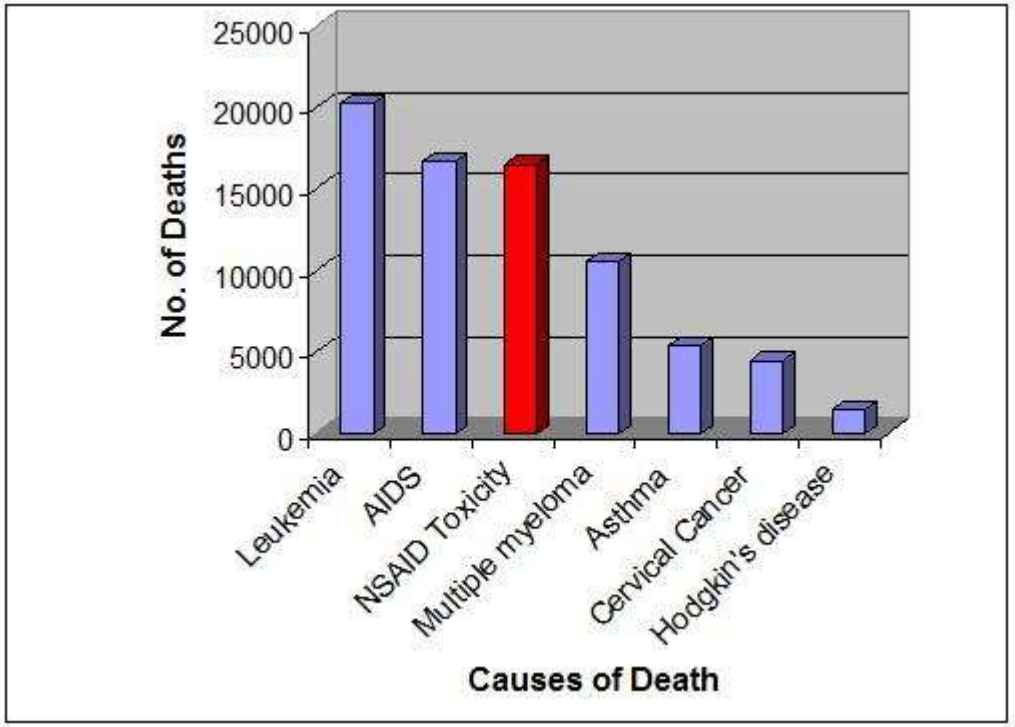
Non-steroidal anti-inflammatory drugs (NSAIDs)

- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Analgesic, anti-inflammatory, and antipyretic
  - OTC drugs
  - The most widely used of all drugs
  - Used to relieve mild to moderate pain
- Gastrointestinal toxicity including bleeding ulcer
- Risk of cardiovascular events
- Kidney damage

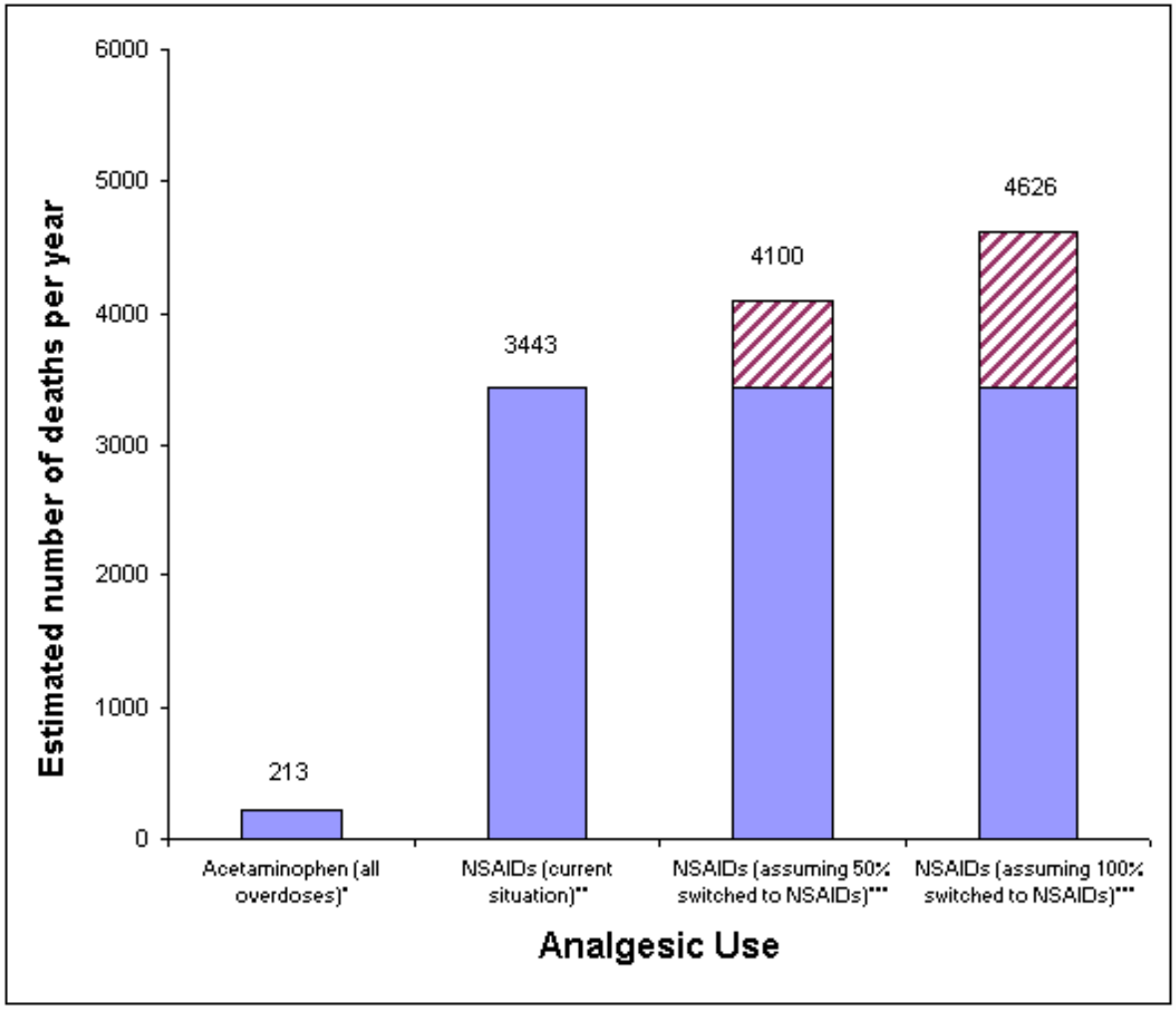


NSAID overdose

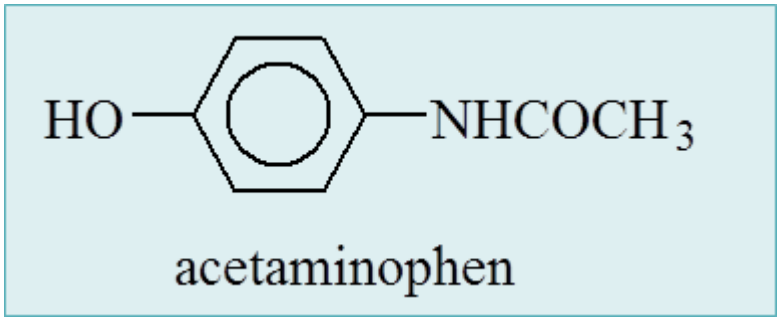
- Symptoms of NSAID overdose are usually mild
  - Gastrointestinal upset, abdominal pain, vomiting and diarrhea
  - 5% to 10% of patients experience convulsions. Metabolic acidosis is uncommon
  - Rarely, coma, prolonged seizures, apnea, bradycardia, renal failure and death may occur



NSAID overdose



Acetaminophen



- Acetaminophen (paracetamol) is not a NSAID, but a distinct analgesic and fever reducing drug with a similarly broad usage
- Most commonly used OTC analgesic & also most common over dose leading to hospital
  - Overdose is the leading cause of acute liver failure in the developed world
  - 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths due to acute liver failure
  - Kidney toxicity

FDA: combination prescription pain relievers that contain more than 325 mg of acetaminophen per tablet, capsule, or other dosage unit should no longer be prescribed because of a risk of liver damage

Acetaminophen

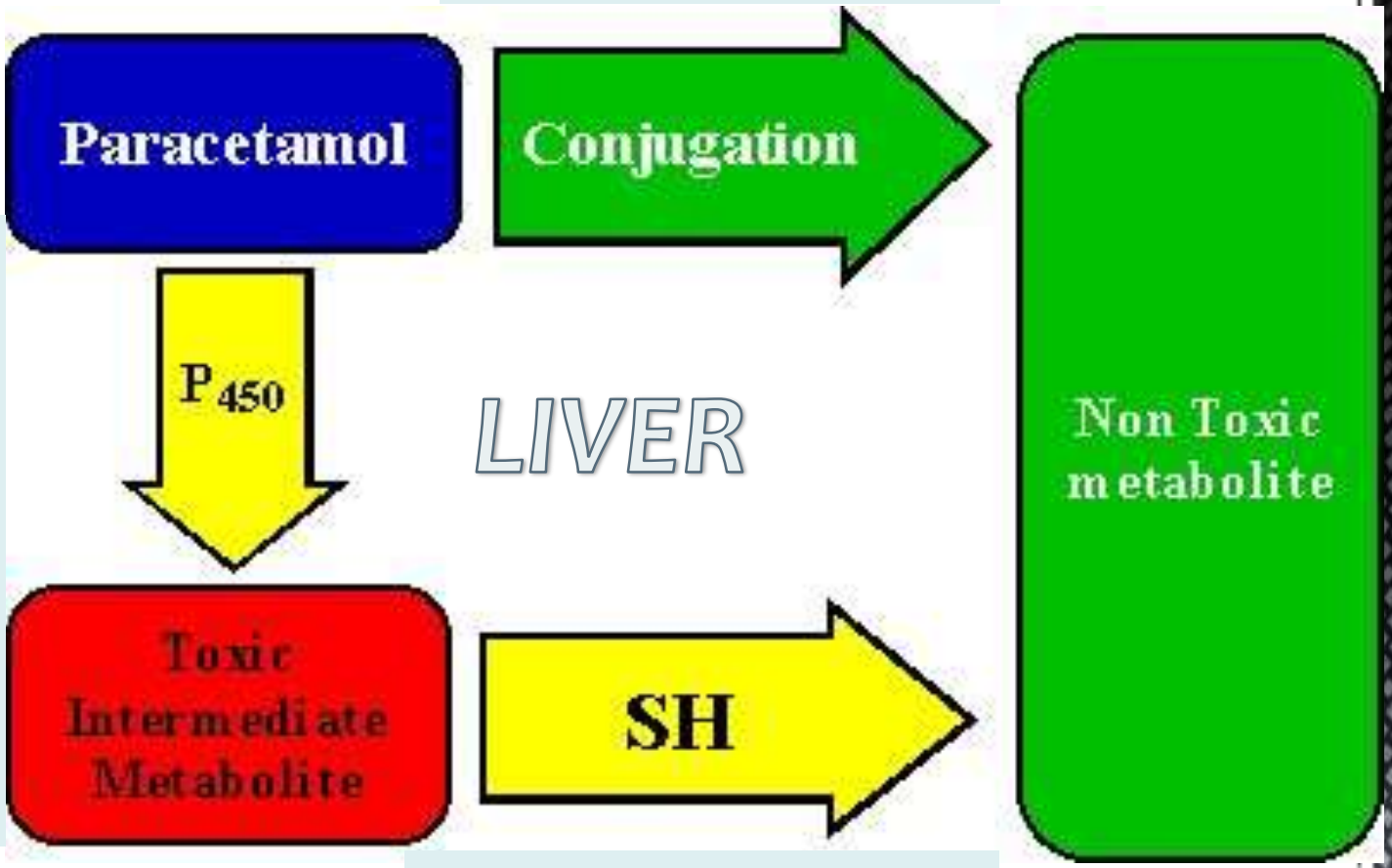
Toxicokinetics

- Relatively safe
- Rapid oral abs with peak levels at 1-2hrs for tablets (30mins for elixir)
- 20% is metabolized by gut wall, rest by the liver
- Elimination T½=~2hrs, ≥4hrs in over dose where
- LETHAL DOSE 15-25g
- Liver damage severe with >10g doses; Children: 150 mg/kg

Acetaminophen

Metabolism

60% glucuronide conjugates
30% to sulfate conjugates



4% is metabolized by the cytochrome P450 mixed-function oxidase system (3A4 at low doses; 2E1 predominantly at high doses) to the potentially toxic reactive intermediate N-acetyl-p-benzoquinoneimine (**NAPQI**).

conjugated with glutathione to form nontoxic cysteine and mercapturic acid conjugates

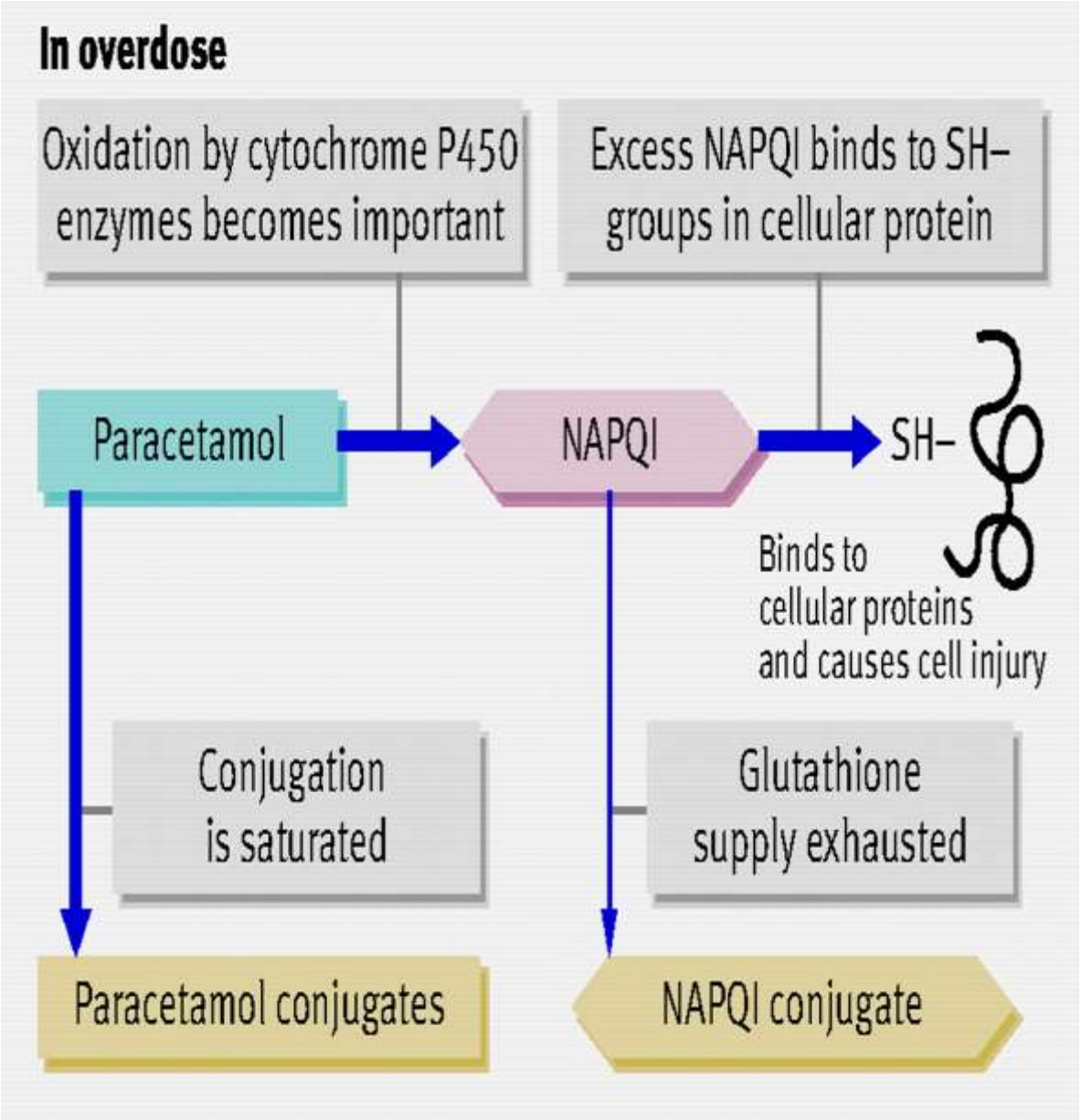
Acetaminophen

Toxicity

NAPQI induces oxidation of enzymes which alter normal cell functions and impairs cell defenses against endogenous reactive oxygen species

Hepatic toxicity becomes evident only when hepatic GSH falls to 30% of baseline

Therapeutic Dose: 10 to 15mg/kg
Toxic Dose: 150 mg/kg



Acetaminophen

Factors that may predispose patients to hepatotoxicity

- Increased frequency and duration of acetaminophen dosing
- Increased capacity for CYP2E1 activation to NAPQI
- Decreased GSH availability
- Decreased capacity for glucuronidation and sulfation
- Alcohol

Acetaminophen Level	**Result Interpretation**
10-20 mcg/mL	Therapeutic levels
Less than 150 mcg/mL 4 hours after ingestion	Low risk of liver damage
Greater than 200 mcg/mL 4 hours after ingestion Or Greater than 50 mcg/mL 12 hours after ingestion	Associated with toxicity and liver damage

Clinical Manifestations

Stage I toxicity

With in 24 hours, No hepatic injury, asymptomatic, N/V/abdominal pain

Stage II toxicity

24 to 72hours, right upper quadrant abdominal pain, anorexia, N/V, Tachycardia and hypotension , Raised liver function test

Stage III toxicity

72 to 96 hours, N/V/abdominal pain, Maximal liver injury (jaundice, coagulopathy, hypoglycemia, and hepatic encephalopathy), Acute renal failure, Death from multiorgan failure

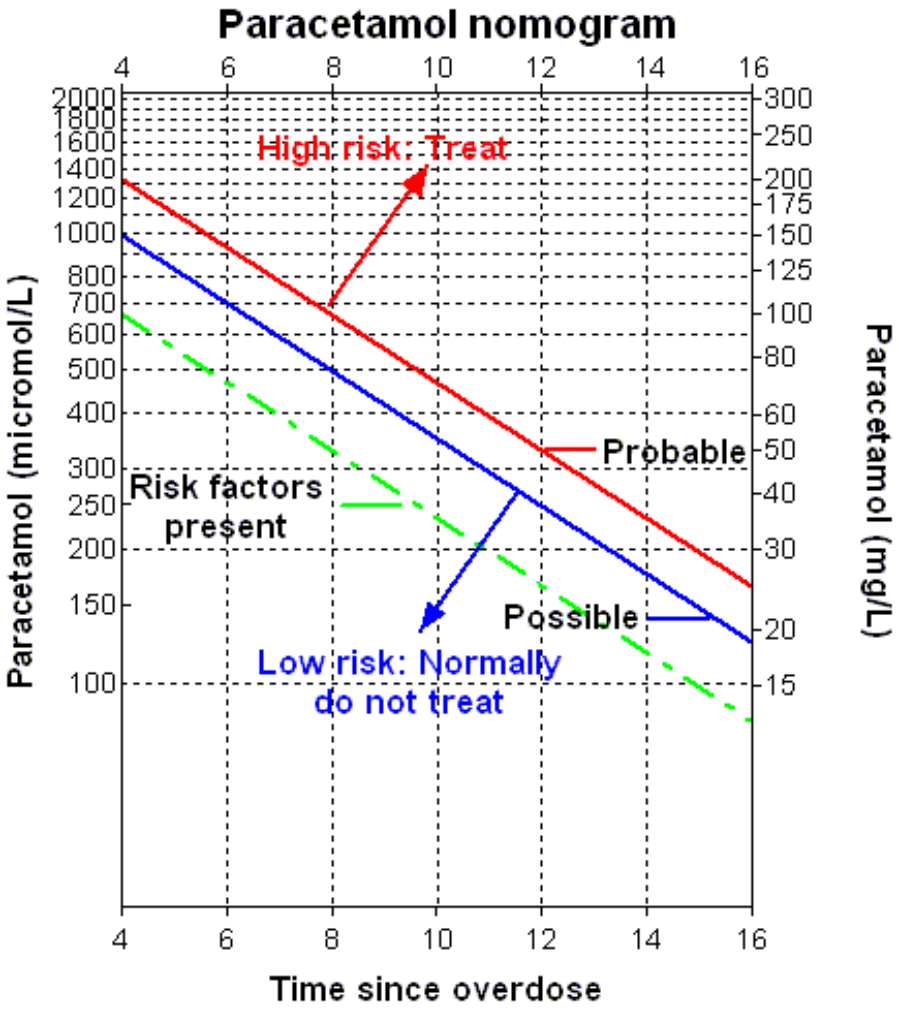
Stage IV toxicity

The recovery phase, Patients who survive stage III

Monitoring and Testing

Laboratory tests

- **Serum acetaminophen levels**
  - Management is dependent on the serum acetaminophen level and the time of ingestion
  - Rumack/Matthew nomogram
  - Paracetamol concentrations taken between 4 and 24 hours after ingestion



Monitoring and Testing

Laboratory tests

- Liver function tests
  - alanine aminotransferase [ALT]
  - aspartate aminotransferase [AST]
  - bilirubin [total and fractionated]
  - alkaline phosphatase
- Prothrombin time (PT) with international normalized ratio (INR)
- Glucose
- Renal function studies (electrolytes, BUN, creatinine)
- ECG
- Lipase and amylase (in patients with abdominal pain)
- Other tests to consider
  - Serum salicylate level: in unconscious patients or those in whom there is a suspicion of co-ingestion of salicylates
  - Urine drug screen: may be used in patients who are unconscious to determine if other substances have been taken

Monitoring and Testing

Special clinical considerations

- Glutathione deficiency
  - people with acute or chronic starvation
  - Eating disorders (e.g., anorexia or bulimia)
  - Patients with chronic debilitating illnesses (e.g., cystic fibrosis, AIDS, alcoholism, or hepatitis C)
- Prior medications
  - Long-term treatment with CYP 450 inductors (e.g., carbamazepine, rifampicin)
  - Long standing alcohol
- Children

Treatment of Acetaminophen Overdose

Out of hospital treatment

- Activated charcoal, with in the first hour after overdose
- Ipecac and Lavage might be used with in 2 hours of ingestion (not common)
- Antiemetics are used to relieve nausea and vomiting, which can result from both acetaminophen toxicity and from Activated charcoal and oral N-acetylcysteine administration

Treatment of Acetaminophen Overdose

N-acetylcysteine

- The mainstay of treatment for paracetamol toxicity
- Antidote for paracetamol
- As early as possible
- Is a sulfhydryl donor, replenishes glutathione stores
- Loading dose of 140 mg/kg then 70 mg/kg given every 4 hours
- Total treatment duration of 72 hours
- Should be given even if the history is unclear but a potentially toxic acetaminophen ingestion is suspected. NAC should be administered while awaiting a serum Acetaminophen level if the patient presents close to or later than 8 hours after an acute ingestion

Treatment of Acetaminophen Overdose

- N-acetylcysteine
  - Sulphurous compound:
    - Causes vomiting when given by mouth or nausea when given intravenously
    - Asthma, family history of drug allergy, and women
    - Treated by interrupting the acetylcysteine infusion and providing symptomatic relief with an antihistamine such as chlorpheniramine and nebulized salbutamol

- Liver transplantation, patients with severe hepatotoxicity and potential to progress to hepatic failure
  - Metabolic acidosis
  - Renal failure
  - Coagulopathy
  - Encephalopathy

ACETAMINOPHEN

Case study

A **21-year-old woman** was brought to the emergency department (ED) by her friend when he learned that she ingested approximately **30 (325-mg) acetaminophen tablets** in an attempted suicide. He was unaware of any previous significant medical or psychiatric illness but reported that she was seen in another ED several days earlier for **persistent headaches**. He said that she did **not abuse alcohol** or any other drugs.

The patient was able to provide a history and admitted to taking approximately 30 tablets approximately **3 hours before** coming to the hospital because she wanted to kill herself. Shortly after taking the tablets she developed **a bad stomach ache, felt extremely nauseated, and vomited** once. She denied taking any other medications or alcohol in the suicide attempt.

SALICYLATES

- Salicylate-containing medications have been widely used in the world
  - Aspirin
  - Topical products containing salicylates, such as Ben-Gay, salicylic acid, and oil of wintergreen or methyl salicylate
- Continues to be responsible for a significant number of cases of morbidity and mortality every year
- Salicylism, acute or chronic poisoning

OTC Analgesic Exposures
64% acetaminophen
19% ibuprofen
17% aspirin

OTC Analgesic Fatalities
62% aspirin
34% acetaminophen
04% ibuprofen

SALICYLATES

Toxic dose

- Less than 150 mg/kg - no toxicity to mild toxicity
- 150-300 mg/kg – Mild to moderate toxicity
- 301-500 mg/kg - Serious toxicity
- Greater than 500 mg/kg - Potentially lethal toxicity

Toxicokinetics

- Aspirin is a weak acid (pKa = 3.5)
- Rapidly absorbed (peak ~1hr or 4-6 if enteric coated)
- ~5-10% is excreted unchanged as salicylic acid
- ~90% oxidation, glycine conjugation, and glucoronide conjugation
- Therapeutic T½=2-4.5hr, but in over dose T½~18-36hr

SALICYLATES

Toxic mechanisms

Acid-base, fluid, and electrolyte abnormalities

Phase 1
hyperventilation resulting from direct respiratory center stimulation, respiratory alkalosis and compensatory alkaluria last as long as 12 hours

phase 2
Metabolic acidosis, interrupts aerobic respiration, Krebs cycle and lactate accomulation last 12-24 hours

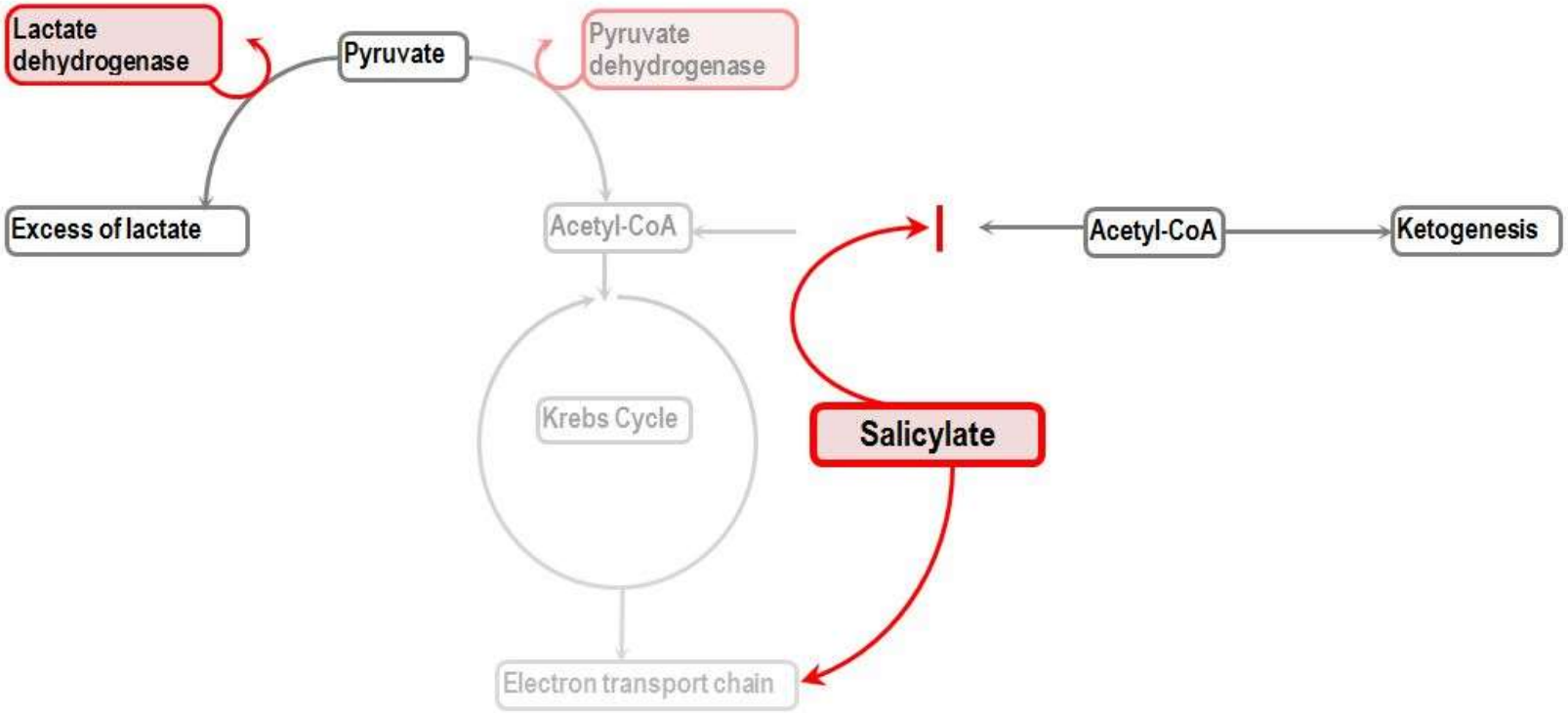
Phase 3
Dehydration, hypokalemia, and fever
4-6 hours after ingestion in a young infant or 24 hours or more in adults

Metabolic acidosis
Affect TCA (↑glucose utilization, ↑lactic acid) & Urea (↑ammonia) Cycles

Glucose metabolism
Hypoglycemia, ↑tissue glycolysis, ↓glucose synthesis

Other effects
Inhibit Vit K dependent factors II, VII, IX & X → ↑INR

Toxic mechanisms



SALICYLATES

Clinical features

- Hyperthermia is an indication of severe toxicity
- **Acute intoxication**
  - Gastric effects: N & V, Gastritis
  - CNS effects: N & V, tinnitus, confusion, hallucinations, seizures
  - Metabolic effects: Hyperventilation, Acid-base disturbance (respiratory alkalosis, metabolic acidosis), dehydration, electrolyte disturbances, fever
- **Chronic intoxication**
  - More common in elderly
  - Lower GI symptoms & higher non-specific neuro symptoms
  - Confusion, delirium, dehydration, metabolic acidosis, cerebral oedema

SALICYLATES

Lab tests

- **Salicylate level**
  - If enteric coated preparations, serial salicylate levels (2 hourly)
  - 15-30 mg/dL: therapeutic level
  - Higher than 40-50 mg/dL: symptomatic
  - Above 100 mg/dL: life-threatening toxicity
- **Arterial blood gas (ABG)**
  - Respiratory alkalosis
  - Metabolic acidosis
- **Electrolytes, BUN/creatinine, glucose**
  - Anion-gap metabolic acidosis
  - Hypokalemia
  - Baseline renal function
- **Imaging studies**
  - Abdominal radiograph
  - Computed tomography (CT) scanning of the abdomen
  - Endoscopy

SALICYLATES

Management

- **Asymptomatic**
  - Charcoal 1g/kg
  - I.V. bicarbonate infusion 1mmol/kg/hr to correct any acidosis (pH <7.3)

- **Symptomatic**
  - Charcoal 1g/kg unless altered conscious state
  - Whole-bowel irrigation, hemodialysis
  - I.V. fluid resuscitation to correct dehydration (use N. Saline)
  - I.V. bicarbonate infusion 1mmol/kg/hr, after initial slow bolus of 2mmol/kg, (Alkalization, urine pH >7.5)
  - Potassium replacement (20–40 mEq KCl per liter)
  - Respiratory support ± haemodialysis in case of convulsion and coma
  - STABILIZATION THERAPY

SALICYLATES

Case study

A **22-years-old woman** came to the emergency department complaining of **abdominal pain, nausea, and vomiting**. She had a history of **depression** but stated that she currently was not being treated by a psychiatrist or taking any psychiatric medications. Upon further questioning, the patient said that **6 hours earlier** she had been severely depressed and had ingested **at least half a bottle of aspirin tablets** in a suicide attempt, after which she **vomited once**. She **denied tinnitus** but said that she was **short of breath**. She denied significant past medical or surgical problems.


Medscape®

Digitalis toxicity

Hasan Alhaddad, MSc
Department of Pharmacology and Toxicology
College of Pharmacy/ University of Baghdad
2014

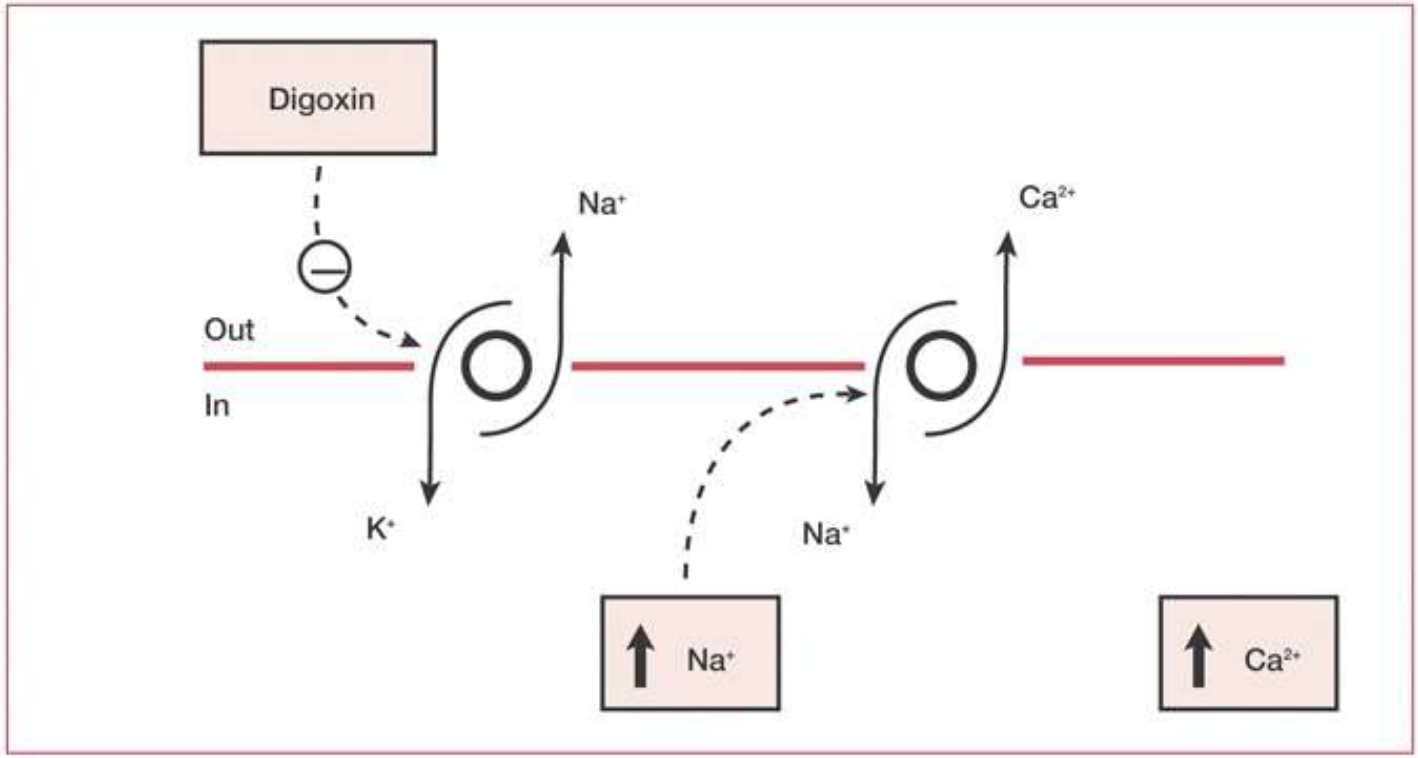
Cardiac glycosides

- Digitalis is the oldest compound in cardiovascular medicine
- Cardiac glycosides include digoxin, digitoxin, digitalis and ouabain
- +ve inotropic, -ve chronotropic
- Heart failure, Atrial fibrillation, Atrial flutter
- Low TI

Mechanism Of Pharmacological Action

- Potent inhibitors of cellular Na+/K+-ATPase
  - This ion transport system moves 3 sodium ions out of the cell and brings 2 potassium ions into the cell
  - Necessary for cell survival
  - Subsequent inhibit the Na+-Ca++ exchanger
    - Three sodium ions are exchanged for each calcium
    - An increase in intracellular sodium concentration competes for calcium through this exchange mechanism leading to an increase in intracellular calcium concentration, leading to **increases contractility (inotropy)**
- Increase vagal efferent activity to the heart, reduces sinoatrial firing rate (decreases heart rate; **negative chronotropy**) and reduces conduction velocity of electrical impulses through the atrioventricular node (**negative dromotropy**)

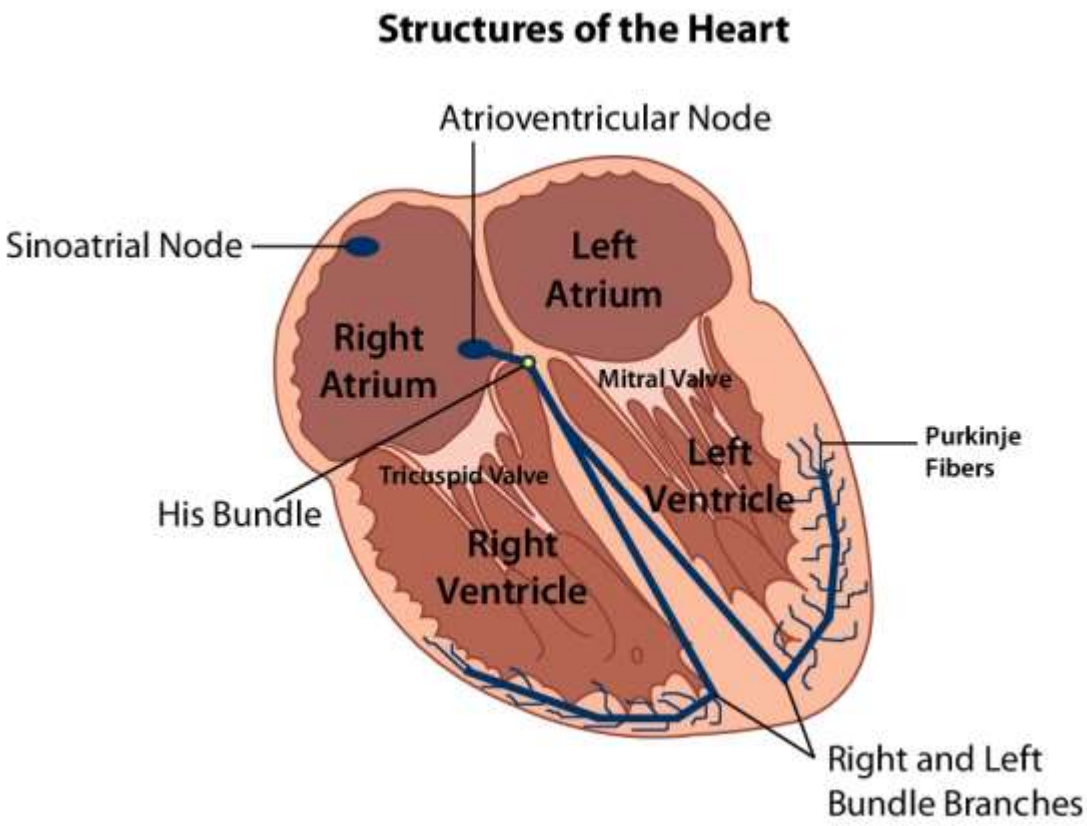
Mechanism Of Pharmacological Action

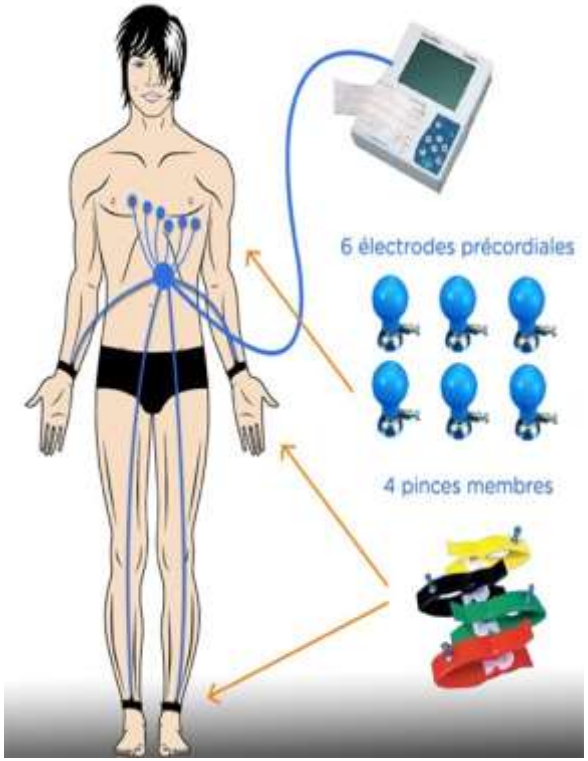


Kinetics

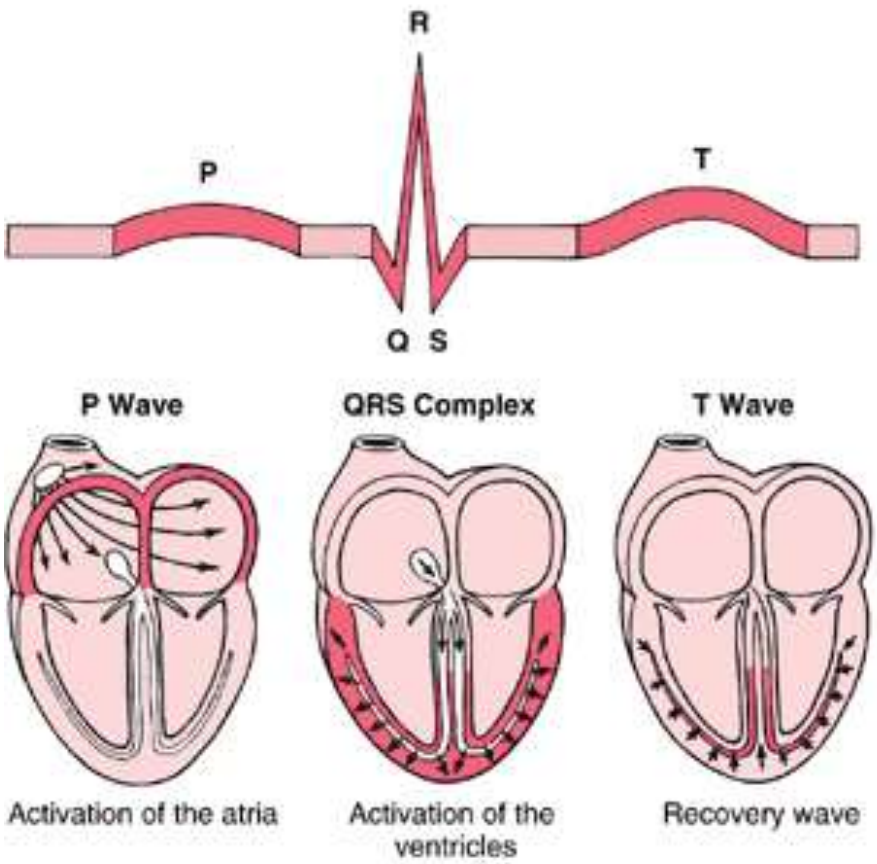
Volume of Distribution	Protein Binding	Half Life	Time to peak (serum)
5-7 L/kg	25%	Age, Renal, and cardiac function dependent Approximately 38 Hours (parent drug)	Oral: 1-3 hours Distribution phase: 6-8 hours Steady state: 7-10 Days

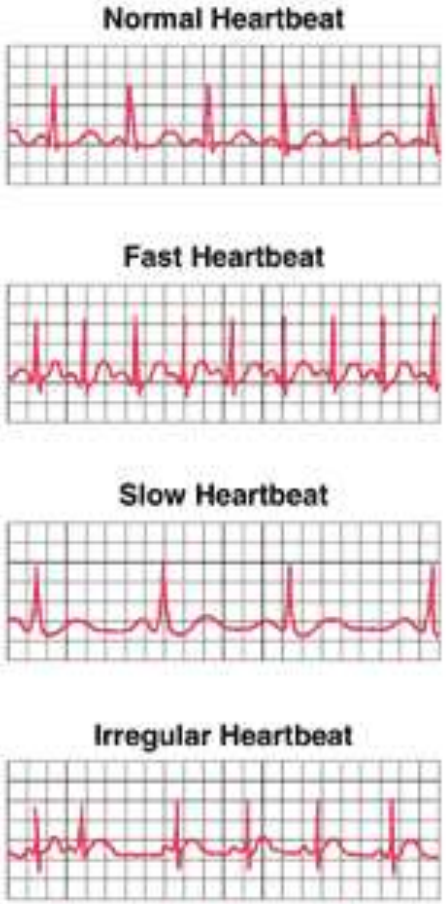
Electrocardiography (ECG)





ECG


R
P
T
Q S
P Wave
QRS Complex
T Wave
Activation of the atria
Activation of the ventricles
Recovery wave


Normal Heartbeat
Fast Heartbeat
Slow Heartbeat
Irregular Heartbeat

Digitalis toxicity

- life-threatening condition, 1,500/year
- In 2011, there were 2,513 cases involving cardiac glycosides reported to U.S. poison control centers. Of these, 90 experienced major effects (i.e, life threatening resulting in prolonged hospitalization) and 26 died
- Low TI
  - Therapeutic levels are 0.6 to 2 ng/mL
  - levels of toxicity between therapeutic and toxic ranges
- Acute toxicity
  - cardiac effects
  - nausea and vomiting
- Chronic toxicity
  - cardiac effects
  - nonspecific symptoms include fatigue, malaise, and visual disturbances

Digitalis toxicity

- Causes
  - High levels of digitalis in the body (over dose)
  - Accumulation during chronic treatment
  - Decreased tolerance to the drug, have normal levels of digitalis in blood
- Risk factors
  - Electrolyte Imbalance
    - Potassium loss (thiazide)
    - Low levels of magnesium
    - Hypercalcemia
  - Quinidine, flecainide, verapamil, amiodarone.
  - Kidney failure and dehydration

Signs/symptoms of acute toxicity

Gastrointestinal

nausea, vomiting, abdominal pain

Neurological

weakness, confusion, Photophobia

Electrolyte

Hyperkalemia
(> 5.5 mEq/L is a poor prognostic sign)

Cardiac

Palpitations, bradycardia, heart block, several types of arrhythmias, and Shortness of breath

Signs/symptoms of chronic toxicity

Gastrointestinal

Less than that of acute digoxin toxicity (nausea, anorexia)

Neurological

confusion, drowsiness, headache, hallucinations

Visual

sensitivity to light, yellow halos around lights, blurred vision

Diagnosis

- Serum digoxin level
- Electrolytes
- Renal function studies
- ECG

Diagnosis

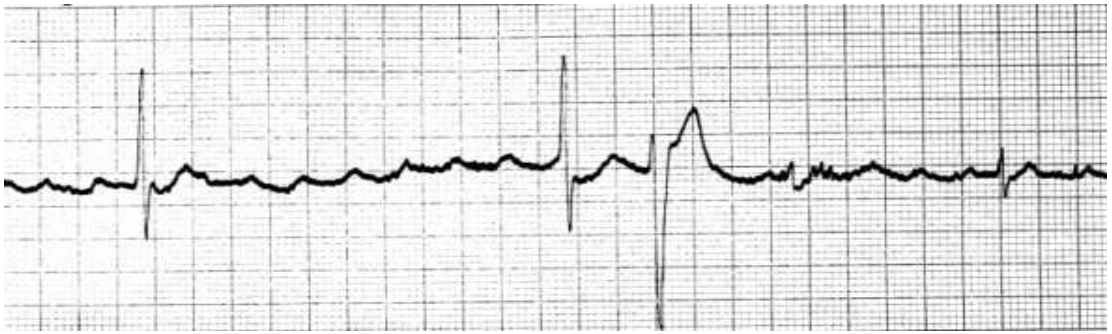
- Serum digoxin level
  - Toxicity begins >2.0 ng/mL
  - May be misleading in the acutely poisoned patient
  - False-negative assay results may occur with acute ingestion of non-digoxin cardiac glycosides (eg, foxglove or oleander)
  - Digoxin's long distribution phase results in high serum levels for 6-10 hours prior to completed tissue distribution

Diagnosis

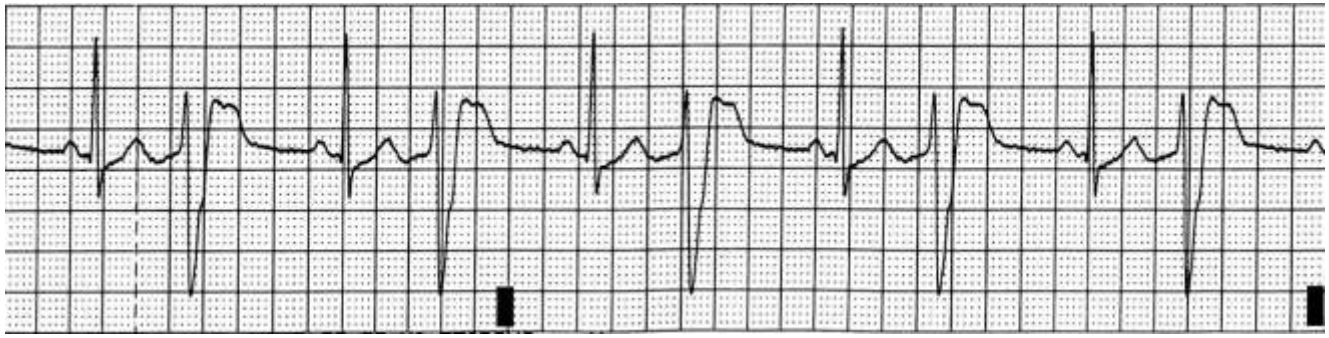
- Electrolytes
  - Hyperkalemia
  - Chronic toxicity: hypokalemia and hypomagnesemia
- Kidney function tests
  - BUN
  - Creatinine

Diagnosis

- ECG
  - May cause almost any dysrhythmia
    - atrial tachycardia with a 2:1 conduction
    - bidirectional ventricular tachycardia
    - atrial fibrillation with a slow ventricular response



atrial tachycardia with block



Sinus rhythm with frequent PVCs in a pattern of ventricular bigeminy

Treatments

Decontamination/enhanced elimination

For acute overdose: Activated charcoal, multiple dose activated charcoal, gastric lavage

Enhanced elimination (dialysis, hemoperfusion) does not effectively remove digoxin due to large volume of distribution and relatively high protein binding

Treatments

Digoxin immune Fab (ovine)

- Antidote, highly effective in treating life-threatening signs of digoxin toxicity such as hyperkalemia, hemodynamic instability, and arrhythmias
- Primary treatment of digoxin toxicity
- Indications:
  - Ingestion of 10 mg of digitalis (in children, 4 mg)
  - Serum digoxin level greater than 8 ng/mL in adults at steady state
  - Hyperkalemia (greater than 5 mEq/L)
  - Altered mental status
  - Rapidly progressive signs and symptoms of toxicity

Treatments

- DigiFab (40 mg of Fab), binds 0.5 mg digoxin
- 30 minute slow IV infusion
- Acute ingestion of unknown amounts and serum concentration of digoxin:
  - 20 vials of Digoxin immune fab (ovine)
  - Can split dose into 10 vials followed by another 10 vials to avoid a febrile reaction
- Chronic ingestion unknown serum digoxin concentration
  - 6 Vials of Digoxin immune fab (ovine) in adults and Children > 20 Kg
  - 1 Vial of Digoxin immune fab (ovine) in infants and Children < 20 Kg

Treatments

For known amounts of digoxin

Dose In Vials = **Digoxin ingested (mg) X 1.6**

Round up to the nearest vial

Treatments

For known digoxin serum concentration

$$\text{Dose In Vials} = \frac{\text{(Serum Digoxin ng/mL) x Weight (kg)}}{100}$$

Round up to the nearest vial

Treatments

Digoxin immune Fab

- Adverse Effects
  - Digitalis withdrawal: exacerbation of HF, rapid ventricular response and postural hypotension
  - Hypokalemia
  - Phlebitis
  - Fever, May occur with doses above 10 vials
- Warning
  - Patients who require digoxin's inotropic action may deteriorate secondary to the withdrawal of digoxin
  - Additional inotropic support may be required for these patients (e.g, dopamine, dobutamine or vasodilators)

Treatments

Electrolyte imbalance

- Hyperkalemia, use insulin plus glucose, and sodium bicarbonate if the patient is acidotic
- Hemodialysis may be necessary for uncontrolled hyperkalemia
- Correct hypokalemia (usually in chronic intoxication)
- Concomitant hypomagnesemia may result in refractory hypokalemia

Dysrhythmias

- Short-acting beta blockers (eg, esmolol) may be helpful for supraventricular tachyarrhythmias with rapid ventricular rates, but may precipitate advanced or complete AV block
- Phenytoin and lidocaine are useful for ventricular tachycardia
- Phenytoin can suppress digitalis-induced tachydysrhythmias
- Atropine has proved helpful in reversing severe sinus bradycardia
- Magnesium sulfate may terminate dysrhythmias

Digoxin Toxicity: Case Study

76 year old woman with history of atrial fibrillation, hypertension, renal impairment, breast cancer, osteoarthritis. Stroke 1 month prior to admission.

Medications: digoxin 250 mcg once daily, amlodipine, lisinopril, indapamide
SR, simvastatin, clopidogrel, bisoprolol, omeprazole, erythromycin

Presents with nausea, vomiting, change in vision, lethargy

VS: BP "normal"; HR 35-38 bpm

Labs

Digoxin levels: prior to admission: 3.4 ng/mL (0.8-2 ng/mL normal range for this lab)	On admission: 2.9 ng/mL	Increased digoxin dose from 125 mcg/day to 250 mcg/day 28 days ago

Digoxin Toxicity: Case Study

Summary: elderly patient with renal impairment, signs/symptoms of (chronic) digoxin poisoning with elevated digoxin level

Potential drug interactions:

Amlodipine	Bisoprolol	Erythromycin
(Ca^{+2} channel blocker) can increase digoxin level and enhance digoxin AV blocking effect	(ß blocker) can enhance digoxin's bradycardic effect	(macrolide antibiotic) can increase digoxin level

Digoxin Toxicity: Case Study

Received digoxin-specific antibody fragments (Fab)

Weight 108 kg

Digoxin level: 2.9 ng/mL

Fab Dose In Vials = $\frac{\text{(Serum Digoxin ng/mL) x (Weight in kg)}}{100}$

3 vials administered

Digoxin Toxicity: Case Study

6 hours post digoxin Fab infusion: digoxin 1.9 ng/mL

At discharge (91 hours post digoxin Fab infusion): digoxin 1 ng/mL, HR 65 bpm, digoxin toxicity signs/symptoms resolved

Monitoring

HR: improved (35-38 bpm to 65 bpm at discharge)	BP: remained stable	EKG: unchanged from baseline (atrial fibrillation)	K^+ not provided in this report (although this was a chronic toxicity not acute)

Digoxin Toxicity: Case Study

Approaches to digoxin poisoning in the chronically poisoned patient will depend on the status of the patient (signs/symptoms, age, renal function, cardiac status)

This was an elderly patient with impaired renal function who clearly had digoxin toxicity and an elevated level.

The clinical decision was made to treat promptly with digoxin Fab rather than prolong her clinical course.


Thank
You!

TOXICITIES FROM DRUGS OF ABUSE

Hasan Alhaddad, MSC
Department of Pharmacology and Toxicology
College of Pharmacy/ University of Baghdad, 2014

DRUGS OF ABUSE

- People abuse (misuse) substances such as drugs, alcohol, and tobacco for varied and complicated reasons
- Many first try drugs out of curiosity, to have a good time, because friends are doing it, or in an effort to improve athletic performance or ease another problem, such as stress, anxiety, or depression
- Society pays a significant cost
  - Direct damage to health by substance abuse and its link to physical trauma
  - Strong connection between crime and drug dependence and abuse
- Many street drugs have no therapeutic benefits. Any use of these drugs is a form of drug abuse

DRUGS OF ABUSE

Types of Abused Drugs

- **Depressants**: depress functions of central nervous system, cause calm and bring about sleep (alcohol, barbituates). Tranquilizers are depressants
- **Stimulants**: increase alertness and activity (cocaine, amphetamines)
- **Steroids**: promote muscle growth (androgen, testosterone, anabolic steroids)

DRUGS OF ABUSE

Alcohol

Beer, Liquor, gin
Calming and drowsy effects
High potential for abuse and addiction

Nicotine

Cigarettes, Cigars, Snuff
Addictive substance of tobacco
Stimulant or sedative
30% of total cancers, CVD, Chronic bronchitis

DRUGS OF ABUSE

Heroin

Smack, Junk, Black tar
Most widely abused opiate, extremely addictive
No medical use
Rush of pleasure followed by drowsiness and N/V

Cocaine

Coke, Crack
Powerful stimulant, Increase energy and decrease appetite
Heart disturbances, strokes, and respiratory failure

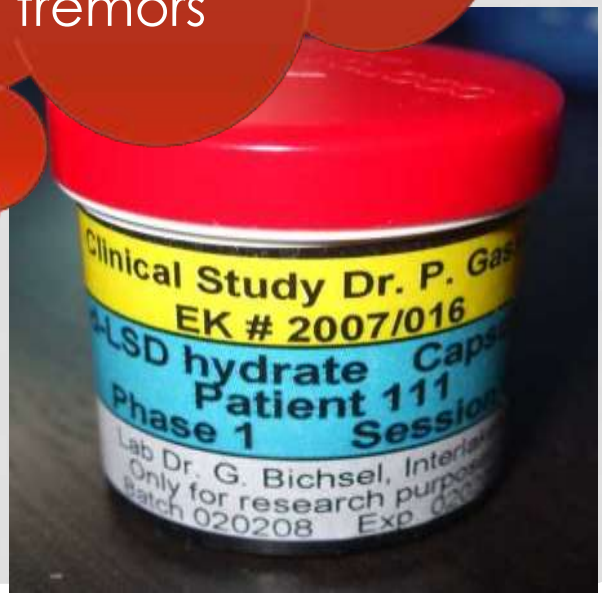
DRUGS OF ABUSE

Marijuana

Weed, Hash, Pot
Cannabis Sativa
Most common drug used
Euphoria then depression
Impairs memory and attention, and slows reaction time

Hallucinogens

Mescaline
LSD (Lysergic Acid Diethylamide)
Hallucination:distortion of perception of reality and time
Mydriases, fever, and tremors



DRUGS OF ABUSE

Methamphetamine

Speed, Ice
Strong stimulant, very addictive
Brain toxicity, fever, and convulsion
Chronically: violent behavior, insomnia, and anxiety

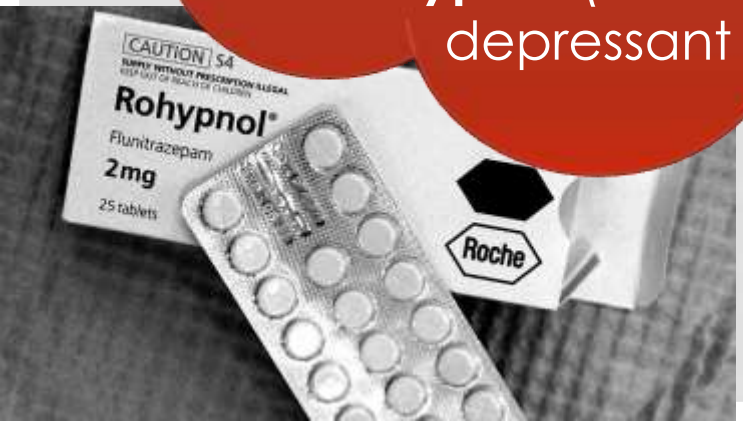
DRUGS OF ABUSE

MDMA

Ecstacy, Love drug
Methylenedioxymethamoh etamine
Stimulant and hallucinogen
Chills and muscle crumping
Overdose: unconsciousness and convulsions

Date Rape Drugs

Colorless and tasteless, victims are unable to resist assault and recall what happened next day
GHB: depressant has relaxing effect (party goers) and muscle growth (body builders), it cause coma and death at high dose
Rohypnol (flunitrazepam): depressant drug



DRUGS OF ABUSE

Inhalants

Glue, Sniff
Household products
Feeling high
Permanent brain damage and death

Anabolic steroids

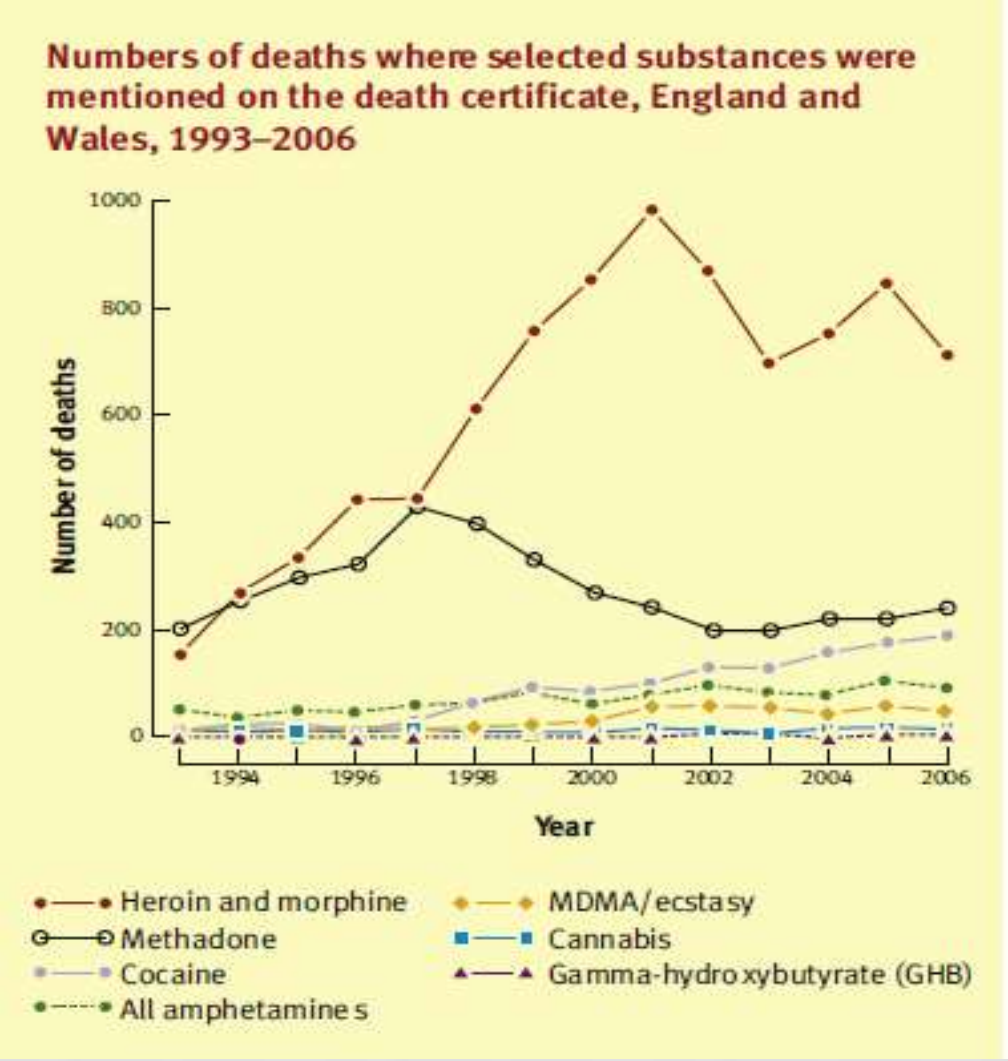
Steroids, Jym candies
Male sex hormones analogues
Strokes, hair loss and acne
Psychological dependence

Dissociative drugs
Ketamine,Detromethorphan, and PCP

TOXICITIES FROM DRUGS OF ABUSE

- Toxicity caused by drugs of abuse is a frequent reason for presentation to hospital
- Associated with toxic effects on almost every system of the organism
- Stimulants produce excitement, increased heart rate, and rapid breathing, while depressants do the opposite
- Drug overdose symptoms vary widely depending on the specific drug used, but may include:
  - Abnormal pupil size
  - Agitation
  - Convulsions
  - Death
  - Hallucinations
  - Nausea and vomiting
  - Unconsciousness (coma)

TOXICITIES FROM DRUGS OF ABUSE



TOXICITIES FROM DRUGS OF ABUSE

Common clinical features of toxicity with selected drugs of abuse

Drug group	Features of acute toxicity
Sympathomimetic stimulants	• Tachycardia, hypertension, mydriasis, sweating • Euphoria, agitation, confusion • Anorexia • Trismus[a] • Arrhythmias[b] • Myocardial ischaemia/infarction[b] • Circulatory collapse, pulmonary oedema[b] • Hyponatraemia[a] • Seizures[b] • Intracerebral haemorrhage or cerebral infarction[b,c] • Metabolic acidosis[b] • Hyperthermia, rhabdomyolysis, malignant encephalopathy[b] • DIC, multi-organ failure[a]
GHB and precursors	• Drowsiness, confusion, amnesia, coma • Nausea, vomiting • Myoclonus, hypotonia, • Hypothermia • Seizures • Bradyarrhythmia, hypotension • Respiratory depression or arrest • Metabolic acidosis, hypokalaemia, hyperglycaemia, hypernatraemia
Ketamine	• Nausea, vomiting • Blurred vision • Ataxia • Agitation, paranoid psychosis, perceived loss of control • Hypertension, tachycardia • Hyperpyrexia • Reduced consciousness, seizures and respiratory impairment

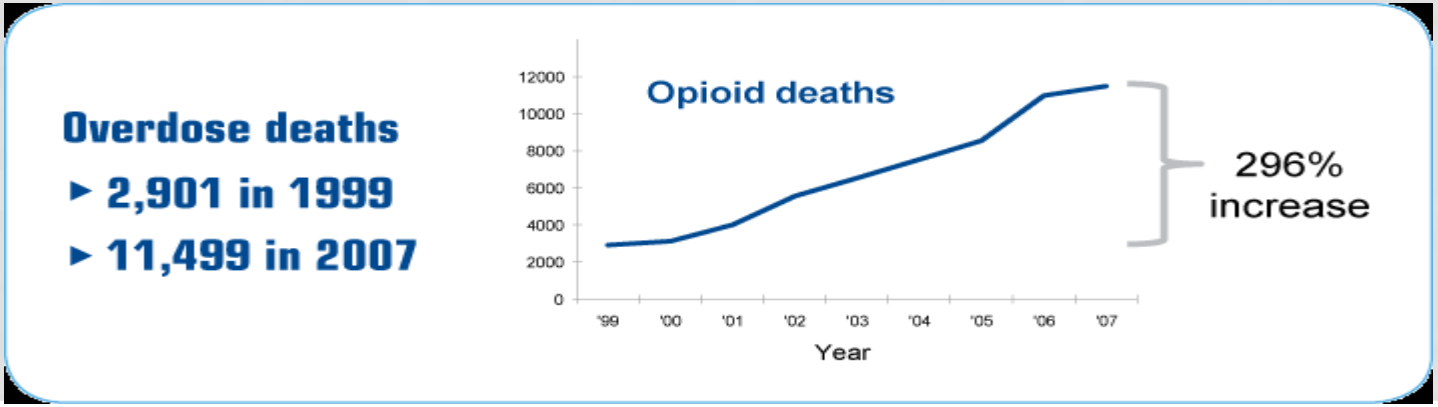
DIC, disseminated intravascular coagulation

[a] Especially MDMA
[b] Especially cocaine
[c] Especially amphetamines

TOXICITIES FROM DRUGS OF ABUSE

Opioids

- Heroin use remains a substantial public health problem and deaths from respiratory depression and cardiovascular collapse following overdose
- Naloxone is still the mainstay of therapy for severe opiate toxicity
- Substitution therapy with methadone or buprenorphine
- The morbidity and mortality associated with cocaine use is high: in the USA, 40% of emergency department visits due to illicit drugs involve cocaine
- Acute coronary insufficiency and arrhythmias are common toxicities



TOXICITIES FROM DRUGS OF ABUSE

Cannabis

- Cannabis (marijuana, hashish) is the most widely used recreational agent
- Although not often associated with acute toxicity requiring hospital admission, there is increasing recognition of its cardiovascular, respiratory and central effects
- Respiratory effects, tachycardia and hypotension or hypertension, and psychosis

TOXICITIES FROM DRUGS OF ABUSE

Ecstasy

- Acute effects are attributable to hyper-stimulation of the nervous systems via increased release and inhibited re-uptake of serotonin, norepinephrine and dopamine
- Hyperpyrexia, altered consciousness, disseminated intravascular coagulation, multi-organ failure and death

Inhalants

- Inhale the toxic chemicals of common products, the concentration of the fumes can be thousand times greater than the maximum permitted in industrial settings
- Experimentation, Cost effectiveness, and Easy availability
- Hallucinations, loss of self-control, violent behavior, nausea, unconsciousness or even death

TOXICITIES FROM DRUGS OF ABUSE

Michael Jackson died of acute propofol and benzodiazepine intoxication after suffering cardiac arrest at his home

Elvis Presley died of a cardiac arrhythmia; legend has it that he was seated on the toilet at the time. His death was liked to many different drugs. One report, found fourteen different drugs in Elvis' system, ten in significant quantity

comments

welcome

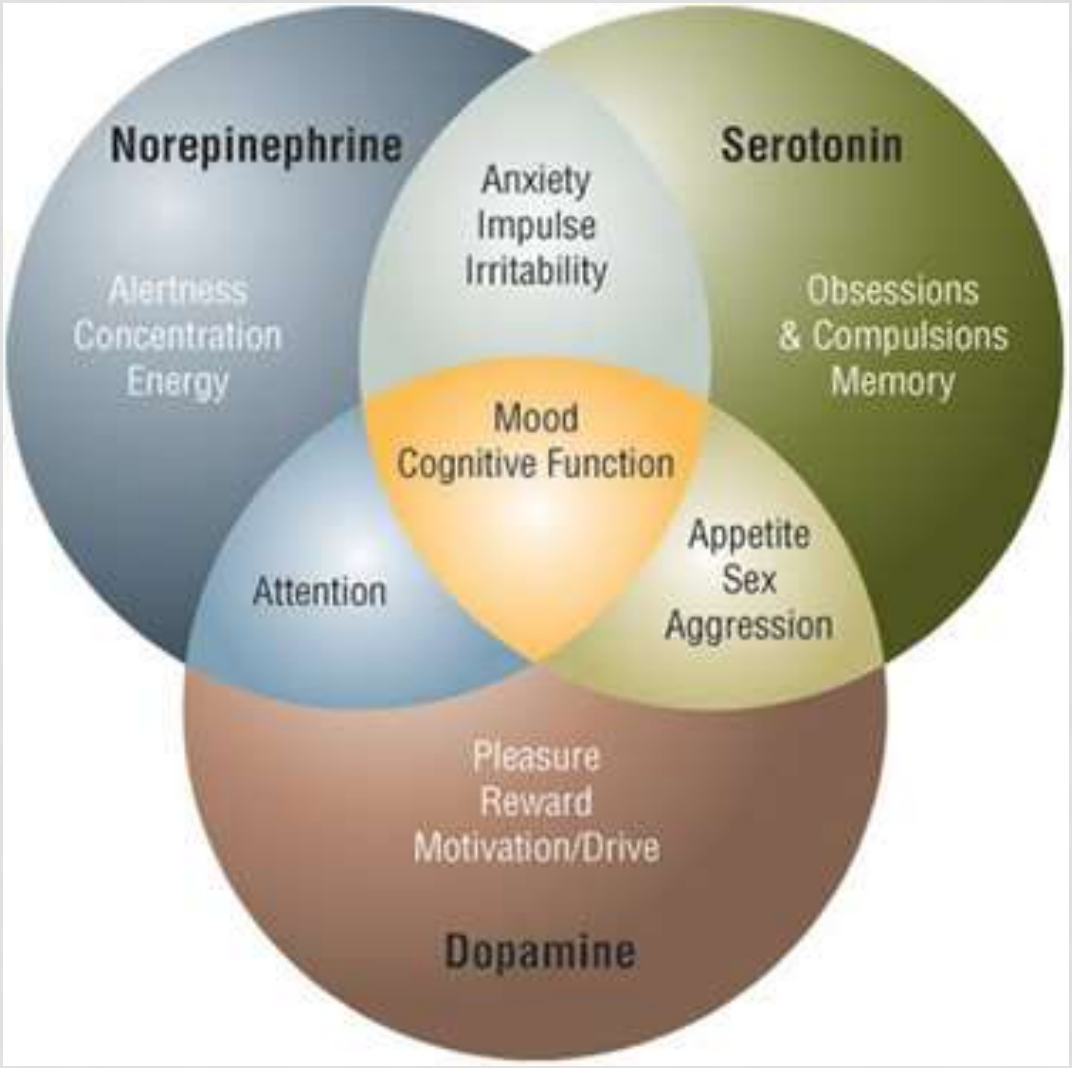
TOXICITIES FROM ANTIDEPRESSANTS

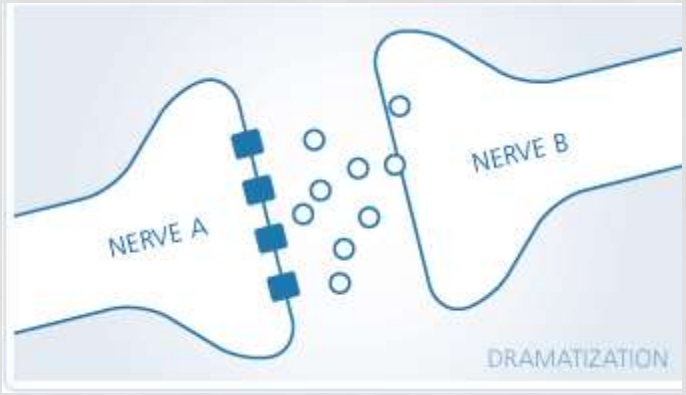
Hasan Alhaddad, MSc
Department of Pharmacology and Toxicology
College of Pharmacy/ University of Baghdad, 2014

ANTI-DEPRESSANT DRUGS

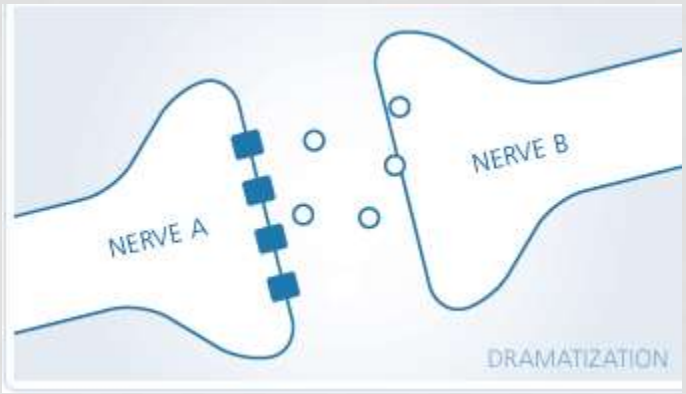
- Drugs used for the treatment of:
  - Major depressive disorder
  - Dysthymia
  - Anxiety disorders
  - Obsessive compulsive disorder
  - Eating disorders, chronic pain, neuropathic pain and, in some cases, dysmenorrhoea, snoring, migraines, attention-deficit hyperactivity disorder (ADHD), substance abuse and sleep disorders
- The pathophysiology of depression is complex and not completely understood
  - Monoamine hypothesis

ANTI-DEPRESSANT DRUGS





Normal



Depression

ANTI-DEPRESSANT DRUGS

- Depression knows no age boundaries
  - 10% to 15% of children and adolescents have some symptoms of depression
  - Major depression strikes about 1 in 12 adolescents
  - Among them, 1 in 14 will commit suicide as a young adult
- Depression is the most frequent psychiatric disorder in people dying by suicide
  - Self-poisoning is a common method of suicide, especially in women
  - Antidepressants are frequently used for self-poisoning

ANTI-DEPRESSANT DRUGS

- **Antidepressant Drugs and the Food and Drug Administration Black Box Warning, 2004**

PROZAC®
FLUOXETINE CAPSULES, USP
FLUOXETINE ORAL SOLUTION, USP
FLUOXETINE DELAYED-RELEASE CAPSULES, USP

WARNING

Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Prozac or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). (*See* WARNINGS, Clinical Worsening and Suicide Risk, PRECAUTIONS, Information for Patients, *and* PRECAUTIONS, Pediatric Use.)

ANTI-DEPRESSANT DRUGS

- 4 major classes of antidepressant drugs

Monoamine oxidase inhibitors

Used only to treat depression which is resistant to the other classes of antidepressants because of their serious toxicity

Phenlzine, Tranylcypromine, and Isocarboxazid

Selective Serotonin Reuptake Inhibitors SSRI

obsessive-compulsive disorders, panic disorder, alcoholism, obesity, migraine headache, and chronic pain syndromes

Citalopram, and Fluoxetine

Less side effects

Cyclic Antidepressants

Neuralgic pain, migraines, enuresis, and attention deficit hyperactivity disorder

NE and serotonin reuptake inhibition, anti-muscarinic activity

Imipramine, amitriptyline, maprotiline and amoxapine

Atypical Antidepressants

Serotonin reuptake inhibition with other neurotransmitter activity

Venlafaxine, Duloxetine, and Bupropion

MAO INHIBITORS TOXICITY

- The clinical toxicity of MAOIs falls into 3 clinical syndromes

Acute toxicity from overdose

-Symptoms may be delayed 6 to 24 hours
-Sympathetic hyperactivity which is followed by cardiovascular collapse
-Hyperthermia, seizures, and hypertension
-Renal failure and dehydration

Serotonin syndrome

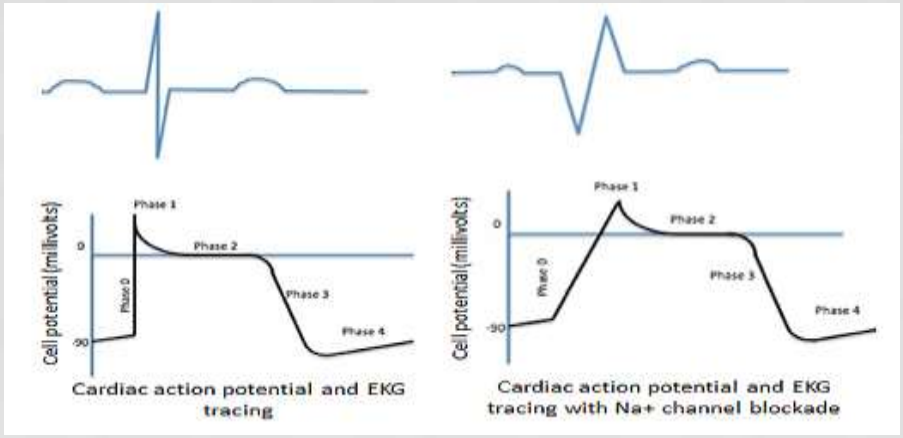
-Life threatening complication of antidepressant
-Altered mental status, increased neuromuscular tone, and autonomic excitation
-Prolonged duration of risk for the development of the syndrome after the discontinuation of the drug due to long duration of action
-"washout" period of at least 2 weeks

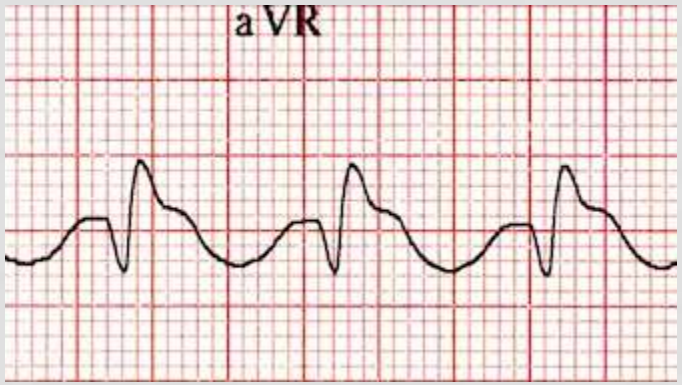
Hypertensive crises

-Food-drug and drug-drug interactions
-Pharmacologically active dietary amines (eg, tyramine) are ingested by Patients
-Indirectly acting sympathomimetic agents (eg, cocaine, amphetamine)
-Hypertension and tachycardia, headache, and altered mental status
-Usually last only several hours compared to MAOI overdoses in which symptoms can last several days

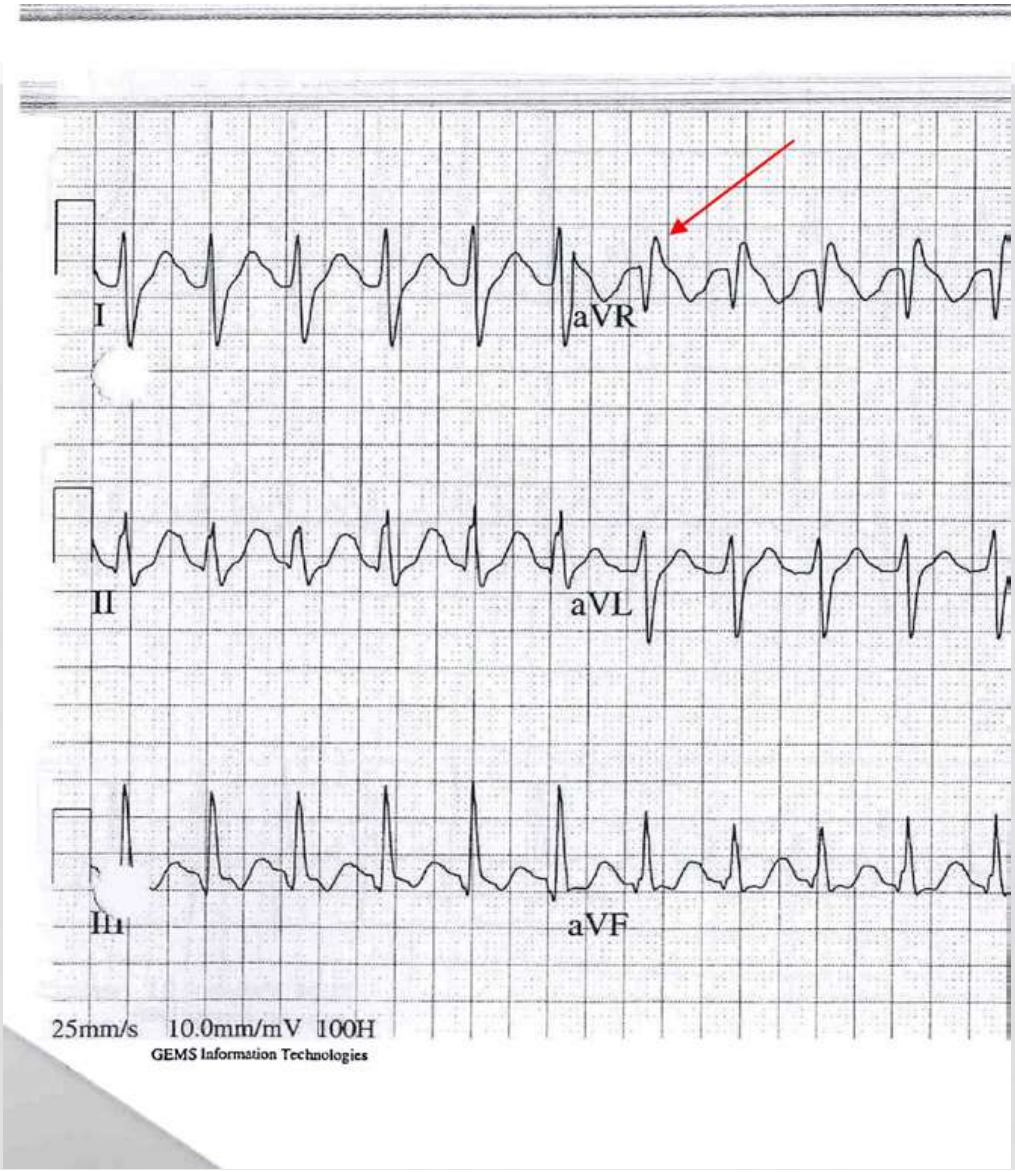
CYCLIC ANTIDEPRESSANTS TOXICITY

- Acute cardiovascular toxicity is primarily responsible for the morbidity and mortality
- Sinus tachycardia is the most common dysrhythmia
- Refractory hypotension is probably the most common cause of death from CA overdose (Na channel blockade)
- Seizures and altered mental status are the primary manifestations of CNS toxicity
- Anticholinergic effects
  - Dilated Pupils, dry mouth, dry flushed skin, hyperthermia, urinary retention





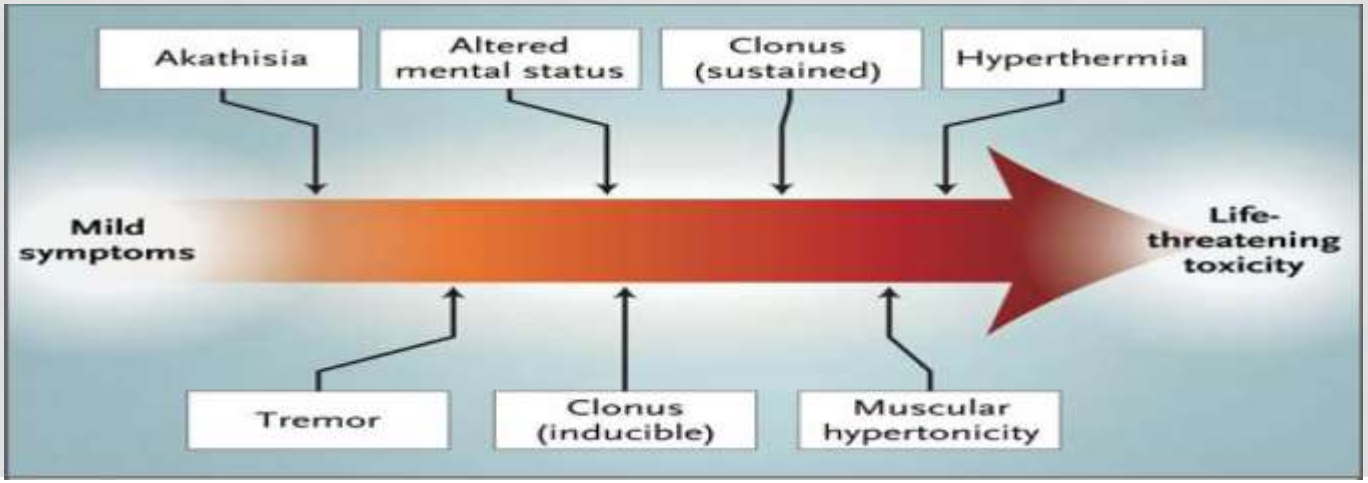
CYCLIC ANTIDEPRESSANTS TOXICITY



Electrocardiogram of patient with tricyclic antidepressant toxicity. QRS interval, 130 milliseconds; R wave in lead aVR, 4 mm (arrow)

SSRI TOXICITY

- Wide therapeutic index
- Mild or no symptoms after an overdose
- Acute signs and symptoms include nausea, vomiting, dizziness, blurred vision, tachycardia, and CNS depression
- Serotonin Syndrome "serotonin toxicity"
  - Uncommon
  - Clinical manifestations may range from mild confusion, tachycardia, and tremor to coma, hyperthermia, and muscular rigidity
  - Combination of serotonergic agents



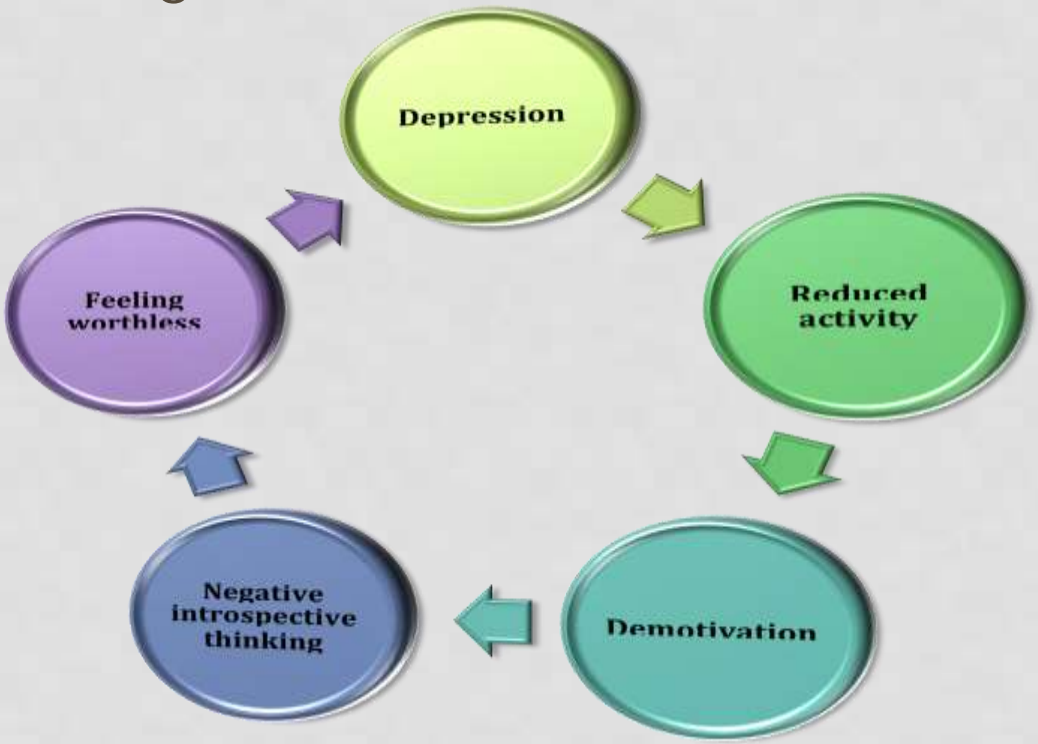
ATYPICAL ANTIDEPRESSANTS TOXICITY

- Each present unique toxicities in overdose

Class	Mechanism	Toxicity
Duloxetine (Cymbalta, Eli Lilly Indianapolis, IN)	• *NE reuptake inhibitor* • *Serotonin reuptake inhibitor*	• Limited information, expected to be the same as venlafaxine
Nefazodone (Serzone, Bristol-Myers Squib, Princeton, NJ)	• *Serotonin reuptake inhibitor* • *Serotonin antagonism*	• Dizziness • Dry mouth • Mild sedation
Trazodone (Desyrel Apothecon, Princeton, NJ)	• *Serotonin reuptake inhibitor* • *Serotonin antagonism* • *α1 adrenergic blockade*	• CNS depression • Orthostatic hypotension • Priapism • SIADH • Seizures
Mirtazapine (Remeron, Organon, West Roseland, NJ)	• *α 2 adrenergic blockade* • *Serotonin reuptake inhibitor*	• Sedation, altered mental status • QTc prolongation • Agranulocytosis
Bupropion (Wellbutrin, Zyban, GlaxoSmithKline, Research Triangle Park, NC)	• *Dopamine reuptake inhibitor* • *NE and serotonin reuptake inhibitor*	• Anticholinergic toxicity • Wide-complex tachycardia • QTc interval prolongation • Seizures • Symptoms may be delayed up to 12-18 h if extended release
Venlafaxine (Effexor, Wyeth Pharmaceuticals, Madison, NJ)	• *NE reuptake inhibitor* • *Serotonin reuptake inhibitor* • *Dopamine reuptake inhibitor*	• CNS depression, seizures • Hyperthermia • QTc and QRS prolongation, ventricular tachycardia, ventricular fibrillation • Hypotension

DIAGNOSTIC TESTING

- There are no specific diagnostic tests
- Electrocardiogram (ECG), specially for CAs
- Antidepressant serum concentrations are not available immediately in most hospital settings



TREATMENTS

- Airway, ventilation, and circulation should be assessed and managed
- Activated charcoal
- Seizures
  - Benzodiazepines
  - Phenobarbital
- Hypertension associated with MAOI toxicity
  - Nitroprusside continuous infusion
  - Phentolamine mesylate
  - β-adrenergic antagonists C/I: (potent interaction with MAOIs, leading to a greater than expected drop in blood pressure and dizziness).
  - a-methyldopa are C/I:(aromatic L-amino acid decarboxylase, which converts L-DOPA into dopamine. Dopamine is a precursor
    for norepinephrine (noradrenaline) and subsequently epinephrine (adrenaline)

TREATMENTS CONT.

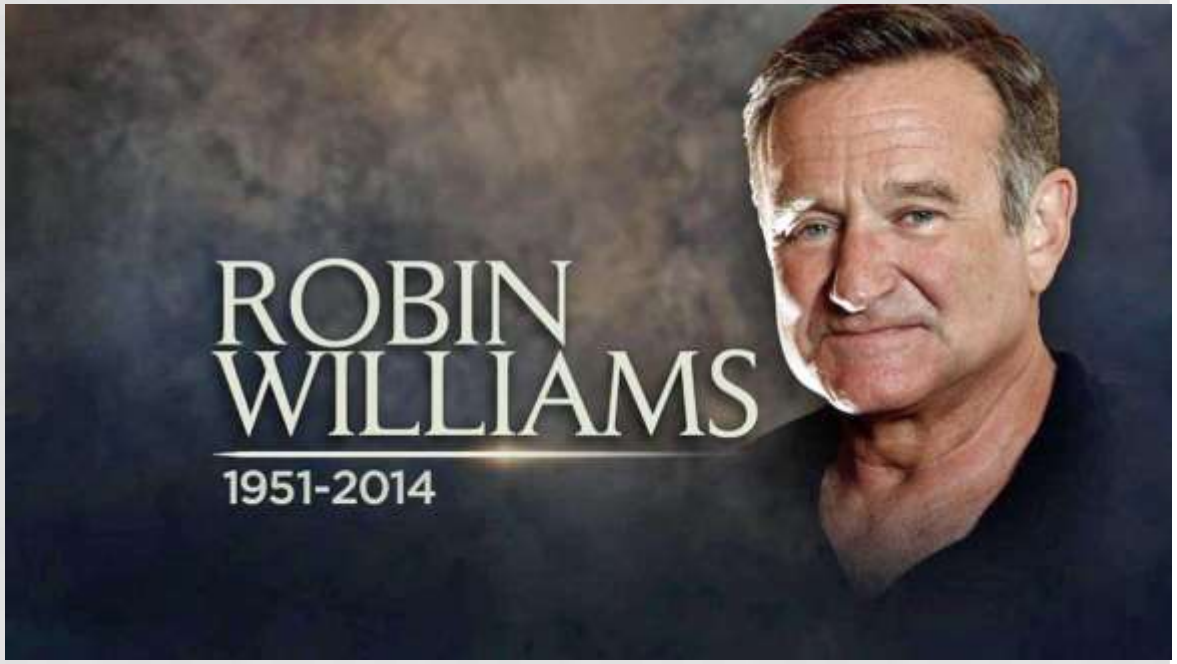
- Neuromuscular rigidity (MAOI toxicity, serotonin syndrome)
  - Benzodiazepines (Lorazepam and Diazepam)
  - Cyproheptadine
- Wide-complex dysrhythmias
  - $NaHCO_3$ boluses

***proposed mechanisms of action of sodium bicarbonate include: (1) treatment of drug overdoses whereby the offending agent has sodium channel blocking properties; (2) urinary and serum alkalinization to enhance the elimination of drugs by "ion trapping" and minimize drug distribution, respectively; (3) promoting the solubility of drugs or toxins that may otherwise precipitate in the kidney resulting in renal failure; and (4) neutralization of toxins that produce severe acidemia.

  - Lidocaine
  - Magnesium sulfate

Dorothy Dandridge, 1965
Imipramine overdose

The first African-American to be nominated for an Academy Award for Best Actress, the 42-year-old Dandridge was found dead by her manager from what was diagnosed as "acute drug intoxication." Her death was ruled to be due to an accidental overdose of Tofranil, an antidepressant that she took for what today might be diagnosed as bipolar disorder



Oscar-winning actor and comedian Robin Williams was found hanged Williams had reportedly been battling depression, according to a statement from his press representative

FOOD POISONING

Hasan Alhaddad, MSc
Department of Pharmacology and Toxicology
College of Pharmacy/ University of Baghdad
2014

FOOD POISONING

- Food poisoning (foodborne illness)
  - Illness caused by eating contaminated food
  - Infectious organisms (bacteria, viruses and parasites) or their toxins are the most common causes of food poisoning
  - Contamination of food may occur at any point of processing or production, or at home if food is incorrectly handled or cooked
  - Cross-contamination is often the cause
- Most often, food poisoning is mild and resolves without treatment, however, some people need to go to the hospital
- It is more commonly occurred after eating at picnics, school cafeterias, large social functions, or restaurants

FOOD POISONING

- Food poisoning is a common, costly -yet preventable- public health problem
- WHO estimates that food and waterborne diarrheal diseases kill about 2.2 million people annually, 1.9 million of them are children
- In USA
  - Each year roughly 1 in 6 Americans (or 48 million people) get sick,
  - 128,000 are hospitalized
  - 3,000 die of foodborne diseases
  - Yearly loss of up to $17 billion
- In UK
  - Foodborne diseases affect around a million people annually
  - 20,000 people receive hospital treatment
  - 500 deaths
  - Cost nearly £1.5 billion

FOOD POISONING

- In Iraq, although Food Poisoning outbreaks occurred frequently, they are rarely notified, investigated or documented
- A mass outbreak of organo-mercury poisoning due to consumption of treated grain by farmers and their families occurred in Iraq in 1971-72, leading to admission of 6,530 cases, and 459 deaths
- In 2013, an outbreak of Food Poisoning involving more than 100 persons attending a restaurant in Tikrit. One of them was dead
  - Staphylococcus aureus and Salmonella typhimurium were the responsible pathogens
  - Contaminated food stuff and un-hygenic food-handlers practices were the source

CAUSES OF FOOD POISONING

- Many bacterial, viral or parasitic agents, and chemicals cause food poisoning

Contaminant	Onset	Foods affected and means of transmission
Campylobacter	2 to 5 days	Meat and poultry, Contamination during processing - feces contact meat surfaces. Milk and water
Clostridium botulinum	12 to 72 hours	Improperly canned commercial foods, smoked or salted fish, potatoes baked in aluminum foil
Clostridium perfringens	8 to 16 hours	Meats, stews and gravies
Escherichia coli O157:H7	1 to 8 days	Beef contaminated with feces during slaughter. Milk and contaminated water
Staphylococcus aureus	1 to 6 hours	Meats and prepared salads. Spread by hand contact, coughing and sneezing
Hepatitis A	28 days	Raw, ready-to-eat produce. Spread by an infected food handler
Listeria	9 to 48 hours	Hot dogs, luncheon meats, unpasteurized milk and cheeses. Spread through contaminated soil and water

CAUSES OF FOOD POISONING

- Other causative agents:
  - Giardia lamblia
  - Noroviruses (Norwalk-like viruses)
  - Rotavirus
  - Salmonella
  - Shigella
  - Vibrio vulnificus
- Norovirus is a contagious virus responsible for more than half of food poisoning cases
- Salmonella is the most common pathogens that caused hospitalizations
- Escherichia Coli found in the intestines of all humans and animals. Certain strains can cause illness when ingested. The bacteria may contaminate meat during processing. It can also seep into foods that are not prepared safely

CAUSES OF FOOD POISONING

Toxins

- There are many toxins that can cause food poisoning. Some are produced by bacteria on or in food and others are produced by plants and animals/fish or other organisms that are ingested. There are many plants and animals/fish that can be poisonous under certain conditions but they are encountered infrequently or under special conditions

Bacteria	Plants	Animals/fish/other
enterotoxins	Mushroom toxins	Scombroid toxin
exotoxins	Belladona	Ciguatera toxin
cytotoxins	Ricin	Sasitoxin
Neurotoxins	Hemlock	Tetrodotoxin

CAUSES OF FOOD POISONING

Chemicals

- Certain chemicals are considered toxins that can cause food poisoning
- Mercury, found in drinking water and in fish such as tuna and marlin
- Other examples of chemicals that can be toxic if enough contaminates food and water are pesticides, polychlorinated biphenyls, and lead

Food allergy

- Is an abnormal response to a food triggered by body's immune system
- Some foods, such as nuts, milk, eggs, or seafood, can cause allergic reactions in people with food allergies
- Treatments ??

SYMPTOMS OF FOOD POISONING

- Start within hours after eating the contaminated food, or they may begin days or even weeks later
- Sickness caused by food poisoning generally lasts from a few hours to several days
- Common signs and symptoms
  - Nausea, Vomiting, Watery diarrhea, Abdominal pain and cramps, Fever
- Specific bacteria may cause these signs and symptoms
  - Clostridium botulinum: weakness, blurred vision, difficulty speaking and swallowing, respiratory failure and death
  - Salmonella spp., Shigella spp., and Campylobacter: fever, chills and bloody diarrhea
  - Escherichia coli (E. coli): hemorrhagic colitis (diarrhea with very little stool and large amounts of blood), occurring up to 3 days after eating contaminated food
  - Mushroom poisoning: stomach upset, delirium (confusion), vision difficulties, heart muscle problems, kidney failure, death of liver tissue, and death if left untreated

RISK FACTORS FOR FOOD POISONING

- Older adults
  - Immune system may not respond as quickly and as effectively to infectious organisms compared to youngers
- Pregnant women
  - Changes in metabolism and circulation may increase the risk of food poisoning
- Infants and young children
  - Immune systems have not fully developed
- People with chronic disease
  - Reduces the immune response
  - Diabetes, liver disease, AIDS, and chemotherapy or radiation therapy for cancer

DIAGNOSIS OF FOOD POISONING

- History
  - Duration, Symptoms , Kind of food
- Physical exam
  - Signs of dehydration
- Diagnostic tests, to identify the infectious organism
  - Blood test
  - Stool culture

- It is necessary that large numbers of the organisms be present in a food for it to be hazardous
  - The laboratory reports the number of organisms present per gram of food
- For Staphylococcus aureus, the current method is to screen for enterotoxin first, culturing for the organism will occur only if necessary
- Other bacteria, any number of organisms present in a ready-to-eat food may be significant
  - For these kinds of agents, the laboratory reports their presence or absence. Their presence in a ready-to-eat food should be considered significant

TREATMENTS OF FOOD POISONING

- Treatment for food poisoning typically depends on the source of the illness, if known, and the severity of symptoms
- Lavage and activated charcoal
- Control nausea and vomiting
- Replacing fluids and electrolytes (such as sodium, potassium, magnesium, and chloride)
  - Diarrhea
  - Persistent diarrhea or vomiting may need hospitalization
- Antibiotics
  - Not commonly indicated
  - and/or the symIndicated when the kind of bacteria is determined ptoms are severe
  - The sooner treatment begins, the better

TREATMENTS OF FOOD POISONING

Other Drug Therapies

- Antitoxin to neutralize toxins from C. botulinum (only given within the first 72 hours)
- Amitriptyline to control the numbness and tingling from ciguatera poisoning
- Apomorphine or ipecac syrup to cause vomiting and help rid the body of toxins
- Atropine for mushroom poisoning H.W.
- Diphenhydramine and cimetidine for fish poisoning H.W.
- Mannitol for nerve-related symptoms of ciguatera poisoning H.W.

PREVENTION

Encourage your people to:

- Wash hands, utensils and food surfaces often
- Keep raw foods separate from ready-to-eat foods
- Cook foods to a safe temperature
- Refrigerate or freeze perishable foods promptly
- Defrost food safely
- Throw it out when in doubt


KEEP
CALM
AND
Avoid Food
Poisoning