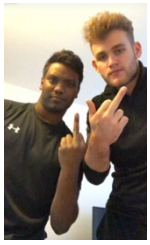
XOXO

Pharma ‘21



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1a. General Pharmacology

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1. Meaning of materia medica

- = Latin term that has now generally replaced by “pharmacology”
- In the 17th century when physical science, reliance, observation and experiments started to get more important as well as theoretical medicine. Physicians in Great Britain began to use the term “material medica” which means the science of drug preparation and the medical use of drugs
- Origin, preparation, doses and mode of administration

Pharmacology

- Is the branch of biology concerned with the study of drug action, where a drug can be broadly defined as any man-made, natural or endogenous molecule which exerts a biochemical or phycological effect on the cell, tissue, organ or organism
- From the Greek word pharmakon = drug/medicine and logos = study/science
- General pharmacology: pharmacodynamics and pharmacokinetics
- Special pharmacology: the study of specific drug properties (PK/PD of specific drugs)
- The study of *how they affect a biological system and interact between living organisms, how they alter normal biological functions*

Pharmacodynamics

- Describes how medications affect biological activates “what the drug does to the body”
- The study of the biochemical and physiological effects of drugs, their mechanism of action and side effect occurrence
- Principles of drug action on the body
  - Stimulation: enhancement of biological action, except epinephrine effect on the heart
  - Depression: depression of a biological action, ex. Barbiturates on CNS
  - Replacement: replacing a naturally occurring substance, ex. TH replacement
  - Cytotoxic: toxic effect on either organisms or neoplastic cells
- Mechanism of drug action via cell proteins:
  - Receptors
  - Ion channels
    - Ligand gated, e.g., Nm, Nn, GABAa, receptors, 5-HT receptor
    - Voltage-gated, e.g., blockers of Na^+ channels in local anesthetics
    - Signal gated, e.g., Sulfonylureas
  - Enzymes
  - Transporter carriers/proteins
  - Structural proteins with DNA

Pharmacokinetics

- How the body handles a medication “what the body does to the drug”.
- The study of the alteration in concentration of a drug on its journey throughout the body.
- The pharmacokinetic parameters allow the clinician to design and optimize treatment regimens, including route of administration, amount and frequency of each dose and the duration of treatment.
- Properties: absorption, distribution, metabolism, excretion

2. Characteristic of pharmacokinetics (1, 31, 60, 62)

Absorption

Absorption = ***Movement of drug from site of administration into circulation***
There are different ways of crossing the membrane for small molecules:

- **a. *Passive transport* – Diffusing through the lipid membrane**
  - Easy passage through the membrane by small, lipophilic and non-ionized molecules
  - = **Passive transport** → No need for energy
    - Size of particles ***has to be small*** – smaller than in active transport
    - Level of ionization – ***has to be non-ionized***
- **b. Aquaporins – Diffusing through aqueous pores**
  - Little bit bigger molecules → Water
- **c. Active transport – Solute carriers or other transporters**
  - Most drugs are transferred by carriers
  - → **Facilitated transport:**
    - = Still ***no need for energy***, because it is **going down concentration gradient**
    - With facilitated transport, the rate of transportation is limited (limited number of carriers)
    - Specific transporters (membrane proteins) → Transporters or ion channels
  - → **Active transport:**
    - **Against concentration gradient** → ***Need of energy*** (= ATP-dependent)
    - Carrier mediated transport
    - Like mentioned, either facilitated or active has some limit (some maximum)
      - ♦ This maximum is based on the number of transporters we have
      - ♦ More transporters = higher maximum
- **d. Pinocytosis**
  - Another possibility how the absorption may happen is using pinocytosis
  - This is for example for bigger molecules, maybe some peptides (like ***insulin***)
    - This principle is used in the BBB, how insulin can easily penetrate through blood brain barrier
  - Pinocytosis means that the drug must be dissolved in some fluid, and the vacuole is slowly moving though the barrier and then it goes outside on the other side
  - Pinocytosis means brining a bigger molecule from one side to the other side
    - Invagination of part of cell membrane with trapping the extracellular constituents
    - Released intracellularly or transcellular extrusion on the other site
    - E.g., Insulin transport through blood brain barrier

Factors influencing the rate and extent of absorption:

- **Lipid solubility**
  - **High** lipid **solubility** = **faster transportation through membrane**
  - Low lipid solubility = transportation takes much longer time
- **pH partition (ionization)**
  - In basic environment → acids are ionized (and vice versa)
    - An example is acetylsalicylic acid (aspirin), a weak **acid** → ***non-ionized*** in acidic environment
      - ♦ Non-ionized = absorbed more easily
  - Whenever we have drugs which are acidic, they will be absorbed much faster in the stomach than in the intestine → where pH is increased
  - Weak bases are ionized in acidic environment = cannot be absorbed in stomach
    - → Passer into small intestine, where the pH is higher, this will reduce the ionization
      - ♦ → So, basic drugs can be absorbed in small intestine

aDme = Distribution

- After a drug has been absorbed into plasma, it must be distributed to target organ
- Rate and extent of distribution depends on:
  - **Chemical structure of drug**
    - More lipophilic agents will be eliminated faster from the blood, because ***blood is hydrophilic***
      - ♦ So, lipophilic drugs can reach the brain faster
  - **Rate of blood flow**
    - Faster blood flow = higher exposure to the drug and it can work much faster

- **Binding of drug to proteins in blood**
  - Different drugs can be bound to different plasma proteins
  - The strength of binding may be responsible for interaction
    - If we have 2 different drugs both bound to the same protein, they can replace each other, so they will influence the concentration of free drug of the other drug
- **Elimination process**
  - If there is more drug free, it is eliminated faster
  - If it is bound to plasma protein it cannot cross the glomerulus into primary urine
  - So, it will stay there and circulate until the balance between bound and unbound form is moved (shifted) into the balance into bound form, and it must be released, and then slowly it is prolonged the elimination process

% Bound

- **% Bound drug = [bound drug]/([Bound drug]+[Free drug]) x100**
- Renal failure, inflammation, fasting, malnutrition can reduce plasma proteins = ↑ free drugs
  - Competition from other drugs can also affect % bound
- Renal failure: → we lose albumin
- Liver impairment: → we don't make sufficient amount of albumin
- Inflammation: → decreased amount of % bound → much higher amount of free drugs
  - In this situation, the percentage of bound can be dramatically changed and suddenly we will have much higher amount of free drug which is available for some effects

Volume of distribution

- = Represents **how extensively a medication is distributed throughout the body**
  - ***Vd = Concentration of drug (C)/total concentration of drug in system (D)***
- Volume of distribution is a ***theoretical volume*** and determines the ***loading dose***
  - Loading dose = the first dose we give to reach certain concentration in target organ
    - **Loading dose = Cp $_{(Target\ organ)}$ x VD**

Important effects of pH partitioning

- **Urinary acidification:**
  - Will accelerate the excretion of weak bases and lower excretion of weak acids
- **Urinary alkalinization** has the opposite effects
  - Will accelerate the excretion of weak acids and lower excretion of weak bases
- **CNS:**
  - If we **increase the pH** (by bicarbonate), weak acids will become immediately **ionized** after crossing BBB back into the blood = cannot go back into CNS (ionized = can't pass BBB)
    - And vice versa, if we decrease pH – drugs can go back into CNS → increasing toxicity
  - We can used this when we need to remove something from the brain fast

adMe = Metabolism

- = The process of converting a medication into a less (or more) active form
  - In most cases, metabolic reactions turn an active medication in to a less active, or inactive metabolite which is then ready to be excreted
  - Some medications are administered in an inactive form (pro-drug), which needs to be metabolized to an active form within the body before they can produce their effect
- Generally, metabolic reactions in liver can be divided into 2 major phases:
- **Phase 1** is called **<u>detoxification phase</u>** → ***Monooxygenase P450 system***
  - Where the drug is metabolized into inactive metabolites → detoxifying the drugs
    - It can also be into active metabolites, via different processes
  - The major metabolizing complex is ***cytochrome P450***
    - It converts **non-polar**, **lipid-soluble** medications into **more polar** and **water-soluble** metabolites
  - These isoenzymes can be selective to certain drugs, so they have special substrates, and some drugs may influence these isoenzymes (inducers vs. inhibitors)
    - So that is the point where we may have many interactions
- **2nd phase → <u>Conjugation reactions</u>**
  - Here the drugs are conjugated or joined with another compound (for example glucuronic acid)
    - Can also be methylation, acetylation or sulfation)
  - These reactions make the metabolites **highly polar** → so they cannot penetrate cell membranes
    - Thus, they will get **trapped in the urine** and eliminated by kidneys

Genetic variability of CYP450

- Some people have fewer enzymes or enzymes which work more slowly and less effectively against certain medications
  - Can lead to accumulation of the medication in the body → resulting in dangerous side effects
- In contrast, some people are rapid metabolizers → inactivates medications so fast that it's difficult to achieve a high enough level of medication in blood

Examples from antitussives:

- **Codeine:**
  - People **with ↑ activity of CYP450** → ↑ formation of morphine with opioid effects → ↑ risk of morphine side effects
- **Dextromethorphan:**
  - People **with ↓ activity of CYP P450**, dextromethorphan will be accumulated in higher concentrations → hallucinations

Inducers vs. inhibitors of cytochrome P450:

- **Inducers CYP** → decrease plasma concentration of drug (decrease effect of drug, insufficient treatment)
  - Example: Barbiturates, rifampicin, phenytoin, carbamazepine, smoking (reason why smokers need more coffee!)
- **Inhibitors of CYP** → increase plasma concentration of drug (accumulation, toxic to patient)
  - Examples: cimetidine, macrolides, ketoconazole and grapefruit juice

admE = Excretion

Excretion via kidney

- The major function of the kidney is to clear metabolic waste material and foreign substances (like medications)
- Blood is filtered in the glomerulus → as the filtrate makes its way through tubule, some drugs may be absorbed
- Polar or too big molecules cannot cross the tubular cells → get trapped inside tubular fluid and are eliminated via urine
- The pH of urine will affect excretion: (Most drugs are either weak acids or weak bases)
  - We can use this in overdosing of drugs:
  - Overdose of weak acid (aspirin) → alkalize the urine by bicarbonate → becomes polar → excreted
  - Overdose of weak base (amphetamines) → acidify the urine by ammonium chloride → becomes polar → excreted

Excretion via bile and feces

- Orally administered drug which don't get absorbed through the GIT are directly passed in feces
- Some drug which are absorbed in GIT enter the enterohepatic circulation to get to the liver
  - bind to bile → excreted back to the intestine and leave the body through feces

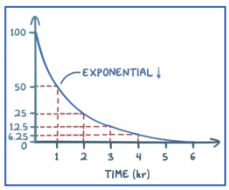
Excretion via exhalation

- Many inhaled anesthetics get eliminated by lungs through exhaled air

Other → small amounts can be excreted by breast milk, sweat, saliva and tears

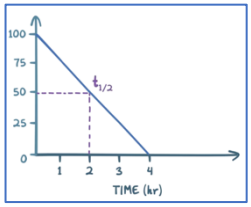
Clearance

- Clearance = the volume of medication cleared from plasma
- Total body clearance = renal clearance + hepatic clearance + lung clearance + other
  - = Rate of elimination/concentration of drug in plasma



Rate of elimination (1st order vs. 0 order kinetics)

- Determined by elimination kinetics
- Most medications are eliminated through 1st order kinetics
  - = Rate of elimination is directly proportional to the concentration of the medication in the body
    - The absolute amount eliminated per unit of time may change
    - But the fraction which is eliminated always stays the same
  - For example, if we start with plasma concentration of 100 mg/l and we eliminate 50% of it each hour
    - After 1 hour → 50 mg/l, after 2 hours → 25 mg/l, 3 hours → 12,5 mg/l, 4 hours → 6,25 mg/l
    - The curve will show ***exponential decrease*** in the plasma concentration of the medication
    - This also determines the ***half-life*** of the medication = the time required for plasma concentration of medication to be reduced by half (in this case = 1 hour)
- There are few medications which are eliminated through 0 order kinetics
  - E.g., phenytoin, warfarin and aspirin
  - The rate of elimination is **constant** → independent of the concentration of the medication in the body
    - The mg eliminated per unit of time stays the same! But the fraction eliminated changes
  - For example, we start with plasma concentration of 100 mg/l, and we always eliminate 25 mg/l each hour
    - After 1 hour → 75 mg/l, after 2 hours → 50 mg/l, after 3 → 25 mg/l, after 4 hours = 0



3. Ways of drug administration (9) + 4. Route of administration (49)

Systemic		Local
Enteral	**Parenteral**	**Mucosal** Mouth, throat, airways, ear, nose, eye, vagina, uterus, rectum
Peroral	Intravenous (i.v.)	**Skin**
Rectal	Intramuscular (i.m.)	**Intra-articular**
Sublingual	Subcutaneous (s.c.)	**Intra-thecal/epidural**
	Intra-arterial (i.a.)	
	Transdermal	
	Inhalational	
	Intranasal	

3. Ways of drug administration (9) + 4. Route of administration (49)
Intro:

- The enteral route of administration is the most common route
- The enteral route of administration includes every drug that is absorbed through the oral mucosa or the rectum
- Here we have:
  - **Peroral** (p.o.)
  - **Rectal** (p.r.)
  - **Sublingual** (s.l.)
- From this group, the dominating one is the peroral route of administration
  - It is preferred by every patient who is able to swallow and is conscious

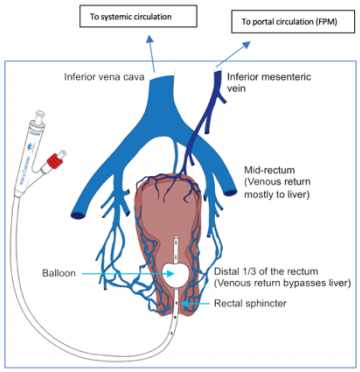
1. Peroral route of administration:

- The most commonly used, the most desirable, the safest and easiest way of administering drugs
- However, it is the most difficult pathway for the drug
- Two- to five-fold differences in the rate or extent of GIT absorption – depending on the dosage form

Advantages	Disadvantages
- Safest and most common, convenient and economical route of administration	- Limited absorption of some drugs - **First-pass effect** due to biotransformation - Patient compliance is necessary - Drugs may be metabolized before systemic absorption

Bioavailability

- Generally, the bioavailability of oral drugs follows the order:
  - Solution > Suspension > Capsule > Tablet > Coated tablet
- Bioavailability = the fraction (or %) of the drug which reaches systemic circulation
  - Drugs that are administered by the **intravenous** route are **100% bioavailable**, because the entire amount administered reaches systemic circulation
  - **Oral drugs** are **not** 100% bioavailable, because some of the drug is not absorbed, but is instead lost in feces and some of the drug is destroyed by the liver before it reaches general circulation
- The **main limiting factor** of peroral route of administration is **first pass metabolism**
  - The GIT is drained by the portal vein and through the portal vein it is transported to the liver
  - So, before the drug reaches systemic circulation, it is transported into the liver where the proportion (higher or lower) can be dissolved
- So, when the drug has a very high proportion of the first pass metabolism, we have 2 options
  - 1. Alternative route of administration if it's possible
    - IV, rectal, subcutaneous, inhaled, transdermal, sublingual etc. …
    - E.g., nitrates used to treat chest pain (angina)
      - Because nitrates are metabolized extensively by the liver on first pass, they must be given via an alternative route, like **sublingually** or IV
  - 2. Or, we can use the drug in very high portion



2. Rectal route of administration

- *Systemic* and *local* effects
- Useful for those who find it difficult to swallow, or keep down medication (children)…
- No drug-food interactions, gastric emptying rate
- **Enema, rectal suppositories, gel**

- **Advantages:**
  - Rectal route of administration is ***only partly accompanied by first-pass metabolism***
    - Because only upper part of the veins which supply the rectum terminate in the portal vein
    - Lower part of the veins that supply the rectum are terminated in the systemic circulation
    - Approx. 50% of the drug is transported to the liver and undergo first-pass metabolism
  - Another advantage is that this is useful for patients that are unconscious or have problem swallowing, for children

- **Disadvantage:**
  - On the other hand, the dose given by this route should by very high
  - The rectum has no villi → very limited surface for absorption compared to the GIT
  - The dose can lead to irritation of rectal mucosa and other additional side effects

3. Sublingual route of administration

- Factors affecting the sublingual absorption
  - **Lipophilicity of drug**
  - **Solubility in salivary secretion**
  - **pH and pKa of the saliva**
  - **Binding to oral mucosa**
  - **Thickness of oral epithelium**
  - **Oil to water partition coefficient**

- **Advantages:**
  - Rapid and extensive drug absorption – a relatively rapid onset of action
  - Low dosage gives high efficacy (***no first-pass MTB***), ↓SE
    - **<u>This is the only enteral route of administration with no first-pass metabolism</u>**
    - → There is a direct transport of the drug through the sublingual mucosa to the blood stream to the systemic circulation
  - Drug is protected from degradation due to pH and digestive enzymes
  - Used in emergency conditions, for administration of antianginal drugs → ***nitroglycerine***
  - Fast dissolution or disintegration in the oral cavity, without the need for water or chewing

- **Disadvantages:**
  - ***Unsuitable for prolonged administration***
    - Not suitable for longer treatments because there is a very significant fluctuation in the drug bioavailability depending on the composition of the saliva
    - Composition of the saliva changes during the day and can strongly affect the proportion of the drug that is absorbed
    - Thus, not suitable for long-term medication when we want to maintain stable plasma level of the drug
  - Also, ***not all drugs are absorbed through the oral mucosa***, we only have several of them
    - These drugs have to exhibit really high lipophilicity
    - Everything which has small molecules can potentiality be absorbed through the mucosa, but the second factor is the polarity of the molecule
  - Cannot be used when a patient is uncooperative or unconscious
  - The patient should not smoke while taking sublingual medication

Parenteral way of drug administration

Systemic		Local
Enteral	**Parenteral**	**Mucosal** Mouth, throat, airways, ear, nose, eye, vagina, uterus, rectum
Peroral	**Intravenous (i.v.)**	**Skin**
Rectal	**Intramuscular (i.m.)**	**Intra-articular**
Sublingual	**Subcutaneous (s.c.)**	**Intra-thecal/epidural**
	Transdermal	
	Inhalational	

A. Intravenous route of drug administration (i.v.)

- Intravenous route of administration is used especially when we want to ***treat the patient for long-term***
- The dose of the drug should be adjusted, so we use infusion in which the rate can be adjusted
  - The main advantage is that this way we apply large volume, that is not possible to be administered through intramuscular administration
- Also, we can administer drugs which are not totally pH equal to the blood stream

- **Advantages:**
  - *Rapid action*
  - **Bioavailability is 100%** (***no*** gut, ***no*** first pass metabolism)
    - = Very small dose is required
  - Very large volume infusions of the drug can be given
  - Drug dose titration
  - Drugs can be delivered at a uniform rate
  - Drugs causing even high intensity of irritation and hypertonic solutions can be administered

- **Disadvantages:**
  - Thrombophlebitis and venous thrombosis, necrosis, hemolysis, anaphylaxis
  - Only aqueous solutions of the drug can be administered
  - Once the drug has been administered, it can't be removed
  - Toxicological risk and local side effects can limit the use of intravenous route of administration

B. Intramuscular route of drug administration

- Intramuscular route of administration can also have very rapid and prolonged effects
  - It depends on the formulation of the drug, especially the pharmaceutical auxiliary agent
- We can obtain very rapid onset and very acute effect and similarly to intravenous route, it can serve for prolonged effect
  - E.g., Intramuscular injection that is applied once each month is an option for a contraception
  - Or hormonal replacement therapy is also done via intramuscular route
    - The dissolution of the hormones from the site of application last up to 1 month

- **Advantages:**
  - Depot preparations (suspensions) – prolonged drug effects
  - Drugs that cause mild irritation can be injected
  - Small volume of the drug can be given
  - The more vascular the muscle is – the faster the absorption is
  - Absorption rate is between IV (intravenous) and SC (subcutaneous)

- **Disadvantages:**
  - **Local hematoma, an abscession, damage to the nerve**
  - **Large volumes cannot be administered**
  - Similar to intravenous route, here also the main problem accompanied by site of application is local irritation, damage of peripheral nerve
    - In worst case scenario, necrosis can occur

C. Subcutaneous route of drug administration

- Subcutaneous route is the ***slowest*** of these 3 (i.v., i.m., s.c.) ***in terms of onset of effect***
- Bioavailability of the drug strongly depends on the vascular supply
  - Similar to sublingual route, the bioavailable is limited by the actual vascular supply which can be changed by the vegetative nervous system, environmental condition and so on
  - This can lead to the fluctuation of drug plasma level

- **Advantages**
  - Smooth **absorption over a long period of time**
  - Minimized risk as compared to i.v.
  - **No assistance is needed → can be done by self-administration**
  - **Depot preparations** for sustained action can be made

- **Disadvantages**
  - **Slower rate of drug absorption compared to i.v. and i.m. route**
  - **Drugs causing irritation can't be administered – sloughing and necrosis**
  - **Only small volumes can be administered**
  - The local side effects are very frequent, this relatively often prompts the change of application
    - We need to take the vascular supply into account
    - Educate patients how to change sites to obtain maximally corresponding bioavailability
    - Recommended change is sides of the belly or between hips
      - Don't change between individual anatomic sites

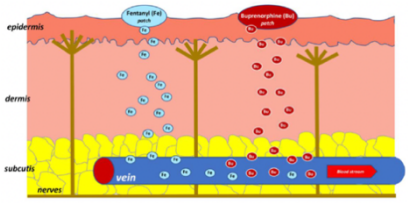


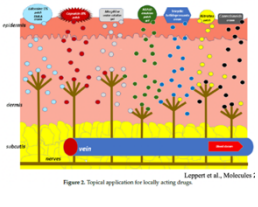
Figure 1. Transdermal application for systemically acting drugs.

D. Transdermal route of administration

- The main advantage of transdermal route is ***no first pass metabolism***
  - There are no side effects from the GIT
- But again, the limited factor is the vascular supply

- **Advantages**
  - The avoidance of problems associated with a disturbed absorption of a drug from the GIT or other GI problems (i.e., swallowing difficulties, nausea, vomiting), as well as the elimination of the first pass effect through the liver
  - Low concentrations of drugs and small fluctuations of their concentration in the blood serum – long-lasting effect with lower number of AE (adverse event)
  - Simplicity and convenience of administration, increases compliance, and improves patient's quality of life
  - The local irritation is minor, but it is possible because the skin reaction can also be dramatic against the transdermal patches, can be much more dramatic than the administration through injection

(Transdermal vs. topical route of drug administration)


Leppert et al., Molecules 2

- There is only a small difference in technique between transdermal and topical so these last 3 presented should be very simply counted among the local and systemic route of administration because it all depends on which drug is used as a remedy
  - If it is fentanyl, we know that the analgesia will be very systemic
  - But when we use e.g., lipophobic antibiotic, there will be only skin effect on the skin lesions

E. Inhalation/pulmonary route of drug administration

- In pulmonary route can be obtained local mucosal effect (asthma), and also systemic effects (anesthesia)
- **Advantages**
  - Direct delivery of microgram drug quantities to the site of action with fewer systemic SE than oral therapy = local therapy
  - Delivery of drug via the airways into the bloodstream = systematic therapy
  - Rapid onset of action
  - A non-invasive method of delivering drug directly to the site of action, reducing systemic SE, and enabling lower doses than might otherwise be required
  - Improved bioavailability over orally delivered pharmaceuticals
- There is one specific risk factor, sensitive persons can react to administration of the drug into the airways by bronchospasm

Can be potentially a life-threatening condition

5. Enteral way of drug administration (2, 32)

Systemic		Local
Enteral	**Parenteral**	**Mucosal** Mouth, throat, airways, ear, nose, eye, vagina, uterus, rectum
Peroral	Intravenous (i.v.)	**Skin**
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Sublingual	Subcutaneous (s.c.)	**Intra-thecal/epidural**
	Intra-arterial (i.a.)	
	Transdermal	
	Inhalational	
	Intranasal	

Intro:

- The enteral route of administration is the most common route
- The enteral route of administration includes every drug that is absorbed through the oral mucosa or the rectum
- Here we have:
  - **Peroral** (p.o.)
  - **Rectal** (p.r.)
  - **Sublingual** (s.l.)
- From this group, the dominating one is the peroral route of administration
  - It is preferred by every patient who is able to swallow and is conscious

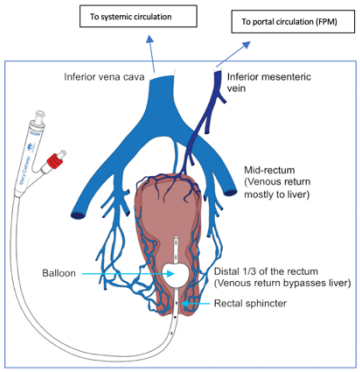
1. Peroral route of administration:

- The most commonly used, the most desirable, the safest and easiest way of administering drugs
- However, it is the most difficult pathway for the drug
- Two- to five-fold differences in the rate or extent of GIT absorption – depending on the dosage form

Advantages	Disadvantages
- Safest and most common, convenient and economical route of administration	- Limited absorption of some drugs - **First-pass effect** due to biotransformation - Patient compliance is necessary - Drugs may be metabolized before systemic absorption

Bioavailability

- Generally, the bioavailability of oral drugs follows the order:
  - Solution > Suspension > Capsule > Tablet > Coated tablet
- Bioavailability = the fraction (or %) of the drug which reaches systemic circulation
  - Drugs that are administered by the **intravenous** route are **100% bioavailable**, because the entire amount administered reaches systemic circulation
  - **Oral drugs** are **not** 100% bioavailable, because some of the drug is not absorbed, but is instead lost in feces and some of the drug is destroyed by the liver before it reaches general circulation
- The **main limiting factor** of peroral route of administration is **first pass metabolism**
  - The GIT is drained by the portal vein and through the portal vein it is transported to the liver
  - So, before the drug reaches systemic circulation, it is transported into the liver where the proportion (higher or lower) can be dissolved
- So, when the drug has a very high proportion of the first pass metabolism, we have 2 options
  - 1. Alternative route of administration if it's possible
    - IV, rectal, subcutaneous, inhaled, transdermal, sublingual etc. …
    - E.g., nitrates used to treat chest pain (angina)
      - Because nitrates are metabolized extensively by the liver on first pass, they must be given via an alternative route, like **sublingually** or IV
  - 2. Or, we can use the drug in very high portion



2. Rectal route of administration

- *Systemic* and *local* effects
- Useful for those who find it difficult to swallow, or keep down medication…
- No drug-food interactions, gastric emptying rate
- **Enema, rectal suppositories, gel**
- The rectum is devoid of villi
  - Thus, absorption is often slower depending on dosage form

- **Advantages:**
  - Rectal route of administration is ***only partly accompanied by first-pass metabolism***
    - Because only upper part of the veins which supply the rectum terminate in the portal vein
    - Lower part of the veins that supply the rectum are terminated in the systemic circulation
    - Approx. 50% of the drug is transported to the liver and undergo first-pass metabolism
  - Another advantage is that this is useful for patients that are unconscious or have problem swallowing, for children

- **Disadvantage:**
  - On the other hand, the dose given by this route should by very high
  - Because there is very limited surface for absorption compared to the GIT
  - The dose can lead to irritation of rectal mucosa and other additional side effects

3. Sublingual route of administration

- Factors affecting the sublingual absorption
  - **Lipophilicity of drug**
  - **Solubility in salivary secretion**
  - **pH and pKa of the saliva**
  - **Binding to oral mucosa**
  - **Thickness of oral epithelium**
  - **Oil to water partition coefficient**

- **Advantages:**
  - Rapid and extensive drug absorption – a relatively rapid onset of action
  - Low dosage gives high efficacy (***no first-pass MTB***), ↓SE
    - **<u>This is the only enteral route of administration with no first-pass metabolism</u>**
    - → There is a direct transport of the drug through the sublingual mucosa to the blood stream to the systemic circulation
  - Drug is protected from degradation due to pH and digestive enzymes
  - Used in emergency conditions, for administration of antianginal drugs → ***nitroglycerine***
  - Fast dissolution or disintegration in the oral cavity, without the need for water or chewing

- **Disadvantages:**
  - ***Unsuitable for prolonged administration***
    - Not suitable for longer treatments because there is a very significant fluctuation in the drug bioavailability depending on the composition of the saliva
    - Composition of the saliva changes during the day and can strongly affect the proportion of the drug that is absorbed
    - Thus, not suitable for long-term medication when we want to maintain stable plasma level of the drug
  - Also, ***not all drugs are absorbed through the oral mucosa***, we only have several of them
    - These drugs have to exhibit really high lipophilicity
    - Everything which has small molecules can potentiality be absorbed through the mucosa, but the second factor is the polarity of the molecule
  - Cannot be used when a patient is uncooperative or unconscious
  - The patient should not smoke while taking sublingual medication

6. Peroral way of administration (50)

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7. Parenteral way of drug administration (3, 33, 48)

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C. Subcutaneous route of drug administration

- Subcutaneous route is the ***slowest*** of these 3 (i.v., i.m., s.c.) ***in terms of onset of effect***
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- **Advantages**
  - Smooth **absorption over a long period of time**
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D. Transdermal route of administration

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- **Advantages**
  - People with swallowing difficulties, or vomiting
  - Low concentrations of drugs and small fluctuations of their concentration in the blood serum – long-lasting effect with lower number of AE (adverse event)
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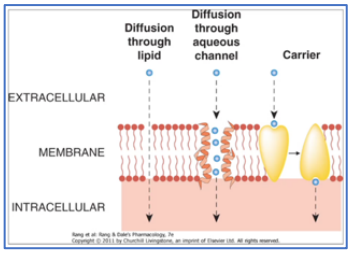
8. Drug absorption (34)

Pharmacokinetics = What the body does to a drug
Absorption – Distribution – Metabolism - Elimination

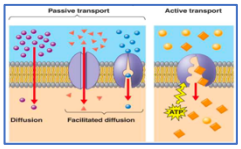
Absorption

Absorption = ***Movement of drug <u>from site of administration</u> into <u>circulation</u>***
There are different ways of crossing the membrane for small molecules:

- **a. *Passive transport* – Diffusing through the lipid membrane**
  - Easy passage through the membrane by small, lipophilic and non-ionized molecules
  - = **Passive transport** → No need for energy
    - Size of particles ***has to be small*** – smaller than in active transport
    - Level of ionization – ***has to be non-ionized***



- **b. Aquaporins – Diffusing through aqueous pores**
  - Little bit bigger molecules → Water
- **c. Active transport – Solute carriers or other transporters**
  - Most drugs are transferred by carriers
  - → **Facilitated transport:**
    - = Still ***no need for energy***, because it is **<u>going down concentration gradient</u>**
    - With facilitated transport, the rate of transportation is limited (limited number of carriers)
    - Specific transporters (membrane proteins) → Transporters or ion channels
  - → **Active transport:**
    - **<u>Against concentration gradient</u>** → ***Need of energy*** (= ATP-dependent)
    - Carrier mediated transport
    - Like mentioned, either facilitated or active has some limit (some maximum)
      - This maximum is based on the number of transporters we have
      - More transporters = higher maximum



- **d. Pinocytosis**
  - Another possibility how the absorption may happen is using pinocytosis
  - This is for example for bigger molecules, maybe some peptides (like ***insulin***)
    - This principle is used in the BBB, how insulin can easily penetrate through blood brain barrier
  - Pinocytosis means that the drug must be dissolved in some fluid, and the vacuole is slowly moving though the barrier and then it goes outside on the other side
  - Pinocytosis means brining a bigger molecule from one side to the other side
    - Invagination of part of cell membrane with trapping the extracellular constituents
    - Released intracellularly or transcellular extrusion on the other site
    - E.g., Insulin transport through blood brain barrier

Factors influencing the rate and extent of absorption:

- <u>Lipid solubility</u>
  - **High** lipid **solubility** = **faster transportation through membrane**
  - Low lipid solubility = transportation takes much longer time
- <u>pH partition (ionization)</u>
  - In basic environment → acids are ionized (and vice versa)
    - An example is acetylsalicylic acid (aspirin), a weak **acid** → ***non-ionized*** in acidic environment
      - Non-ionized = absorbed more easily
  - Whenever we have drugs which are acidic, they will be absorbed much faster in the stomach than in the intestine → where pH is increased
  - Weak bases are ionized in acidic environment = cannot be absorbed in stomach
    - → Passer into small intestine, where the pH is higher, this will reduce the ionization
      - → So, basic drugs can be absorbed in small intestine

An example of pharmacokinetic interaction for absorption:

- When we take drugs which ↑ gastric pH – proton pumps or antacids (for example due to peptic ulcer)
  - We use **<u>proton pump inhibitors</u>**, or maybe **<u>antacids</u>**
  - In case we co-administer an acid (e.g., aspirin) with the proton pump inhibitors, you will **increase the pH**, so the **absorption of aspirin will be limited**

Another example of pharmacokinetic interaction for distribution

- ***Warfarin*** (anticoagulant) protein bound ≈ 98% (**high protein binding drug** = **long-acting drug**)
  - Most of the drug is bound to plasma protein, so only small part is available for activity
- If patient takes ***aspirin*** at the same time, aspirin has same binding protein → aspirin displaces warfarin so the % bound of warfarin decreases
  - That means that the concentration of free warfarin in plasma will increase
  - This means that there will be increased action of warfarin → increased bleeding!

9. Drug distribution (5, 35, 39)

aDme = Distribution

- After a drug has been absorbed into plasma, it must be distributed to target organ
- Rate and extent of distribution depends on:
  - **Chemical structure of drug**
    - More lipophilic agents will be eliminated faster from the blood, because ***blood is hydrophilic***
      - So, lipophilic drugs can reach the brain faster
  - **Rate of blood flow**
    - Faster blood flow = higher exposure to the drug and it can work much faster
  - **Binding of drug to proteins in blood**
    - Different drugs can be bound to different plasma proteins
    - The strength of binding may be responsible for interaction
      - If we have 2 different drugs both bound to the same protein, they can replace each other, so they will influence the concentration of free drug of the other drug
  - **Elimination process**
    - If there is more drug free, it is eliminated faster
    - If it is bound to plasma protein it cannot cross the glomerulus into primary urine
    - So, it will stay there and circulate until the balance between bound and unbound form is moved (shifted) into the balance into bound form, and it must be released, and then slowly it is prolonged the elimination process

Plasma proteins that bind drugs

- → **Acidic drugs mostly bind to albumin**
- → **Alkalic (basic) drugs mostly to beta globulin**
- We also have special transporters, like for hormones, for thyroxine, or for sexual hormones binding globulins

% Bound

- **% Bound drug = [bound drug]/([Bound drug]+[Free drug]) x100**
- Renal failure, inflammation, fasting, malnutrition can reduce plasma proteins = ↑ free drugs
  - Competition from other drugs can also affect % bound
- Renal failure: → we lose albumin
- Liver impairment: → we don't make sufficient amount of albumin
- Inflammation: → decreased amount of % bound → much higher amount of free drugs
  - In this situation, the percentage of bound can be dramatically changed and suddenly we will have much higher amount of free drug which is available for some effects

Volume of distribution

- = Represents **how extensively a medication is distributed throughout the body**
  - ***Vd = Concentration of drug (C)/total concentration of drug in system (D)***
- Volume of distribution is a ***theoretical volume*** and determines the ***loading dose***
  - Loading dose = the first dose we give to reach certain concentration in target organ
    - **Loading dose = Cp $_{(Target\ organ)}$ x VD**

Important effects of pH partitioning

- **Urinary acidification:**
  - Will accelerate the excretion of weak bases and lower excretion of weak acids
- **Urinary alkalinization** has the opposite effects
  - Will accelerate the excretion of weak acids and lower excretion of weak bases
- **CNS:**
  - If we **increase the pH** (by bicarbonate), weak acids will become immediately **ionized** after crossing BBB back into the blood = cannot go back into CNS (ionized = can't pass BBB)
    - And vice versa, if we decrease pH – drugs can go back into CNS → increasing toxicity
  - We can used this when we need to remove something from the brain fast

10. Drug biotransformation (27, 36, 44)

- **Pharmacokinetics = what the body does to the drug**
  - **Absorption, distribution, metabolism and elimination**

Metabolism

- **=** The process of converting a medication into a less (or more) active form
  - In most cases, metabolic reactions turn an active medication in to a less active, or inactive metabolite which is then ready to be excreted
  - Some medications are administered in an inactive form (pro-drug), which needs to be metabolized to an active form within the body before they can produce their effect
- Generally, metabolic reactions in liver can be divided into 2 major phases:
- **Phase 1** is called **detoxification phase** → ***Monooxygenase P450 system***
  - Where the drug is metabolized into inactive metabolites → detoxifying the drugs
    - It can also be into active metabolites, via different processes
  - The major metabolizing complex is ***cytochrome P450***
    - It converts **non-polar**, **lipid-soluble** medications into **more polar** and **water-soluble** metabolites
  - These isoenzymes can be selective to certain drugs, so they have special substrates, and some drugs may influence these isoenzymes (inducers vs. inhibitors)
    - So that is the point where we may have many interactions
- **2nd phase** → **Conjugation reactions**
  - Here the drugs are conjugated or joined with another compound (for example glucuronic acid)
    - Can also be methylation, acetylation or sulfation)
  - These reactions make the metabolites **highly polar** → so they cannot penetrate cell membranes
    - Thus, they will get **trapped in the urine** and eliminated by kidneys

Genetic variability of CYP450

- Some people have fewer enzymes or enzymes which work more slowly and less effectively against certain medications
  - Can lead to accumulation of the medication in the body → resulting in dangerous side effects
- In contrast, some people are rapid metabolizers → inactivates medications so fast that it's difficult to achieve a high enough level of medication in blood

Examples from antitussives:

- **Codeine:**
  - People **with ↑ activity of CYP450** → ↑ formation of morphine with opioid effects → ↑ risk of morphine side effects
- **Dextromethorphan:**
  - People **with ↓ activity of CYP P450**, dextromethorphan will be accumulated in higher concentrations → hallucinations

Inducers vs. inhibitors of cytochrome P450:

- **Inducers CYP** → decrease plasma concentration of drug (decrease effect of drug, insufficient treatment)
  - Example: Barbiturates, rifampicin, phenytoin, carbamazepine, smoking (reason why smokers need more coffee!)
- **Inhibitors of CYP** → increase plasma concentration of drug (accumulation, toxic to patient)
  - Examples: cimetidine, macrolides, ketoconazole and grapefruit juice

11. Drug interactions (12, 18, 42, 63)

- Factors that predispose or favor drug interactions:
  - **Old age**, **polypharmacy**, **concomitant diseases**…
    - Elderly people especially, are treated continuously with more than one drugs for chronic diseases such as hypertension, heart failure, arthritis, osteoporosis etc.
    - The potential for drug interaction is therefore substantial and "polypharmacy" is an important factor to consider when prescribing to this group.

- Drug interaction is a situation in which a substance (drug) affects the activity of another drug when they are administered together, the effect can be:
  - **Synergistic**: The drug increase effect of the other drug when administered together
  - **Antagonistic**: The drug decrease effect of the other when administered together

Pharmacodynamic interactions – examples

- Beta-blockers diminish the effectiveness of **beta-adrenoceptor agonists** such as **Salbutamol**
  - The reason why we coadminister glucocorticoids!
- **MAO-inhibitors** = increase catecholamines in synaptic cleft – **Tyramine** is a precursor of catecholamines
  - Can lead to "cheese reaction" hypertensive crisis
  - Patient on MAO-inhibitors should avoid tyramine-rich food
- **Warfarin** competes with vitamin K, preventing hepatic synthesis of various coagulation factors
  - If patient takes vitamin K supplements →decreased effect of warfarin
- The risk of bleeding, caused by **Warfarin** is increased by drugs that cause bleeding by different mechanisms (e.g., **Aspirin**)
- Synergistic effect of benzodiazepines + barbiturates or alcohol → can lead to respiratory depression

Pharmacokinetic interaction

Absorption interactions:

- When we take **PPIs** or **antacids**, we increase gastric pH
  - In case we co-administer an acid (e.g., aspirin) = decreased absorption of aspiring
- Absorption of **tetracyclines** is influenced by divalent cations (X^{2+}) – **especially calcium and magnesium**
  - Antacids contain calcium = decrease absorption of tetracyclines
- Another example is the addition of adrenaline to local anesthetic injections; the resulting vasoconstriction slows the absorption of the anastatic, thus prolonging its local effect.

Drug distribution interactions

- One drug may alter the distribution of another, by competing for a common binding site on plasma albumin or tissue protein
  - Displacement of a drug from binding sites in plasma or tissues transiently increases the concentration of free drug, and toxicity can occur.
- Warfarin (anti-K anticoagulant) is highly protein bound to albumin
  - Aspirin has same binding protein → displaces warfarin → ↑ free warfarin → increased bleeding!

Metabolism interactions

- CYP450 (Cytochrome P450 enzyme)
- CYP450 is involved in metabolism of many drugs
- **Inducers CYP** → decrease plasma concentration of drug (decrease effect of drug, insufficient treatment)
  - Example: Barbiturates, rifampicin, phenytoin, carbamazepine, smoking (reason why smokers need more coffee!)
- **Inhibitors of CYP** → increase plasma concentration of drug (accumulation, toxic to patient)
  - Examples: cimetidine, macrolides, ketoconazole and grapefruit juice

Excretion interactions

- Changing of pH may increase excretion of certain drugs
  - Increased pH → increased excretion of acids
  - Decreased pH → increased excretion of bases

12. Drug elimination (10, 40)

Pharmacokinetics = what the body does to the drug

- 1. absorption into circulation
- 2. distribution to various tissues in the body
- 3. Metabolized and broken down
- 4. And finally eliminated/excreted in urine or feces

Excretion via kidney

- The major function of the kidney is to clear metabolic waste material and foreign substances (like medications)
- Blood is filtered in the glomerulus → as the filtrate makes its way through tubule, some drugs may be absorbed
- Polar or too big molecules cannot cross the tubular cells → get trapped inside tubular fluid and are eliminated via urine
- The pH of urine will affect excretion: (Most drugs are either weak acids or weak bases)
  - We can use this in overdosing of drugs:
  - Overdose of weak acid (aspirin) → alkalize the urine by bicarbonate → becomes polar → excreted
  - Overdose of weak base (amphetamines) → acidify the urine by ammonium chloride → becomes polar → excreted

Excretion via bile and feces

- Orally administered drug which don't get absorbed through the GIT are directly passed in feces
- Some drug which are absorbed in GIT enter the enterohepatic circulation to get to the liver
  - bind to bile → excreted back to the intestine and leave the body through feces

Excretion via exhalation

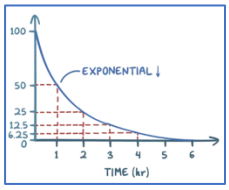
- Many inhaled anesthetics get eliminated by lungs through exhaled air

Other → small amounts can be excreted by breast milk, sweat, saliva and tears

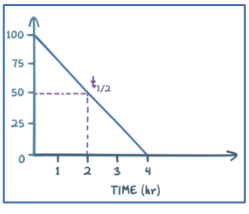
Clearance

- Clearance = the volume of medication cleared from plasma
- Total body clearance = renal clearance + hepatic clearance + lung clearance + other
  - = Rate of elimination/concentration of drug in plasma

Rate of elimination (1st order vs. 0 order kinetics)



- Determined by elimination kinetics
- Most medications are eliminated through 1st order kinetics
  - = Rate of elimination is directly proportional to the concentration of the medication in the body
    - The absolute amount eliminated per unit of time may change
    - But the fraction which is eliminated always stays the same
  - For example, if we start with plasma concentration of 100 mg/l and we eliminate 50% of it each hour
    - After 1 hour → 50 mg/l, after 2 hours → 25 mg/l, 3 hours → 12,5 mg/l, 4 hours → 6,25 mg/l
    - The curve will show ***exponential decrease*** in the plasma concentration of the medication
    - This also determines the ***half-life*** of the medication = the time required for plasma concentration of medication to be reduced by half (in this case = 1 hour)
- There are few medications which are eliminated through 0 order kinetics
  - E.g., phenytoin, warfarin and aspirin
  - The rate of elimination is **constant** → independent of the concentration of the medication in the body
    - The mg eliminated per unit of time stays the same! But the fraction eliminated changes
  - For example, we start with plasma concentration of 100 mg/l, and we always eliminate 25 mg/l each hour
    - After 1 hour → 75 mg/l, after 2 hours → 50 mg/l, after 3 → 25 mg/l, after 4 hours = 0
    - The curve will show a ***straight line***



13. Receptors – definition and principles of drug action (8)

- ***Pharmacodynamics*** = how the drug affects the body
  - In order to have an effect, most medications have to reach their target cells and bind to a receptors
  - (Not all drugs bind to receptors – for example antacids which neutralize acid)
- Receptor = specialized proteins, can be located either on the cell membrane or inside the cell
  - It can bind to a ligand and get triggered to alter their shape or activity
- This binding gives rise to a signal cascade of intracellular molecules (the 2nd messengers)
  - This ultimately results in some change in the function of the cell

Localization of receptors:

→ Intracellular receptors

- Typically found in the cytoplasm or nucleus of the cell
- They recognize small lipophilic ligands → ***steroids*** (can easily cross cell membrane)
- Once bound to their ligand, the receptor-ligand complex attaches to specific DNA sequences which activate or inhibit specific genes
- In case of steroids → nuclear receptor is bound to heat shock protein, which dissociates when steroid hormone is bound
- = slow onset of action + long effect

→ Cell membrane receptors

- They are embedded into the plasma membrane and bind to ligands which are too large or polar to cross membranes
- Rapid onset of action + long effect
- They can be categorized into 3 main types:
- **1. Ligand-gated ion channels**: (***ionotropic***)
  - They form channels or pores that open up once they bind to their specific ligand
  - They allow ions like chloride, calcium, sodium and potassium to passively flow into the cell down their concentration gradient
  - Good example → GABA-A receptor → chloride ion influx → hyperpolarization
- **2. G-protein coupled receptors (7 transmembrane receptors) (*α1 = Gq*, *α2 = Gi*, *β1,2,3 = Gs*)**
  - Ligand binds to the end sitting outside the cell, and the end which ends within the cell activates the G-protein
    - G-proteins contain alpha, beta and gamma subunits
      - Normally, the alpha subunit binds to GDP → G protein is inactive
      - When a ligand binds to the receptor – the G protein changes its shape, causing the alpha subunit to release the GDP and allowing GTP to bind
      - This causes the alpha subunit to detach and trigger other proteins in the signaling pathway
  - There are 3 types of G proteins: Gq, Gi and Gs
    - Gq → activates phospholipase C → cleaves a phospholipid in the cell membrane (with a really long name) into IP3 and DAG
    - Gs stimulates adenyl cyclase → adenyl cyclase takes ATP and removes 2 phosphate molecules and increases the formation cAMP
    - Gi inhibits adenyl cyclase → decreases the formation of cAMP
  - IP3, DAG and cAMP then stimulate or inhibit different enzymes in the molecular pathway
- **3. Enzyme-coupled receptors (*insulin receptors*)**
  - These are usually single-pass transmembrane proteins
  - The extracellular end of the receptor binds to ligands and their intracellular end has enzyme activity
  - The enzymatic domain is usually a protein kinase which phosphorylates other molecules
  - Ligand binds → conformational change in the enzyme → 2nd messengers are activated inside the cell
    - → 2nd messengers get phosphorylated by tyrosine kinases which then active other proteins in the signal pathway

14. Mechanism of action of drugs at molecular level (7, 37)

In pharmacology, the term mechanism of action (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor

Definition

- ***Pharmacodynamics*** (= What the drug does to the body, = drug action): Study of the biochemical and physiologic effects of drugs, their mechanisms of action and side effect occurrence
- ***Pharmacokinetics*** = What the body does to the drug (absorption – distribution – metabolism – elimination)

Mechanism of action of drugs at molecular level

- Target – molecules, receptors, ion channels
- A. ***Receptor*** (any molecule that can bind with a specific molecule)
  - ***Specificity***: (for one receptor or subtype of receptor)
  - ***Selectivity***: (the degree to which a drug acts on a given site relative to other sites)
  - ***Sensitivity***: (binds "easily" to the receptor, is sensitive to binding to the receptor)
  - Characteristics of the receptor: high selectivity, low concentration of agent is required to induce effect
  - Receptor + molecule → receptor-molecule (drug) complex → Biological effects
- B. ***Macromolecules*** – proteins (glycoproteins, lipoproteins) located on, under, or within cell membrane that interact with a drug to produce a biological effect or transmit information across cell membrane
- C. ***Ligand*** – molecules (drugs, hormones, neurotransmitters) that bind to a receptor.
  - Each ligand may interact with multiple receptor subtypes → binding leads to inactivation or activation of receptor (↑/↓ cell function)

Theory of drug action

- Fischer's "**Lock and key**" hypothesis → modified into **"hand in glove" model**
  - "Lock and key" theory describes the interaction between receptor, agonist and intracellular pathway
  - But now we have modification "**hand in glove**" → This includes the ***flexibility of the receptor*** (the receptors can wrap around the drug)
    - Step 1 – initial binding
    - Step 2 – The change in structure of the receptor
    - Step 3 – Change in confirmation of the receptor – Activation of intracellular pathway

Affinity and intrinsic activity

- **Affinity:** it is the ability of a drug to bind to the receptor
- **Intrinsic activity:** it is the ability of a drug to activate a receptor following receptor occupation
  - = Ability to produce the effect!!

- **Agonist and antagonist**
  - **1. Agonists:** = Drugs that are able to stimulate the receptors
    - Bind to receptors and mimic the regulatory effects of the endogenous signaling compounds
  - **2. Partial agonists:**
    - Agents that are only partly effective as agonists
    - For example, beta blockers with intrinsic sympathomimetic activity (ISA) = partly stimulates the receptor
  - **3. Inverse agonists:**
    - An inverse agonist is a ligand that binds to the same receptor-binding site as an agonist and not only antagonizes the effects of an agonist but, moreover, exerts the opposite effect by suppressing spontaneous receptor signaling (when present)
  - **4. Antagonists:**
    - Drugs bind to a receptor and prevent the action of an agonist, but do not have action on its own

Different types of antagonists:

- **1. Competitive antagonists:**
  - Antagonist competes with agonist for the same receptor site
  - ***Reversible binding*** → Necessary to have higher concentration of agonist to achieve same response
    - = their inhibitory effect can be surmounted by higher concentration of the agonist
  - Competitive agonists and antagonists are used as antidote → for example atropine is the antidote for therapy of cholinergic agonists
- **2. Non-competitive antagonists: (irreversible antagonists)**
  - Bind covalently – irreversible
  - The danger of irreversible antagonists is intoxication → because here we don't have drugs with antidote effect
    - Intoxication has to be treated only symptomatically, we have to control the physiological function
- **3. Allosteric antagonists:**
  - Antagonist binds to a site different to that of an agonist
  - No matter how much agonists → antagonism cannot be overcome – Insurmountable
  - Negative allosteric modulation (also known as allosteric inhibition) occurs when the binding of one **ligand** decreases the affinity for substrate at other active sites

Down-regulation of receptors

- Is an agonist-induced decrease in the total of cell surface receptors
- Slower onset and more prolonged effect than desensitization, occurs over hours to days.
- Intensity and duration of action are limited because of this process. Cells responsiveness to ligand is diminished

Up-regulation of receptors

- Long term therapy of antagonist → op-regulation (synthesis of new receptors) → Rebound effect (more drug needed to be bound)

15. Adenylate cyclase/cAMP system (15)

G-protein coupled receptors (7 transmembrane receptors) (*α2, M2, M4 = Gi*, *β1,2,3 = Gs*)

- Ligand binds to the end sitting outside the cell, and the end which ends within the cell, activates the G-protein
  - G-proteins consists of 3 subunits: alpha, beta and gamma subunits
    - Normally, the alpha subunit binds to GDP → **G protein is inactive** (subunits stay together)
    - When a ligand binds to the receptor – the G protein changes its shape, causing the alpha subunit to release the GDP and allowing GTP to bind → activating the protein
    - This causes the alpha subunit to detach and trigger other proteins in the signaling pathway
- To act on other proteins, the alpha subunit turns
- There are 3 types of G proteins: Gq, Gi and Gs
- Gs and Gi utilize cAMP as second messenger
- Gs:
  - α subunit of Gs protein ***stimulates*** adenylate cyclase → activated adenylate cyclase takes ATP and removes 2 phosphate molecules, transforming it into cAMP
  - cAMP moves throughout the cytoplasm and binds to the enzyme ***protein kinase A***
  - Protein kinase A has 2 parts:
    - A regulatory subunit and a catalytic subunit
    - cAMP binds to the regulatory subunit of protein kinase A → freeing up the catalytic subunit
    - Catalytic subunit dissociates and is free to phosphorylate target proteins which trigger cellular response
  - Examples: β1, β2, β3
- Gi:
  - α subunit of Gi protein inhibits adenylate cyclase
    - This causes negative feedback on protein Gs
    - = ↓ cAMP → inactivates cells
  - Examples: α2, M2, M4

16. Phospholipase C / inositol phosphate (45)

G-protein coupled receptors (7 transmembrane receptors) (*Gq – α1, H1, M1 and M3*)

- Ligand binds to the end sitting outside the cell, and the end which ends within the cell, activates the G-protein
  - G-proteins consists of 3 subunits: alpha, beta and gamma subunits
    - Normally, the alpha subunit binds to GDP → **G protein is inactive** (subunits stay together)
    - When a ligand binds to the receptor – the G protein changes its shape, causing the alpha subunit to release the GDP and allowing GTP to bind → activating the protein
    - This causes the alpha subunit to detach and trigger other proteins in the signaling pathway
- To act on other proteins, the alpha subunit turns
- There are 3 types of G proteins: Gq, Gi and Gs
- The alpha subunit of Gq proteins activates the enzyme phospholipase C, which is found in the cell membrane
  - Phospholipase C then cleaves a phospholipid called phosphatidylinositol 4,5-bisphosphate into IP3 and DAG
  - IP3 is soluble and diffuses freely through the cytoplasm and into the endoplasmic reticulum, where it opens up calcium channels
    - Since the calcium concentration is higher in the endoplasmic reticulum than in the cytoplasm, calcium flows out of endoplasmic reticulum, to the cytoplasm
    - ↑ Calcium concentration in the cytoplasm leads to depolarization
  - DAG remains attached to the cell membrane and binds to Protein kinase C (also need calcium to be activated)
    - Once calcium concentration goes ↑ - protein kinase C starts to activate proteins by adding phosphoryl groups to them
- For example: α1, H1, M1 and M3

GCPR (Gq) —> a+GDP —> a+GTP —> Phospholipid —> Phospholipase C —> IP3+DAG —> IP3 interacts with ER —> Increased calcium release; DAG acts just like cAMP in the AC mechanism and activates protein kinases which in turn activate enzymatic pathways. --> GnRH + TRH + Angiotensin II USE THIS MECHANISM

1b. Prescription

17. Prescription – structure, rules of prescription (21, 51)

18. Solid forms of remedies – classification, manner of prescription (23, 53)

19. Liquid forms of remedies – classification, manner of prescription (22, 52)

20. Soft forms of remedies – classification, manner of prescription (24)

17. Prescription – structure, rules of prescription (21, 51)

Intro – Prescription:

- ❖ Drugs are classified into 2 according to prescription:

1 **Over the counter drugs:**
   - ➢ Drugs sold directly to consumer without prescription

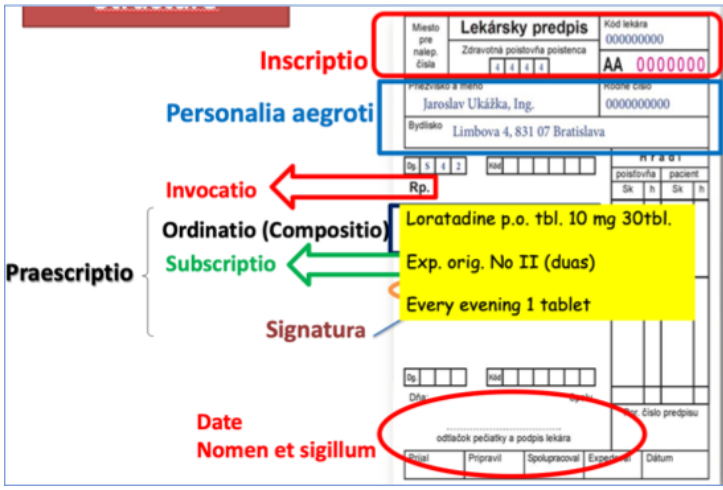
2 **Rx Drugs:**
   - ➢ Drugs that require a medical prescription

Intro - Medicinal form:

- ❖ Medicinal form is the basic characteristic of drug and is very strongly connected with route of administration
- ❖ Medical form can be → **Solid, liquid, soft medicinal forms**

Intro - Validity of Prescription:

1 **Common drugs – 7 days**
2 **Opioids – 3 days**
3 **Antibiotics – 3 days**
4 **Prescription from first aid ambulance – 1 day**



Structure of Prescription

1 Inscriptio
   - ➢ Code of physician, health care insurance number of patient

2 Personalia aegroti
   - ➢ Patients full name, address, social security number

3 Prescriptio – consist of:

A. Invocatio
   - ➢ Invocatio means the abbreviation of Rp. (Recipe = to take)

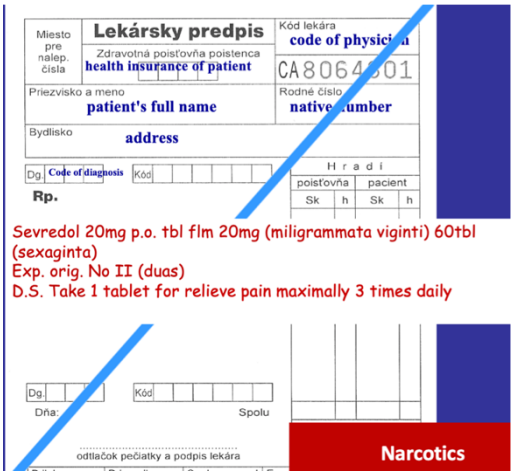
B. Ordinatio – Done in this order:
   a) **Generic/trade name of drug**
      - **Generic name** used if → **p.o. administration, 1 active substance**
      - **Trade name** used if → **NOT** p.o. administration, more than 2 active substances
        (With some exceptions e.g., narcotics always trade name)
   b) **Way of drug administration** (in abbreviation e.g., p.o.)
   c) **Medical form in abbreviation** (e.g., Tbl.)
   d) **Strength of drug** = active ingredient in one single dose (e.g., for tbl, single dose is 1 tbl)
   e) **Size of package** (e.g., 1 box consist of 60 tbl, then we write → 60 tbl)

C. Subscriptio
   - ➢ Contains directions for pharmacist about quantity of drug needed
   - ➢ Here we write in Latin language types of packages and number of packs
     (In abbreviation and roman numerals)
     - E.g., Exp. orig. No. II (duas)

D. Signatura
   - ➢ Contains direction for the patient, written in native language of the patient
     - With some exception, e.g., when medication is supplied into hands of doctor → then we write <u>"ad manus medici"</u>

Subscriptio – Different type of packages:

1. **Divided medicinal forms** (e.g. tbl, inj...)
   a. Exp. Orig = scat. Orig → original box
   b. Amp. Orig → original ampulla
2. **Non-divided medicinal forms** (e.g. solution, gel...)
   a. Exp. Orig = scat. Orig → original box
   b. Lag. Orig. → original bottle
   c. Tub. Orig → original tube



Rules of prescription:

- Has to be written by pen (not pencil), on a special printed matter
- Special rule for **scheduled drugs** (opioids)
  - Label with oblique blue stripe
  - Prescription (1 original + 2 copies)
  - 1 kind of drug ONLY
  - Number of packings should not exceed number needed for therapeutic period of 30 days
  - Strength of drug, size of package and number of packings in Latin language
- When choosing to use Generic or trade name ask:
  - What is rote of administration?
    - If p.o. = Generic, if not p.o. = trade name
  - How many active ingredients?
    - 1 = generic, more than 1 = trade name
  - Is this an exception? (e.g., narcotics, antiarrhythmic…)
    - Then use trade name
- **Non-dividing drugs (soft + liquid) always use exp. Orig**
- **Soft** medicinal form, always use **exp. Orig.**

18. Solid forms of remedies – classification, manner of prescription (23, 53)

Intro – Prescription:

- Drugs are classified into 2 according to prescription:

1 **Over the counter drugs:**
   - Drugs sold directly to consumer without prescription

2 **Rx Drugs:**
   - Drugs that require a medical prescription

Scheduled/Controlled drugs:

- *Agents which have some risk of drug abuse*
- There are sticked rules applied for them
- They are classified according to their abuse risk
  - Schedule I = highest abuse potential
  - Schedule III = lowest abuse potential

Intro - Medicinal form:

- Medicinal form is the basic characteristic of drug and is very strongly connected with route of administration
- It described the form and structure of the drug
- Medical form can be → **Solid, liquid, soft medicinal forms**

Solid Drugs

- When we talk about solid drugs, we talk about **Tablets**, **capsules**, **powder**
  - Tablets and capsules for **internal use**
  - Powder for both internal and **external use**

1 **Tablets:**
   - Tablets are only for internal use
   - Tablets can come in many forms which is affects many factors of the drug (e.g., taste or absorption)

Uncoated/Coated	Sublingual/buccal	Effervescent/Sparkling + Chewable	Modified-release/prolonged-release:
• Uncoated don't have anything covering the drug surface • Coated have separated coating • Coated tablets are further classified into: **A. Film coated:** • Covered with thin layer of **polymeric** substance which protects them from environmental conditions (e.g., temp) and removes the smell and taste of drug **B. Enteric coated:** • Covered with layer of **cellulose** • Makes them insoluble in gastric pH → but dissolve in intestine • E.g., ATB	• They consist of active ingredient with much faster onset compared to P.o. • They are often used in emergency situations • Those are also useful for patients unable to swallow tablets	**Sparkling:** • Generally uncoated tablets which in contact with water they produce CO_2 → sparkling • This from makes the tablet have better taste **Chewable:** • Tablets that are chewed and then swallowed • E.g., vitamins for children	**Modified-release:** • Only control rate of drug release - Usually slow release, meaning it releases small amount of drug that is absorbed for longer time **Prolonged-Release:** • Tablets that help maintain drug concentration within therapeutic window for desired period of time

2. Capsules:

- Capsules are cylindrical enveloped in which drug is enclosed used for internal use
  - Generally made from gelatin or starch
- They can be hard or soft
- And like tablets they can be → **Gastric-resistant, modified/prolonged-release**

3. Powder:

- They can be used for both **internal** and **external** use:
  - **Internal** → non-diluted or diluted (with some liquid)
  - **External** → Powders often used in dermatology

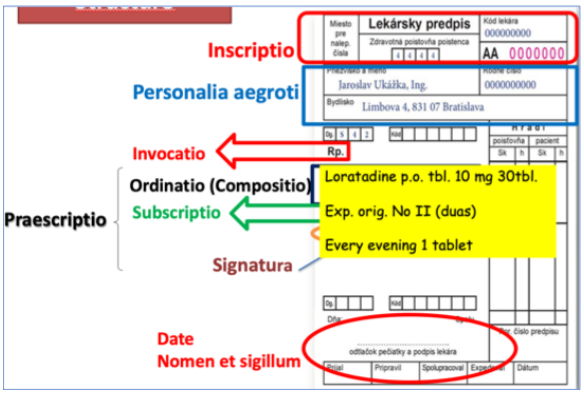
Semisolid drug forms:

- This form is suppositories for different administration

1 **Rectal** (suppositoria rectalia)
2 **Vaginal** (Globuli vaginales)
3 **Transdermal patches** (emplastra transcutanea)

Prescription of Solid drug is normal

Structure of Prescription



1 **Inscriptio**
  - Code of physician, health care insurance number of patients

2 **Personalia aegroti**
  - Patients full name, address, social security number

3 **Prescriptio** – consist of:

A. Invocatio
  - Invocatio means the abbreviation of Rp. (Recipe = to take)

B. Ordinatio – Done in this order:

f) **Generic/trade name of drug**
  - **Generic name** used if → **p.o. administration, 1 active substance**
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    (With some exceptions e.g., narcotics always trade name)

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D. Signatura
  - Contains direction for the patient, written in native language of the patient
    - With some exception, e.g., when medication is supplied into hands of doctor → then we write "ad manus medici"

Prescription of semisolid drugs:

- We always skip the route of administration!
- always use trade name (semisolid not taken p.o.)
- **Ordinatio:**
  - Trade name → medicinal form → size of package (how many doses x how much is single dose)
  - E.g., Spofax supp. 5x2.5.
    - Can also be written only size of 1 single dose (e.g., 2.2g, instead of 5x2.2g)
- **Subscriptio + Signatura** is normal
  - In Subscriptio we can give either whole box (exp. Orig.) or some doses (sup. Orig)

19. Liquid forms of remedies – classification, manner of prescription (22, 52)

Intro – Prescription:

- Drugs are classified into 2 according to prescription:

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Intro - Medicinal form:

- Medicinal form is the basic characteristic of drug and is very strongly connected with route of administration
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Scheduled/Controlled drugs:

- *Agents which have some risk of drug abuse*
- There are sticked rules applied for them
- They are classified according to their abuse risk
  - Schedule I = highest abuse potential
  - Schedule III = lowest abuse potential

Liquid Form:

- Liquid forms are intended from both **internal** and **external** use

For internal use:

- Based on administration they can be applied
- **Peroral:**
  - **Enteral**
    - Solutions
    - Emulsions
    - Suspensions
  - Rectal
    - Enema
- **Parenteral:**
  - **Injections**
  - **Solutions for inhalation**

For external use:

- Used as topical therapy
- Solutions
  - **Ear drops**
  - **Eye drops**
  - **Nasal drops**
  - **Solution for external use**
- Emulsions
- Suspensions

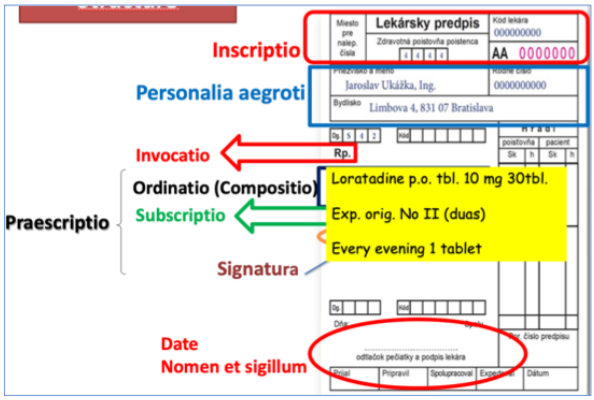
Solution (sol.)	**Emulsion** (emo.)	**Suspensions** (sus.)
• Are liquid preparation that contain 1 or more chemical substances which are dissolved in suitable mixture • They can be in form of: - **Syrup** (sir.) **and drops** (gto.)	• 2 liquid phases that are insoluble to each other - So, 1 liquid dispersed throughout another in form of small particle Has to be shaken before use	• Consist of solid phase which is dispersed though liquid phase • They are insoluble - Contain risk of sedimentation ALWAYS shake before use!

Administration abbreviation:

1. Ophthalmic = int. Opt.
2. Eye = int. Oto.
3. Nasal = int. Nas.
4. Inhalation = inh.
5. Rectal = reo.
6. Vaginal = vag.
7. Injection = inj.

Prescription of Liquid form:

- is like normal (topic 16), except:
  - **Strength of drug** will be in liquid units
    - So, we write "x" amount of active ingredient in "y" amount of liquid
      - E.g., in 5 ml we have 100mg of active ingredient → 100mg/5ml
  - **Package size** we can write amount of dose and package size, or the whole package size
    - e.g., 5x5ml → means that in single dose is 1ml
  - **Subscriptio** we always write **exp. Orig.** for non-dividing dose (so all liquids)
  - **Signatura** → we write single dose in ml (e.g., take 5ml 3 times daily)



Structure of Prescription

1 Inscriptio

- Code of physician, health care insurance number of patient

2 Personalia aegroti

- Patients full name, address, social security number

3 Prescriptio – consist of:

A. Invocatio

- Invocatio means the abbreviation of Rp. (Recipe = to take)

B. Ordinatio – Done in this order:

k) **Generic/trade name of drug**

- **Generic name** used if → **p.o. administration, 1 active substance**
- **Trade name** used if → **NOT** p.o. administration, more than 2 active substances

(With some exceptions e.g., narcotics always trade name)

l) **Way of drug administration** (in abbreviation e.g., p.o.)

m) **Medical form in abbreviation** (e.g., Tbl.)

n) **Strength of drug** = active ingredient in one single dose (e.g., for tbl, single dose is 1 tbl)

o) **Size of package** (e.g., 1 box consist of 60 tbl, then we write → 60 tbl)

C. Subscriptio

- Contains directions for pharmacist about quantity of drug needed
- Here we write in Latin language types of packages and number of packs

(In abbreviation and roman numerals)

  - E.g., Exp. orig. No. II (duas)

D. Signatura

- Contains direction for the patient, written in native language of the patient
  - With some exception, e.g., when medication is supplied into hands of doctor → then we write <u>"ad manus medici"</u>

Subscriptio – Different type of packages:

3. Divided medicinal forms (e.g. tbl, inj...)

c. Exp. Orig = scat. Orig → original box

d. Amp. Orig → original ampulla

4. Non-divided medicinal forms (e.g. solution, gel...)

d. Exp. Orig = scat. Orig → original box

e. Lag. Orig. → original bottle

f. Tub. Orig → original tube

20. Soft forms of remedies – classification, manner of prescription (24)

Scheduled/Controlled drugs:
- *Agents which have some risk of drug abuse*
- There are sticked rules applied for them
- They are classified according to their abuse risk
  - Schedule I = highest abuse potential
  - Schedule III = lowest abuse potential

Intro – Prescription:

- Drugs are classified into 2 according to prescription:

1 **Over the counter drugs:**
   - Drugs sold directly to consumer without prescription

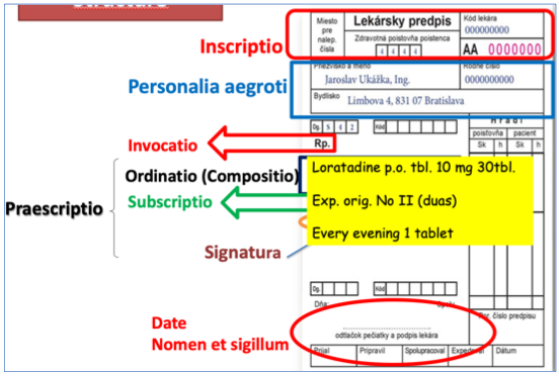
2 **Rx Drugs:**
   - Drugs that require a medical prescription

Intro - Medicinal form:

- Medicinal form is the basic characteristic of drug and is very strongly connected with route of administration
- It described the form and structure of the drug
- Medical form can be → **Solid, liquid, soft medicinal forms**

Soft Forms:

- They come in 3 forms:
  - **Ointments** (ung.), **paste and cream** (crm.)
- They are applied topically



Soft form Prescription:

- They are never given perorally = **ALWAYS use trade name**
  - They are non-dividing form → **always use exp. orig**

Structure of Prescription

1 Inscriptio
   - Code of physician, health care insurance number of patient

2 Personalia aegroti
   - Patients full name, address, social security number

3 Prescriptio – consist of:

A. Invocatio
   - Invocatio means the abbreviation of Rp. (Recipe = to take)

B. Ordinatio – Done in this order:

a) Generic/trade name of drug
   - **Generic name** used if → **p.o. administration, 1 active substance**
   - **Trade name** used if → **NOT** p.o. administration, more than 2 active substances
     (With some exceptions e.g., narcotics always trade name)

b) **Way of drug administration** (in abbreviation e.g., p.o.)

c) **Medical form in abbreviation** (e.g., Tbl.)

d) **Strength of drug** = active ingredient in one single dose (e.g., for tbl, single dose is 1 tbl)

e) **Size of package** (e.g., 1 box consist of 60 tbl, then we write → 60 tbl)

C. Subscriptio
   - Contains directions for pharmacist about quantity of drug needed
   - Here we write in Latin language types of packages and number of packs
     (In abbreviation and roman numerals)
     - E.g., Exp. orig. No. II (duas)

D. Signatura
   - Contains direction for the patient, written in native language of the patient
     - With some exception, e.g., when medication is supplied into hands of doctor → then we write <u>"ad manus medici"</u>

1c. Factors influencing drug action

21. Factors influencing drug action (25, 54, 55)

22. External factors influencing the drug action (14)

23. Internal factors influencing drug action (41)

24. Effects of the drugs on fetus (17, 20, 47, 56)

21. Factors influencing drug action (25, 54, 55)

Classification of factors

External factors	**Internal factors**
• External = something outside of body – **Food** – **Medicinal form** – **Alcohol** – **Smoking**	• Internal = something related to body – **Age** – **Sex** – **Pathological state of patient** – **Genetic factors**

External factors

a. Food

- Eating lipid rich food → absorption of lipophilic agents will be increased
- Food containing a lot of lipids → ↑ bile secretion → ↑ absorption of lipophilic agents
  - this is the reason why vitamin D is added to milk
- **Some drugs may change the pH of urine:**
  - Acidifying meals: meat, fish, eggs, cheese
  - Alkalizing meals: butter, vegetables, fruits
    - For example, barbiturates (acids) → in case we eat alkalizing meals → the elimination of barbiturates will be faster, because the pH will be increased → barbiturates in primary urine will be ionized = cannot be absorbed
- **Food and adverse effects:**
  - Food increased effect of drugs:
    - MAO enzyme is responsible for degrading catecholamines (dopamine, NE, E and serotonin)
    - Tyrosine is a precursor of catecholamines → if there is high availability of tyrosine, a lot of it is metabolized to catecholamines
      - Foods containing high tyrosine = bananas, cheese, chocolate
    - And in case we use MAO-inhibitors, these catecholamines are not destroyed → they accumulate and can lead to hypertensive crisis
- **Foods reducing effects of drug:**
  - If patient's diet contains high amount of vitamin K → reduces effect of warfarin
- **Potassium containing food (banana, potatoes…)**
  - Diuretics lead to decrease in potassium → food containing K^+ = good thing
  - ACE inhibitors lead to increase in potassium → food containing K^+ = bad thing - can lead to hyperkalemia

Caffeine effects on drugs

- Caffeine stimulates secretion of gastric acid
  - This is important, caffeine may increase the risk of impairment of mucous membrane when co-administered with aspirin or glucocorticosteroids
- Caffeine also increases diuresis → excretion of other drugs may be increased

b. Medicinal form

- Liquid
  - Generally, liquid medicinal forms have quicker absorption
  - And usually, they also have lower amount of local adverse effects – because they are at lower risk to attach to mucous membranes
- Solid
  - For some drugs, it is important to rinse them down → bisphosphonates and doxycycline
    - Remember, don't rinse tetracyclines down with milk (formation of chelates)
    - Rinse tetracycline down with lemon tea! → because citric acids bind to calcium = better absorption

Drug excretion

- Urine pH - **acidic** – drugs with acidic nature have ***decreased excretion***
  - Non-ionized = reabsorbed = ↓ excretion
- Urine pH - **basic** – drugs with acidic nature have ***increased excretion***
  - Ionized = not reabsorbed = ↑ excretion
- Urine alkalinization (by administering bicarbonate): - used in the **<u>therapy of barbiturate intoxication</u>**
  - Barbiturates = acids → ↑pH = ionized = ↑ Excretion

c. Alcohol and drug absorption

- **Low concentration of alcohol** → ↑ drug absorption
  - Low concentration of alcohol increases the blood flow in mucous membranes = ↑ drug absorption
- **High concentration of alcohol** – ↓ drug absorption due to pylorospasm
- **Chronic alcohol use:**
  - Can lead to chronic gastritis → lower absorption
    - Alcoholism reduces absorption!
  - Also, can lead to liver impairment → reduced ability to metabolize drugs = reduces effects of drugs

d. Smoking and drug effects

- Smoking increases metabolic clearance of certain drugs → reduce their effect
  - For example, caffeine → Smokers need more coffee to reach the same plasma concentration
- Nicotine also increases plasma levels of cholesterol and TAGs

Internal factors

a. Age

In elderly

- Generally, the GIT is "not as it used to be" → leads to reduced absorption
  - ↓ absorption, ↓ secretion, ↓ acidity, venostasis, ↓ motility, ↓ emptying, changes in bacterial flora
- Oppositely, because the skin is more fragile → the absorption of skin is increased!
  - Be careful when using corticosteroids in local forms → can lead to systemic side effects
- Drug biotransformation
  - The biotransformation is generally decreased → the half-lifes are generally prolonged
    - It means that we need to use lower concentrations of drugs
  - ↓ enzyme activity, ↓ liver blood flow, ↓ activity of kidneys – attention to smoking and alcohol

In children

- The secretion of stomach and intestine is not developed, also acidity is reduced
  - So, not so many drugs will be destroyed in stomach
- Children Drug biotransformation
  - Enzymatic systems of liver are not completely developed for full transformation
    - Especially the glucuronidation
  - Can lead to fatal intoxication by chloramphenicol – leading to grey baby syndrome
  - ↓ glomerular filtration → the drugs can accumulate much faster
- Immature CNS and other organs – ↑ susceptibility to morphine → depression of respiratory center

b. Gender

- Women have generally better toleration for barbiturates
  - The reason can be that fat compartment in women is a little bit higher → more storing places (works like a buffer)
- Gravidity dramatically influences the selection process to which drugs to use (getur talað um teratogenicity herna)
- Women have better toleration for barbiturates

c. Pathologic state

- Pathological states dramatically influence drug effects → because it influences pharmacokinetic properties
- We either have reduced or increased absorption:
  - **↓ absorption**
    - Usually due to impairment of epithelium in GIT or if passage is increased (diarrhea)
      - Impairment: Atrophy of intestine epithelia, GIT tumors, ulcerations…
  - **↑ absorption**
    - On the other hand, acute inflammation or acute congestion may lead to increased absorption
    - For example, in the case of acute gastritis, drugs may be absorbed more effectively
- Drug distribution is limited
  - Especially in liver diseases, where we have lower production of albumins and other transporting proteins, or in case of nephrotic syndrome (which is associated with hypoalbuminemia)
  - Similarly, if the cardiac output is reduced, generally blood flow will be reduced
- Drug excretion
  - Reduced by kidneys insufficiency → increases risk of adverse effects, due to lower elimination and accumulation of drugs

- Drugs excreted with bile (especially steroidal hormones) may be affected in case there is some cholestatic liver disease → because then they cannot be eliminated so effectively → can lead to adverse effects and prolonged action

d. Genetic factors

Codeine ↑ activity of CYP → more codeine to morphine = morphine side effects
Dextromethorphan ↓ activity of CYP → accumulation of dextromethorphan = hallucination

- People can either be: (this is especially related to isoniazid)
  - Slow acetylators:
    - The plasma concentration of isoniazid will be ↑ → elimination process is delayed
    - = can lead to adverse effects
  - Fast acetylators:
    - The plasma concentration of isoniazid will be ↓
    - To obtain or to reach sufficient concentration, we need higher doses
    - = leads to lower risk of adverse effects
- Depends on genetic changes in cytochrome P-450

- Polymorphism of hydroxylation – not completely elucidated yet (captopril)
- Insufficient biotransformation of succinylcholine (suxamethonium)
  - Suxamethonium is a skeletal muscle relaxant, it is metabolized by pseudocholinesterases
  - Some patients do not have pseudocholinesterases, so suxamethonium is not metabolized as fast as normally (usually about 10 minutes, but can be prolonged to several hours)

22. External factors influencing the drug action (14)

External factors

- External factors = factors which originate outside of the body and influence drugs
  - **Food**
  - **Medicinal form**
  - **Alcohol**
  - **Smoking**

a. Food

- 3 factors to take into consideration with food
  - How much (***volume***), what you are eating (***quality***) and the ***timing*** of food intake
- Eating lipid rich food → absorption of lipophilic agents will be increased
- Food containing a lot of lipids → ↑ bile secretion → ↑ absorption of lipophilic agents
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    - Remember, don't rinse tetracyclines down with milk (formation of chelates)
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- Gaseous (aerosol)

Drug excretion

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- Smoking increases metabolic clearance of certain drugs → reduce their effect
  - For example, caffeine → Smokers need more coffee to reach the same plasma concentration
- Nicotine also increases plasma levels of cholesterol and TAGs

23. Internal factors influencing drug action (41)

Internal factors = something related to body itself

- **Age**
- **Sex**
- **Pathological state of patient**
- **Genetic factors**

a. Age

In elderly

- Generally, the GIT is "not as it used to be" → leads to reduced absorption
  - ↓ absorption, ↓ secretion, ↓ acidity, venostasis, ↓ motility, ↓ emptying, changes in bacterial flora
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24. Effects of the drugs on fetus (17, 20, 47, 56)

- Factors influencing fetus negatively in addition to drugs/in combination with drugs:
  - ***Stress***, ***age***, ***concomitant disease*** (***diabetes mellitus***), ***genetic*** or ***physical factors***
- Adverse effects = negative impact of several drugs
- Teratogenic agents = agents leading to fetal malformation
- Factors influencing transport through placental membrane
  - (Lipophilic drugs, velocity, size, safe for mother = not safe for fetus)
- Safe drug for mother is not necessarily safe for fetus: Acetylsalicylic acid = impairment of fetal circulation
- ***Period before implantation*** = relatively safe against teratogenic influences
- Embryonic development:
  - ***1st trimester***: increased susceptibility to teratogens (lip cleft, ventricular defect)
  - ***2nd trimester***: teratogenic decreases more and more close to term of birth, but still not recommended to take teratogenic drugs.
- **TERATOGENS:**
  - 1. Group – **evident teratogens**
    - **Vitamin A** and **Methotrexate** (folic acid inhibitor)
  - 2nd Group – **Suspicious to be teratogenic**
    - **Phenytoin**
    - **Alcohol**
  - 3rd group – **potent teratogens or adverse effect inducers**
    - **Benzodiazepines = cleft palate**
  - 4th group - others:
    - **Nicotine** = decreased birth weight, retardation (10 cigarettes)
- Fetal alcohol syndrome = large space between eyes, short nose, retardation
- Fetal hydantoin syndrome = fetal impairment, spina bifida
- Contraceptive pills = uterine adenocarcinoma later in life for child
- Skeletal abnormalities = tetracyclines + cytostatic
- Sulphonamides = kernicterus; chloramphenicol = grey baby syndrome; TTC = bone toxicity

Warfarin as an example → **Teratogenic effects of warfarin**

- **Warfarin embryopathy** (**Di Sala syndrome**)
  - Occurs in children born to mothers exposed to warfarin during the **1st trimester** (5-30%)
  - **Classic features of warfarin embryopathy**
    - **Nasal hypoplasia** (Development of fetal cartilage = vitamin K dependent process)
    - **Chondrodysplasia Puncatata (Epiphyseal and vertebral bone stippling)**
- After 1st trimester of pregnancy, the administration of warfarin is regarded as relatively safe

Drugs during lactation

- Dangerous agents:
  - ATB
    - Sulphonamides
    - Tetracycline
    - Chloramphenicol
    - Isoniazid
  - Hypnotics
  - Drugs modifying endocrine activity are contraindicated

1d. Side effects

25. **Gastrointestinal side effects of drugs (19, 28, 58)**
26. **Liver side effects of drugs (26)**
27. **Liver and kidney side effects of drugs (57)**
28. **Blood side effects of drugs (59)**
29. **Drug allergy (6, 46)**
30. **Drug abuse and dependence (13, 38, 43)**
31. **Drug dependence (4)**
32. **Drugs with tocolytic effect (37)**

25. Gastrointestinal side effects of drugs (19, 28, 58)

Intro – GIT side effects:

- A lot of drugs can cause GIT side effects and disturbances
- GIT side effects can range from mild-severe and located from mouth to anus
  - They can be mild and go away quickly or be severe and lead to life-threatening situation.

Most common side effects:

1 **Diarrhea**
   - Characterized by ↑ flow through the Intestine (There ↑ motility and ↑ fluid in intestine → ↓ mixing of content)
   - Any drug that has an effect on these factors have an risk of causing diarrhea
     - **ANS drugs**
       - Cholinergic agonist cause ↑ GIT motility
       - Beta blocker cause ↑ GIT motility
     - **ATB** can cause diarrhea by interruption with normal flora of GIT
       - Often combined with probiotics to avoid diarrhea
     - **NSAIDS**
     - **Antidiabetics** by ↓ absorption of glucose

2 **Constipation:**
   - *Infrequent passage of stool*
   - Opposite to diarrhea, here is ↓ GIT motility
   - **Etiology of constipation is mostly due to:**
     - **Antimotility + antisecretory drugs:**
       - **Opioids,** antimuscarinic, adrenergic agonist, spasmolytics

3 **Vomiting + Nausea:**
   - Many drugs can cause vomiting and nausea
   - Most common are Centrally action drugs like:
     - **Opioids, NSAID, Anesthetics**

4 **Change in appetite:**
   - Those that **↑ appetite** are e.g. **oral contraceptives**
     - Gestagens physiologically ↑ appetite
   - Those that **↓ appetite** are mostly centrally acting e.g. **antidepressants**

5 **Peptic ulcers:**
   - One of most common cause of **NSAIDs**
     - NSAIDs ⊖ synthesis of prostaglandins → ↑ Gastric acid secretion
       - Prostaglandins are important for ⊖ of gastric acid secretion
   - Ulcer can than lead to more severe GIT disturbances (e.g., gastritis, bleeding…)

Bisphosphonates effects:

- They must be taken on empty stomach w. full glass of water, because they are highly toxic
  - They can cause severe esophagus side effects (e.g., esophagitis)

26. Liver side effects of drugs (26)

Genetic mutations of cytochrome enzyme!!

- If overactive: Codeine → extensive metabolism → more morphine
- If slow: Dextromethorphan → accumulation → hallucinations

Inducers vs. inhibitors of cytochrome P450:

- **Inducers CYP** → decrease plasma concentration of drug (decrease effect of drug, insufficient treatment)
  - Example: Barbiturates, rifampicin, phenytoin, carbamazepine, smoking (reason why smokers need more coffee!)
- **Inhibitors of CYP** → increase plasma concentration of drug (accumulation, toxic to patient)
  - Examples: cimetidine, macrolides, ketoconazole and grapefruit juice

Estrogens → hepatic metabolism → increased clotting factors → Pro-thrombotic effects

Statins are considered as very safe drugs

- **↑ Hepatic enzymes (ALT, AST) → hepatotoxicity is questionable** (only temporary increase in hepatic enzymes)

Oral contraceptives: Blood clots

27. Liver and kidney side effects of drugs (57)

Liver:

Genetic mutations of cytochrome enzyme!!

If overactive: Codeine → extensive metabolism → more morphine
If slow: Dextromethorphan → accumulation → hallucinations

Inducers vs. inhibitors of cytochrome P450:

- **Inducers CYP** → decrease plasma concentration of drug (decrease effect of drug, insufficient treatment)
  - Example: Barbiturates, rifampicin, phenytoin, carbamazepine, smoking (reason why smokers need more coffee!)
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  - Examples: cimetidine, macrolides, ketoconazole and grapefruit juice

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Statins are considered as very safe drugs

- **↑ Hepatic enzymes (ALT, AST) → hepatotoxicity is questionable** (only temporary increase in hepatic enzymes)

Oral contraceptives: Blood clots

Kidney:

→ Statins + fibrates

- **↑ Activity of creatin kinase (10x) → myalgia, myopathy, rhabdomyolysis**
  - (myalgia + myopathy more typical)
  - Rhabdomyolysis = breakdown of skeletal muscles → **nephrotoxicity**

Diuretics

→ Loop diuretics (furosemide + torasemide)

- They inhibit co-transport of Na, K and Cl in loop of Henle = these ions will be lost in urine
  - → Water follows → ↓ plasma volume → ↓ preload → ↓ blood pressure
- **Compensatory mechanisms**:
  - Hyponatremia → exchange of Na+ with proton or potassium = **metabolic alkalosis/hypokalemia**
  - Potassium is reabsorbed back into blood → ↑positive charge inside tubule → positively charged calcium (Ca^{2+}) + magnesium (Mg^{2+}) leaks out = **Hypocalcemia** and **hypomagnesemia**
- When the drug is eliminated, it is exchanged with uric acid and glucose → **hyperuricemia + hyperglycemia**
  - = ***Negative metabolic profile***
- **Ototoxicity (dose dependent, reversible, aminoglycoside ATB)**
  - Due to increased penetration of loop diuretics into the fluid of inner ear
  - A very typical side effect of loop diuretics
- **Dehydration**

→ **Distal tubule diuretics (thiazides + sulfonamides)**

- **Sodium and chloride co-transport** from urine back to blood is **inhibited** → water follows
  - = decreased preload, ↓ cardiac output and ↓ blood pressure
- **Compensatory mechanisms**:
  - Inhibition of Na/Cl cotransporter leads to ↓ Na inside tubular cells → compensation: Na into cell from blood and more calcium into the blood in exchange through the Na/Ca antiporter → hyponatremia + **hypercalcemia** (side effects)
  - Hyponatremia → exchange of Na and proton or potassium = **metabolic alkalosis/hypokalemia**
- **Ion disbalance**
  - **Hyponatremia, Hypokalemia, Hypercalcemia** (in contrast to loops!)
- **Hyperuricemia, Hyperglycemia, Hyperlipidemia, Allergic reaction**
- When the drug is eliminated, it is exchanged with uric acid and glucose → **hyperuricemia + hyperglycemia**
  - = ***Negative metabolic profile***

Non-selective NSAIDs→ Renal function impairment

- Prostaglandins control the perfusion of the kidneys (COX-1!)
- So, another side effect of NSAIDs is **hypoperfusion of the kidneys** and **they reduce GFR**
- **Electrolyte and fluid abnormalities** (edema, hyperkalemia, hyponatremia)
- **Worsening of hypertension**
- In very rare cases, acute renal failure known as **Analgesic nephropathy**:
  - It is the result of prolonged NSAID use
  - And it results in tubulointerstitial nephritis and papillary necrosis (↑ creatinine/BUN ratio, slight ↑ K+)

28. Blood side effects of drugs (59)

WARFARIN

Mechanism of therapy

- Warfarin has **late anticoagulation effect**
  - It takes up to 60 hours for warfarin to produce anticoagulant effects (due to stored clotting factors)
    - The onset of effect of warfarin does not appear until these stores have been depleted
- Warfarin has **early pro-coagulation effect**
  - Because the stores of protein C + S are limited, only for maximally **6 hours**

Start of warfarin treatment:

- 1. *Warfarin* + **immediately acting anticoagulation** → because of ***late anticoagulation effect***
  - Usually, ***heparin*** is used and should be given **first 2 days** (then heparin **is** discontinued)
- 2. On the 3rd day of treatment → Measure INT levels
  - Physiological levels = 0,8-1,2 but we should see **prolongation of INR** → therapeutic range = **2-3**
    - (**2,5-3,5** for patients with artificial valve)
- 3. Then INR levels should be **monitored every 1-4 weeks** (every 12 weeks for stabile patients)

Side effects

- Generally, side effects are rare

- **Bleeding** (the only common side effect – still rare 3%)

Estrogens → Pro-thrombotic effects (cause liver to produce increased levels of clotting factors) → ↑ risk of deep venous thrombosis

Warfarin:

- It takes up to 60 hours for warfarin to produce anticoagulant effects (due to stored clotting factors)
  - The onset of effect of warfarin does not appear until these stores have been depleted
- Warfarin has **early pro-coagulation effect**
  - Because the stores of protein C + S are limited, only for maximally **6 hours**
- = heparin in given along with warfarin the first 2 days

Most common side effects of warfarin + heparin = bleeding

- Watch INR for warfarin
- And aPTT for heparin

29. Drug allergy (6, 46)

- Allergy induced by drug, one of the most common side effects of many drugs.
- **Allergy** = *hypersensitivity disorder of the immune system*
- Allergy reaction will **not occur** after **first exposure**, **but after second one**
  - This is due to first exposure allows the body to create antibodies and memory cells for antigen
  - But some drugs can cause allergic reaction after first exposure (drugs that contain dyes
- **Drug allergy vs drug intolerance:**
  - **Intolerance** is when the body has low threshold to normal dose of drug
    - Show side effect after normal dose of drug
  - **Allergy** is when there are excessive immune responses

Symptoms:

- They can range from mild (e.g., rashes) to severe (e.g., anaphylactic shock)
- Are classified according to time of occurrence:

1 **Immediate (2 min – 2h)**
  - Anaphylactic shock, angioneurotic edema, asthma attack, urticaria

2 **Accelerated (2-24 h)**
  - Urticaria, pruritus, respiratory disorders

3 **Delayed (24 h – 26 days)**
  - Fever, urticaria, pain and edema in joints, lesions…

Most common drug allergies:

1 **Allergy to β-lactams:**
  - Most common side effects of B-lactams
  - Characterised by Hypersensitivity I reaction (production of IgE antibodies)
    - Rashes, angioedema, anaphylaxis and shock

2 **Allergy to analgesics:**
  - Commonly seen for NSAIDs
  - Characterized by rashes and angioedema

Treatment of Drug allergy:

- In case of **anaphylactic shock:**

1 **First step** in suspected anaphylaxis:
  - 0.5 of 1:1000 **epinephrine intramuscularly** (1g epi in 1000 ml)
    - i.v. has risk of dosing error → might cause arrhythmias
    - may be repeated every 5-15 min (in case insufficient response)
  - Epi → ↑ CO + vasoconstriction + airway smooth mm. relaxation
    - This will cause ↑ BP + reduced movement of intravascular fluid into interstitial space → ↓ edema

2. Symptom reliefers:
  - **Antihistamines** (p.o. or i.v.)
  - In case of biphasic reaction (anaphylaxis occurs 72 h after initial episodes):
    - **Glucocorticoids** are used (they have delayed onset of action)

3. Due to massive fluid shift to interstitial space:
  - Give I.v. fluid

- In less severe cases:
  - **Glucocorticoids** (anti-inflammatory) and **Anti-histamines (H1 blockers)**

30. Drug abuse and dependence (13, 38, 43) + Drug dependece (4)

- The basic condition of drug producing drug dependence is its **ability to induce tolerance** and **enhance dopaminergic mediation in the reward pathway of nucleus accumbens**
- WHO defines drug addiction as:
  - ***The state when any substance or product is used to modify physiological systems or pathological states for the benefit of recipient***
  - So, addiction is a state which includes not only the use of illegal agents but ***also the standard approved medication*** (like painkillers or sleep medication)
- **Drug dependence** is included among the classic chronic brain disorders, it is a relapsing clinical state
- It is estimated that between approx. 10-15% of the population suffers from this disorder
- Another term, **drug addiction**, describes the situation which is associated with ***physical dependence***
  - The consequences of the drug intake on tissues
  - Physical dependence is mostly related to the withdrawal syndrome (= complex of symptoms which occur after immediate stopping of the drug intake)
- **Drug abuse** is another term which is widely used to describe drug addiction
  - But the difference it that drug abuse is a mort general term, it includes any recurrent use of any illegal/harmful substances → so, this term also includes the use of anabolic steroids in sports

Tolerance:

- Tolerance = gradual reduction in response to after repetitive drug exposure
- When we talk about "**true tolerance**" we mean the decreased response of repeated use of the drug
- Sometimes tolerance can be induced by a single dose, like is seen after cocaine administration
  - In that case we talk about **acute tolerance**
  - But **chronic tolerance** is much more common, which occurs after repeated use of the drug

Tolerance – mechanism

- Tolerance can be developed by 2 different mechanisms:
  - **Pharmacokinetic tolerance**
    - **Chronic use of drug leads to enhanced clearance (e.g., benzodiazepines)**
  - **Pharmacodynamic tolerance** (true tissue tolerance)
    - **Changes in receptor density (down-regulation → addictive drugs are usually agonists)**
      - **= Reduced number of receptors**
    - **Changes in receptor sensitivity (desensitization, adaption of post-receptor signaling)**
      - **= Reduced affinity of receptors to the drug**

Clinical classification of drug addictions:

- **CNS stimulants**
  - **Nicotine**
  - **Amphetamines and cocaine**
  - **Caffeine**

- **CNS depressants**
  - **Alcohol**
  - **Opiates**
  - **Benzodiazepines and barbiturates**

- **Hallucinogens**
  - **Psychedelics (e.g., LSD, mescalin)**
  - **Dissociative hallucinogens (e.g., ketamine)**

- **Others**
  - **Marijuana (can be also CNS depressant)**
  - **Ecstasy (can be also CNS stimulant)**

Therapy of addiction – general principles

❖ The treatment of drug addiction is a long-term process which should be divided into several steps

- **A. Treatment of acute withdrawal (acute detox, symptomatic support)**
  - When the treatment is associated with overdose, we use acute withdrawal (= acute detox)
  - The treatment of acute intoxication or acute withdrawal phase is mostly symptomatic
  - Our role is to use combination of non-pharmacological and pharmacological approaches which are focused on minimalization of the symptomatology associated with withdrawal syndrome
- **B. Maintenance Treatment (help the brain adapt gradually to the absence of the abused drug)**
- **C. Preventing of Relapse**
  - **Replacement therapy**
    - Nicotine – nicotine as gums, oral sprays, patches etc.
  - **Aversive therapy:**
    - Breaks the association between drug and pleasure → alcohol and disulfiram
  - **Therapy stabilizing chemical/mediators balance in the brain**
    - Alcohol – acamprosate, naltrexone, topiramate
    - Nicotine – bupropion
    - Opiates – buprenorphine, baclofen
  - **Therapy by antagonists/partial antagonists**
    - Nicotine – varenicline
    - Opiates – naltrexone

32. Drugs with tocolytic effect (37)

- Tocolytics = uterine relaxants
- "Toco" = childbirth, "lytic" = to terminate
- They're used to stop premature labor in order to give time for fetal lungs to mature
  - If labor begins too early, the fetal organs (especially the lungs) might not be fully developed
- In this case, labor can be suppressed with uterine relaxants → giving the fetus more time in the uterus to develop
- During this time, the mother can be given glucocorticoids to stimulate maturation of fetal lungs

Uterine relaxants include:

Selective beta-2 agonists (terbutaline)

- Terbutaline stimulates beta 2 receptors (Gs) → stimulates adenylate cyclase → ↑ cAMP
- cAMP then activates protein kinase A then inhibits uterine contraction = relaxation
- Side effects:
  - Stimulates sympathetic system → tachycardia, tremor, anxiety

Calcium channel blockers → nifedipine (dihydropyridine)

- Block the influx of calcium → inhibition of uterine contraction = relaxation
- Side effects:
  - Flushing, dizziness

COX inhibitors → Indomethacin

- Inhibits synthesis of prostaglandins by inhibiting COX enzyme
- "No prostaglandins = no uterine contraction"

Oxytocin receptor antagonist → Atosiban

- Binds and inhibits oxytocin receptors → blocking the signaling pathway which leads to uterine contraction

2. Autonomic nervous system

1. **Cholinergic neurotransmission and receptors (61)**
2. **Cholinergic agonists (42)**
3. **Parasympathomimetics – directly acting (53)**
4. **Parasympathomimetics – inhibitors of ACHE (33)**
5. **Centrally acting inhibitors of ACHE (29)**
6. **Parasympatholytics (43)**
7. **Tertiary parasympatholytics (8)**
8. **Atropine (41)**
9. **Quaternary parasympatholytics (56)**
10. **Agonists of adrenergic receptors (3)**
11. **Alpha – sympathomimetics (16)**
12. **Sympathomimetics – agonists of beta receptors (55)**
13. **Beta$_2$-sympathomimetics (22)**
14. **Alfa-sympatholytics (7)**
15. **Beta-adrenergic receptors antagonists (63)**

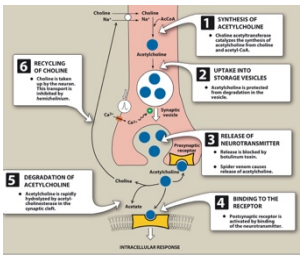
1. Cholinergic neurotransmission and receptors (61)

Parasympathetic nervous system:

- The nervous system is divided into the ***central nervous system*** and the ***peripheral nervous system***
- The peripheral nervous system can be divided into somatic (controls voluntary movements of skeletal muscles) and the autonomic nervous system
  - The autonomic nervous system is further divided into the ***sympathetic*** and ***parasympathetic nervous*** system → PNS controls involuntary movements of smooth muscles and glands of organs
- 2 key features of PNS: ***Craniosacral*** + ***longer pre-ganglionic*** pathway
  - Almost all parasympathetic nerves originate from the cranial nerves
  - Sacral nerves → Responsible for supplying the lower gastrointestinal + urogenital tract with PS fibers

Acetylcholine

Acetylcholine is the primary neurotransmitter of cholinergic neurotransmission



1. Synthesis of acetylcholine:

- Acetylcholine is formed from ***choline*** and ***acetyl CoA*** by the enzyme ***choline acetyltransferase***

2. Storage:

- It is then protected from degradation by storing in the vesicles

3. Release of Ach:

- Depolarization of pre-synaptic membrane will cause exocytosis of Ach into the synaptic cleft

4. Binding to Ach receptors

- Ach binds to cholinergic receptors on both pre- and post-ganglionic neurons
  - Pre-ganglionic receptors (M2) → negative feedback
  - Post-ganglionic receptors → muscarinic or nicotinic receptors

5. Degradation:

- Acetylcholine is rapidly destroyed by ***acetylcholinesterase (ACHE)*** to choline and acetate in synaptic cleft

6. Recycling of choline

- Choline is taken up again (Ach is used in such huge numbers, endogenous synthesis only is not possible)

Cholinergic receptors

- 2 types of cholinergic receptors: Muscarinic + nicotinic

Muscarinic receptors:

- = metabotropic receptors – ***G-protein coupled receptors***
- They are ***7-pass transmembrane receptors*** (1 end sits on the outside and binds Ach, the other end sits on the inside of the cells → this end activated intracellular proteins)

Receptor	Localization	Biochemical effect
M1 (Gq)	Neurons, parietal cells of stomach → *Stimulation of M1 = ↑ secretion*	**↑ IP3, DAG** (***excitation***)
M2 (Gi)	Heart, presynaptic sites → *Stimulation of M2 = ↓ heart rate*	**↓ cAMP** (***inhibition***), **↑ K^+ conductance**
M3 (Gq)	Exocrine glands, smooth muscle (GIT + UGT + resp.), eye → *Stimulation of M3 = ↑ secretion, miosis, ↓ intraoc. pressure*	**↑ IP3, DAG** (***excitation***)
M4 (Gi)	CNS	**↓ cAMP** (***inhibition***)
M5 (Gq)	CNS	**↑ IP3, DAG** (***excitation***)

- M1, M3, M5 are coupled with activated Gq-protein → activates phospholipase C → ↑ IP3 + DAG = activatory function
- M2, M4 are coupled with inhibitory Gi protein → ↓ cAMP
- M2: localized both pre- and post-synaptically
  - Presynaptically, M2 receptors serve as auto-receptors
  - Post-synaptically, their function is to decrease heart rate (negative chronotropic effects)

Nicotinic receptors:

- = ionotropic receptors – after binding of acetylcholine, they open sodium channels (= depolarization)
- Subtypes:
  - **Neuronal – Nn receptors** (found in autonomic ganglia – both PNS and SNS)
  - **Muscular – Nm receptors** (found in neuromuscular junction of skeletal muscles)

Receptor	Localization	Biochemical effect
N_N	Ganglionic	Opening of Ca^{2+}, Na^{+} channels, depolarization
N_M	Skeletal muscle neuromuscular endplates	Opening of Ca^{2+}, Na^{+} channels, depolarization

The main manifestation of parasympathetic nervous system

- The main tissues which exhibit effects under parasympathetic stimulation are especially:
  - **Exocrine glands, Eye, Heart, Smooth muscle**

Stimulation of parasympathetic nerves by **parasympathomimetics:**

- **Exocrine glands:**
  - Increase of secretory function
  - Salivatory glands, bronchial glands and lacrimal glands…
- **Eye:**
  - Due to **contraction of the ciliary muscle**, we can see the **miosis**, and **accommodation**
  - And ***decrease in the intraocular pressure*** (due to contraction of ciliary muscle)
- **Heart:**
  - **Decrease of heartbeat**
- **Smooth muscle:**
  - Contraction of **longitudinal muscles:**
    - The **contraction of the bronchial smooth muscle**
    - It is also manifested by **increased movement in the GIT**
    - And also manifested by the **contraction of the urinary bladder (detrusor) muscle** = urination
  - Relaxation of **circulatory (sphincter) muscles**
    - ***Emptying of the GIT*** and ***urination***

Antagonizing parasympathetic nerves by **parasympatholytics:**

- **Exocrine glands:**
  - ***Decrease secretion***
  - *Causes xerostomia* (= deficiency of the saliva production) → this is the ***main side effect of administration of parasympatholytics***
- **Eye:**
  - Instead for miosis, then we can see **mydriasis** + inability of eye to accommodate to things up-close
  - And the ***increase in the intraocular pressure***
- **Heart:**
  - Heart function, due to ***inhibition*** of ***inhibitory M_2 receptor → increased heart rate***
- **Smooth muscle:**
  - Smooth muscle activity is also influenced in the opposite manner
  - Relaxation of **longitudinal muscles**
    - This is manifested by:
      - **Bronchodilation**
      - **Decrease of GIT motility**
      - And **decrease of contraction of the bladder muscle** (detrusor muscle) = urinary retention
  - Contraction of **circulatory muscles**
    - GIT sphincters activity is then elevated and also the urinary bladder

Receptor	Localization	Biochemical effect
M1 (Gq)	Neurons, parietal cells of stomach → *Stimulation of M1* = ↑ secretion	↑ IP3, DAG (*excitation*)
M2 (Gi)	Heart, presynaptic sites → *Stimulation of M2* = ↓ *heart rate*	↓ cAMP (*inhibition*), ↑ K^+ conductance
M3 (Gq)	Exocrine glands, smooth muscle (GIT + UGT + resp.), eye → *Stimulation of M3* = ↑ secretion, miosis, ↓ intraoc. pressure	↑ IP3, DAG (*excitation*)
M4 (Gi)	CNS	↓ cAMP (*inhibition*)
M5 (Gq)	CNS	↑ IP3, DAG (*excitation*)

Some pharmacological properties of Choline Esters and Natural Alkaloids

Muscarinic agonists	Susceptibility to cholinesterases	Muscarinic activity					
		Cardiovascular	Gastrointestinal	Urinary bladder	Eye (topical)	Antagonism by atropine	Nicotinic activity
Acetylcholine	+++	++	++	++	+	+++	+
Methacholine	+	+++	++	++	+	+++	+
Carbachol	-	+	+++	+++	++	+	+++
Bethanechol	-	±	+++	+++	++	+++	-
Muscarine	-	++	+++	+++	++	+++	-
Pilocarpine	-	+	+++	+++	++	+++	-

2. Cholinergic agonists (42)

- Cholinergic agonists = *drugs that are able to mimic acetylcholine response*

Classification:

- **Direct-acting cholinergic agonists**
  - Endogenous choline esters: ***Acetylcholine***, ***Methacholine***, ***Carbachol***, ***Bethanechol***
  - Naturally occurring alkaloids: ***Muscarine***, ***Pilocarpine***
- **Indirect-acting cholinergic agonist**
  - ACHE inhibitors (reversible or irreversible)

Classification according to structure (Tertiary/quarternary)

- Ability of nitrogen to bind to more alkaloids = decreased lipophilicity
- **Tertiary:**
  - = Lipophilic → can cross BBB → have CNS effects → stimulatory → hallucinations
  - E.g., arecoline (not used in human treatment, abused as betel nuts), pilocarpine
- **Quaternary:**
  - = Limited lipophilicity → cannot cross BBB → no CNS effects
  - Only able to influence M1, M2 and M3 receptors (not M4 and M5 receptors present in CNS)
  - E.g., acetylcholine, methacholine and carbachol

Effects of cholinergic agonist

Dose

Organ	Effect
Glands (M3)	↑ secretion
Eye (M3)	Miosis, ↓ intraocular pressure
Heart (M2)	Bradycardia
Smooth muscle (M3)	Contraction
CNS (M4, M5)	Excitation/Hallucination

Cholinergic agonists have ***dose dependent effect*** of cholinergic agonists

- The lowest doses used in therapeutic practice will ***increase exocrine gland secretion***
  - So, without any significant side effects originating from the heart or smooth muscle, we can treat:
  - **Affected lacrimal gland function**, **Sjögren syndrome**, or **deficiency in saliva production** after radiotherapy, which is a very common consequence of cancer treatment
- Higher systemic doses are also able to influence **ciliary muscle**
  - Because they **induce contraction of ciliary muscle** → they result in the ***miosis***
  - They result in the **ability to accommodate to the near**, but *NOT to the far*
  - And also, because of ciliary muscle contraction, they are able to ***decrease*** **intraocular pressure**
- Further increase in the dose is responsible for **bradycardia**
  - That is a typical parasympathomimetic effect, due to **presence of inhibitory M2 receptors**
- Also, this dose can **stimulate smooth muscle**
  - There is a very high risk for **bronchoconstriction**
  - Also, **increased peristalsis** (*defecation*) and **increase in bladder activity** (*urination*)
- The highest doses are effective for the **brain**
  - Brain is **influenced excitatory → stimulated**
  - Cholinergic agonists act like **psychostimulants**, excessive level of stimulation can lead to **hallucination**

Side effects: Same as for effects, *dose dependent*

- Salivation → sweating → nausea, vomiting, diarrhea, vasodilation, bronchoconstriction → CNS

Some pharmacological properties of Choline Esters and Natural Alkaloids							
Muscarinic agonists	Susceptibility to cholinesterases	Muscarinic activity					
		Cardiovascular	Gastrointestinal	Urinary bladder	Eye (topical)	Antagonism by atropine	Nicotinic activity
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Methacholine	+	+++	++	++	+	+++	+
Carbachol	-	+	+++	+++	++	+	+++
Bethanechol	-	±	+++	+++	++	+++	-
Muscarine	-	++	+++	+++	++	+++	-
Pilocarpine	-	+	+++	+++	++	+++	-

3. Parasympathomimetics – directly acting (53)

- Cholinergic agonists = *drugs that are able to mimic acetylcholine response*

Classification:

- **Direct-acting cholinergic agonists**
  - Endogenous choline esters: ***Acetylcholine***, ***Methacholine***, ***Carbachol***, ***Bethanechol***
  - Naturally occurring alkaloids: ***Muscarine***, ***Pilocarpine***
- **Indirect-acting cholinergic agonist**
  - ACHE inhibitors (reversible or irreversible)

Effects of cholinergic agonist

Dose ↓

Organ	Effect
Glands (M3)	↑ secretion
Eye (M3)	Miosis, ↓ intraocular pressure
Heart (M2)	Bradycardia
Smooth muscle (M3)	Contraction
CNS (M4, M5)	Excitation/Hallucination

Exocrine glands (M3)

- **Stimulation of secretion**
  - (Lacrimal, salivary, digestive, sweat glands)
- The lowest doses are effective for the stimulation of the exocrine glands
- **Clinical use:**
  - Suppress **symptomatology of xerostomia** (= dry mouth)
  - To treat **symptomatology of the dry eye syndrome** (can occur after radiotherapy + is a symptom of *Sjögren's syndrome*)
- **Side effects:** stimulation of sweat glands
- **Drugs:**
  - **Pilocarpine**
  - **Cevimeline** – agonists of M_1 + M_3 receptors

Eye (M3)

- Cholinergic agonists are used very widely in the ophthalmology
- **Clinical use:**
  - Contraction of ciliary muscles → **miosis + ↓ intraocular pressure** (= ***treatment of glaucoma***)
  - Also use to overcome mydriasis caused by excessive use of parasympatholytics
- **Drugs:**
  - **Pilocarpine**
  - **Carbachol**

CVS (M2)

- Generally – bradycardia, vasodilation, hypotension
- **Heart:**
  - Cholinergic agonists decrease heart rate (***negative chronotropic effects*** → cause bradycardia)
  - Decrease in rate of conduction in SA and AV (***negative dromotropic effect***)
  - Decrease in force of contraction (***negative inotropic effect***)
- **Vessels – vasodilation (veins) – <u>synthesis of NO</u>**

Smooth muscle (M3)
→ Respiratory system

- Cholinergic agonists cause **bronchoconstriction**
- The smooth muscles of respiratory system are very significantly supplied by parasympathetic neurons
  - Parasympathetic innervation is mostly provided by the **<u>M3 receptors</u>**
- **Methacholine challenge test**
  - ***Test of bronchial hyperreactivity used as an aid in the diagnosis of asthma***
  - The physiological response seen on stimulation is **bronchoconstriction**
  - The concentration on which patient with hyperreactivity responds by bronchoconstriction is lower than in healthy person

Smooth muscle (M3)
→ Gastrointestinal system

- **Prokinetic drugs**
- **Clinical use**
  - Postoperative abdominal distention, gastric atony or gastroparesis
  - Used especially for hypokinesis of GIT
- **Drugs:**
  - **Bethanechol:** (quarternary)
    - **Oldest compound for the GIT motility stimulation**
  - **Metoclopramide:** (cholinergic + anti-D2 activity)
    - Metoclopramide, except for cholinomimetic activity, also acts as an antagonist on dopaminergic receptors
  - **Itopride:**
    - Combines antidopaminergic activity and cholinomimetic effect, to which is indirect
    - It is based on reversible inhibition of acetylcholine esterase

Smooth muscle (M3)
→ Urinary tract

- Cholinergic agonists ***contract the detrusor muscle*** of the bladder → increase voiding pressure = urination
  - **+ Relaxes of sphincters** = urination
- **Clinical use:**
  - **Atony of bladder** (due to neurological disorders, trauma, cancer or after operation)
- **Drugs**
  - **Bethanechol**

Central nervous system (M4 + M5)

- **Tertiary amines** are able to **penetrate through the blood-brain-barrier** → CNS effects
- No clinical use!
- Effects:
  - **Excitation, euphoria, hallucination … psychosis**
- **Drugs:**
  - **Pilocarpine**
  - **Arecoline**

Side effects of cholinergic agonists

Organ	Effect
Glands	**↑ secretion (salivation, sweating, lacrimation)**
Eye	**Miosis, problems with accommodation far, lacrimation**
Heart	**Bradycardia**
Smooth muscle	**Contraction (bronchoconstriction, diarrhea, excessive urination…)**
CNS	**Excitation/hallucination**

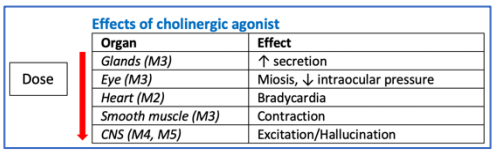
- Cholinergic agonists produce **dose-dependent side effects**
  - Excessive stimulation of the glands
    - Especially salivation and **excessive sweating** are unpleasant, and are very common
  - The **accommodation for objects far** can also be counted among the side effects
  - The most severe is the **extreme bradycardia** and **bronchoconstriction** which arises due to **stimulation of the airways smooth muscle**
    - Further muscle consequences are GIT cramps, diarrhea and problems with urination
  - Higher dose leads to the **excitation of the CNS** and can also lead to **hallucination**

- **Cholinergic poisoning** can be seen as a result of **irreversible inhibitors** of the **acetylcholine esterase**
  - Sometimes the cholinergic intoxication, in terms of the diagnosis, is expressed as **SLUDGE syndrome**
    - Sludge syndrome is the acronym originated from the first letters of the symptoms:
      - **S**alivation, **L**acrimation, **U**rination, **D**efecation, **G**IT distress and **E**mesis

- **Treatment:**
  - **Atropine** is the antidote **used for management for cholinergic poisoning** + reactivators of acetylcholine esterase (pralidoxime)
  - Status of pupils tell us when we have administered enough atropine → miosis = typical symptom of intoxication → mydriasis when atropine starts working

Agonists of nicotinic receptors

- We only have 1 drug available which acts directly through the nicotinic receptors
- **Varenicline**
  - **Therapy of smoking addiction**
  - **Partial agonists α4β2 of nicotinic receptor of CNS**



4. Parasympathomimetics – inhibitors of ACHE (33)

Classification:

- **Direct-acting cholinergic agonists**
  - Endogenous choline esters: ***Acetylcholine***, ***Methacholine***, ***Carbachol***, ***Bethanechol***
  - Naturally occurring alkaloids: ***Muscarine***, ***Pilocarpine***
- **Indirect-acting cholinergic agonist**
  - ACHE inhibitors (reversible or irreversible)

Inhibitors of acetylcholine esterase

- = Indirectly acting cholinergic agonists
- They inhibit acetylcholine esterase which normally degrade Ach in synaptic cleft = indirect agonistic effect
- These are divided into **reversible** and **irreversible**
  - Those which serve for human treatment are reversible
- Reversibly acting inhibitors of the acetylcholine esterase are divided according to their lipid solubility into:
  - **Tertiary** (act both in CNS + periphery)
    - **Physostigmine**
    - **Donepezil**
    - **Rivastigmine**
  - **Quarternary** (act only in periphery)
    - **Neostigmine**
    - **Pyridostigmine**

Drug	Indication
Donepezil, rivastigmine	Alzheimer's disease
Neostigmine	Myasthenia gravis, ileus
Pyridostigmine	Myasthenia gravis
Physostigmine	Parasympatholytic poisoning

Therapeutic use of acetylcholine esterase inhibitors

- They are used as ***antidotes*** due to different intoxications
  - **Intoxication with tertiary parasympatholytics M_1-M_5**
    - ***Physostigmine***
  - **Intoxication/overdose with competitive (non-depolarizing) neuromuscular blocking drugs N_M**
    - ***Neostigmine***
- **Myasthenia gravis N_M**
  - Myasthenia gravis = disease characterized by muscle weakness caused by damage of muscular nicotinic (Nm) receptors
  - In suspicion of myasthenia gravis, we use ***neostigmine test***
    - Neostigmine is administered in small doses → symptoms will improve quickly for short time
  - For therapy, we use ***pyridostigmine***
- **Alzheimer's disease M, N (CNS)**
  - ***Donepezil*** + ***Rivastigmine***

Side effects of cholinergic agonists

Organ	Effect
Glands	**↑ secretion (salivation, sweating, lacrimation)**
Eye	**Miosis, problems with accommodation far, lacrimation**
Heart	**Bradycardia**
Smooth muscle	**Contraction (bronchoconstriction, diarrhea, problems with urination…)**
CNS	**Excitation/hallucination**

- Cholinergic agonists produce **dose-dependent side effects**
  - Excessive stimulation of the glands (***sweating***)
  - The **accommodation for objects far** can also be counted among the side effects
  - The most severe is the **extreme bradycardia** and **bronchoconstriction** which arises due to **stimulation of the airways smooth muscle**
    - Further muscle consequences are GIT cramps, diarrhea and problems with urination
  - Higher dose leads to the **excitation of the CNS** and can also lead to **hallucination**

Irreversible inhibitors of ACHE

- Highly toxic, not used for human treatment
- Irreversible inhibitors of acetylcholine esterase are:
  - Toxic chemical warfare agents like **sarin** (GB), **Soman** (GD) **Tabun** (GA), **VX**
  - Or **organophosphates** that are used as insecticide in agriculture
- All these agents have **high degree of lipophilicity,** they are able to penetrate easily through the skin and mucosa, so, very promptly they can reach their target tissue, including the central nervous system

- **Cholinergic poisoning** can be seen as a result of **irreversible inhibitors** of the **acetylcholine esterase**
  - Sometimes the cholinergic intoxication, in terms of the diagnosis, is expressed as **SLUDGE syndrome**
    - Sludge syndrome is the acronym originated from the first letters of the symptoms:
      - **S**alivation, **L**acrimation, **U**rination, **D**efecation, **G**IT distress and **E**mesis

- **Treatment:**
  - **Atropine** is the antidote **used for management for cholinergic poisoning** + reactivators of acetylcholine esterase (pralidoxime)
  - Status of pupils tell us when we have administered enough atropine → miosis = typical symptom of intoxication → mydriasis when atropine starts working

5. Centrally acting inhibitors of ACHE (29)

Classification:

- **Direct-acting cholinergic agonists**
  - Endogenous choline esters: ***Acetylcholine***, ***Methacholine***, ***Carbachol***, ***Bethanechol***
  - Naturally occurring alkaloids: ***Muscarine***, ***Pilocarpine***
- **Indirect-acting cholinergic agonist**
  - ACHE inhibitors (reversible or irreversible)

Inhibitors of acetylcholine esterase

- = Indirectly acting cholinergic agonists
- They inhibit acetylcholine esterase which normally degrade Ach in synaptic cleft = indirect agonistic effect
- These are divided into **reversible** and **irreversible**
  - Those which serve for human treatment are reversible
- Reversibly acting inhibitors of the acetylcholine esterase are divided according to their lipid solubility into:
  - **Tertiary** (act both in CNS + periphery)
    - **Physostigmine**
    - **Donepezil**
    - **Rivastigmine**
  - **Quarternary** (act only in periphery)
    - **Neostigmine**
    - **Pyridostigmine**

Drug	Indication
Donepezil, rivastigmine	Alzheimer's disease
Neostigmine	Myasthenia gravis, ileus
Pyridostigmine	Myasthenia gravis
Physostigmine	Parasympatholytic poisoning

- Donepezil, rivastigmine and physostigmine have tertiary structure → can cross BBB → CNS effects

Management of Alzheimer's disease

- Alzheimer's disease = neurodegenerative disease
  - The most common form of dementia, changes in behavior…
- In Alzheimer's disease, the levels of acetylcholine are decreased → because tertiary ACHE inhibitors are able to cross the BBB → they are able to increase Ach levels in the brain, resulting in some improvement of symptoms
  - We use especially ***Donepezil*** and ***Rivastigmine***
  - In Alzheimer's disease, the **treatment by inhibitors of acetylcholine esterase** is **only symptomatic**
  - For the symptomatic treatment, we use **long-lasting acetylcholine esterase inhibitors**

Physostigmine – atropine poisoning

- **Lipophilic inhibitor of acetylcholine esterase**
- Physostigmine is used as an antidote for people which overdose on an anti-cholinergic, such as atropine
  - Symptoms of atropine poisoning: **red dry skin**, **atropine fever**, **extremely dry mouth**, **mydriasis**, **cycloplegia**, **extreme tachycardia** (should be also very often a symptom), **paralysis of GIT and UGT**
- Because atropine is a **competitive reversible inhibitor** of **muscarinic** and **nicotinic** receptors, **physostigmine** causes the **persistence of acetylcholine** in **synaptic cleft** and this way, it is able to **displace atropine from the bond**
- During intoxication, it is possible to use repeated administration of this drug
  - Be careful with administration → higher doses increase the risk of cholinergic crisis onset
  - Always check the pupils

6. Parasympatholytics (43)

Parasympatholytics are a class of medications that prevent muscarinic receptors of the parasympathetic nervous system from getting stimulated by acetylcholine

Tertiary vs. quaternary parasympatholytics

- Parasympatholytics are classified according to their structure into tertiary and quaternary
- Tertiary parasympatholytics and quarternary parasympatholytics differ in the number of molecules which are bound to the nitrogen in the central position in the molecule
- ***Tertiary***:
  - Lipophilic → good absorption regardless of route of administration
  - Cross BBB → CNS effects (M1-5)
- ***Quaternary***:
  - Low lipid solubility → limited peroral absorption (should be administered in larger doses)
  - Do not cross BBB → No CNS effects (M1-3)
  - Quaternary parasympatholytics are further divided into non-selective (M1-M3) and selective

The effect of parasympatholytics is dose-dependent

Organ	Effect	Dose of atropine
Glands	**↓secretion**	**0.5 mg**
Eye	**Mydriasis, ↑intraocular pressure**	**0.5-1 mg**
Heart	**↑ frequency**	**0.5-1 mg**
Smooth muscle	**Relaxation** (bronchial, GIT)	**1-2 mg**
CNS	**Excitation/depression**	**5 mg**

Clinical uses

- ***Glands***: Hyperhidrosis, stomatological surgery, treatment of ulcer disease, ZE syndrome, GERD
- ***Eyes***: Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to prolonged mydriasis observed with atropine (7 to 14 days vs. 6 to 24 hours with other agents)
- ***Heart***: Treatment of bradyarrhythmias
- ***GIT*** smooth muscles: Treatment of GIT-spasms (diarrhea, irritable bowel)
- ***CNS***: Parkinson's disease, antiemetic drug (motion sickness)

Side effects and contraindications of parasympatholytics

- **Side effects**
  - **Dry mouth, dry skin, decrease of lacrimation** (! **M_3** glands)
    - Most frequent side effects
  - **Mydriasis + increase in intraocular pressure** (! **M_3** eyes)
  - **GIT paralysis, micturition disturbances** (! **M_3** smooth muscle)
    - Parasympatholytics inhibit contractions of detrusor muscle → urinary retention.
  - **Tachycardia** (! **M_2** heart)
    - Inhibition of inhibitory M2 receptors = tachycardia
  - **CNS disturbances** (**$M_{1,4,5}$**)
    - Only tertiary parasympatholytics
- **Contraindications**
  - **Myocardial disturbances**
    - Because parasympatholytics produce tachycardia
  - **Glaucoma** (especially close angle)
    - Because parasympatholytics ↑ intraocular pressure
  - **Prostate hypertrophy**
    - Because parasympatholytics inhibit contraction of detrusor muscle → urinary retention

7. Tertiary parasympatholytics (8)

Parasympatholytics are a class of medications that prevent muscarinic receptors of the parasympathetic nervous system from getting stimulated by acetylcholine

Tertiary vs. quaternary parasympatholytics

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- ***Tertiary***:
  - Lipophilic → good absorption regardless of route of administration
  - Cross BBB → CNS effects (M1-5)
- ***Quaternary***:
  - Low lipid solubility → limited peroral absorption (should be administered in larger doses)
  - Do not cross BBB → No CNS effects (M1-3)

Tertiary parasympatholytic (=high level of lipophilicity)

- Tertiary parasympatholytics are sometimes divided into *naturally occurring alkaloids* and *synthetic drugs*
- **1. Naturally occurring alkaloids:**
  - **Atropine**
    - A well-known source for atropine is especially *Atropa belladonae*
    - But also, the hemp plants which are native in Southern areas of Africa is a well-known source
  - **Scopolamine**
- **2. Synthetic drugs:**
  - Among the numerous groups of synthetic and semi-synthetic tertiary parasympatholytics, we can mention those which are mostly used in the ***ophthalmology***:
    - **Homatropine**
    - **Tropicamide**
  - We have also several agents with high degree of lipophilicity which serve as agents used occasionally for the management of ***Parkinson's disease***:
    - **Biperiden**
    - **Procyclidine**
      - These are only several examples of anti-Parkinson's drugs, we have many other available, some of them will be mentioned later

Organ system effects of tertiary parasympatholytics

Organ	Effect	Dose of atropine
Glands	**↓secretion**	**0.5 mg**
Eye	**Mydriasis, ↑intraocular pressure**	**0.5-1 mg**
Heart	**↑ frequency**	**0.5-1 mg**
Smooth muscle	**Relaxation** (bronchial, GIT)	**1-2 mg**
CNS	**Excitation/depression**	**5 mg**

- The effect of parasympatholytics is **dose-dependent**

Clinical uses

- ***Glands***: Hyperhidrosis, stomatological surgery, treatment of ulcer disease, ZE syndrome, GERD
- ***Eyes***: Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to prolonged mydriasis observed with atropine (7 to 14 days vs. 6 to 24 hours with other agents)
- ***Heart***: Treatment of bradyarrhythmias
- ***GIT*** smooth muscles: Treatment of GIT-spasms (diarrhea, irritable bowel)
- ***CNS***: Parkinson's disease, antiemetic drug (motion sickness)

Exocrine glands

- **Effects:**
  - **↓ secretion of sweat, Salivary, Lacrimal, Bronchial, GIT**
- **Clinical use:**
  - **Hyperhidrosis** (= excessive sweating)**, stomatological surgery**
- The influence on the exocrine glands is the most frequent side effect of all parasympatholytics
  - → **dry mouth** (75% of all patients that were treated by parasympatholytics reported dry mouth as an apparent side effect)

Eye

- **Effects:**
  - **Mydriasis, cycloplegia, increase of intraocular pressure, dry mucus membranes**
- **Clinical use:**
  - Prevention of ***synechia*** during eye inflammation and surgery, ophthalmoscopy of retina
- **Drugs:**
  - **Homatropine**
  - **Tropicamide**

Heart

- **Effects:**
  - **M2 receptors have inhibitory role – their inhibition leads to TACHYCARDIA**
- **Clinical use:**
  - **Treatment of bradyarrhythmias**
    - Bradyarrhythmia **originated by the vagal nerve overstimulation**, responds perfectly atropine
    - (Other types of bradyarrhythmias are less responsive)
- **Drugs:**
  - **Atropine**

Vessels

- **Vasodilation of microcirculation, inhibition of thermoregulatory sweating**
  - **Vasodilation** and **atropine fever** are a well-known symptoms of **atropine intoxication**

Gastrointestinal smooth muscle

- **Effects:**
  - Relaxation
- **Clinical use**
  - Treatment of GIT spasm (diarrhea, irritable bowel)

CNS

- **Effects:**
  - Decrease of acetylcholine in CNS
- **Clinical use:**
  - Antiparkinsonic drugs
    - In Parkinson's disease, there is overactivity of acetylcholine
    - Parasympatholytics are used to suppress Ach → thereby suppressing tremors
  - Antiemetic drugs (motion sickness → scopolamine, TTS)

8. Atropine (41)

Parasympatholytics are a class of medications that prevent muscarinic receptors of the parasympathetic nervous system from getting stimulated by acetylcholine

- Atropine is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors.
- **Reversible blockade of cholinomimetic action at muscarinic receptors**
  - It binds competitively and prevents ACh from binding to those sites.
- **Non-selective antagonist of M receptors** (inhibition of M1-M5 receptors)
- **Tertiary-lipophilic**
  - Atropine can very easily penetrate through BBB (acts both centrally and peripherally)
- Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days.
- Atropine is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine
- **Lethal does 0.1g (children 0.01g)**
  - When dose of atropine is too high, these metabolites have **strong paralyzing effect of the vessels**
  - Atropine is a drug which is included, in the pharmacopeia, among the **venena**
- Atropine fever and response of the vessels is a very interesting issue
  - It is interesting because **vessels have no muscarinic receptors**
  - However, the **vasodilation**, especially after large doses of atropine is very often seen
    - → Especially in childhood
- **Vasodilation** and **atropine fever** are a well-known symptoms of **atropine intoxication**

The effect of atropine is **dose-dependent**

Organ	Effect	Dose of atropine
Glands	↓secretion	0.5 mg
Eye	Mydriasis, ↑intraocular pressure	0.5-1 mg
Heart	↑ frequency	0.5-1 mg
Smooth muscle	Relaxation (bronchial, GIT)	1-2 mg
CNS	Excitation/depression	5 mg

- The effect of atropine is **dose-dependent**
- **Typical therapeutical** dose in clinical practice varies from **0.5 mg – 2 mg**

Clinical use:

- ***Glands***: Hyperhidrosis, stomatological surgery, treatment of ulcer disease, ZE syndrome, GERD
- ***Eyes***: Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to prolonged mydriasis observed with atropine (7 to 14 days vs. 6 to 24 hours with other agents)
- ***Heart***: Treatment of bradyarrhythmias
- ***GIT*** smooth muscles: Treatment of GIT-spasms (diarrhea, irritable bowel)
- ***CNS***: Parkinson's disease, antiemetic drug (motion sickness)

Atropine as antidote – cholinergic poisoning

- Atropine is used as an antidote for treatment of cholinergic poisoning
- Cholinergic poisoning can be caused by ***irreversible inhibitors of ACHE*** (Satin, soman or organophosphates) or ***muscarine-containing mushrooms poisoning***
  - SLUDGE syndrome = cholinergic crisis
    - Salivation, Lacrimation, Urination, Defecation, GIT distress and Emesis

9. Quaternary parasympatholytics (56)

Parasympatholytics are a class of medications that prevent muscarinic receptors of the parasympathetic nervous system from getting stimulated by acetylcholine

Tertiary vs. quaternary parasympatholytics

- Parasympatholytics are classified according to their structure into tertiary and quaternary
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  - Lipophilic → good absorption regardless of route of administration
  - Cross BBB → CNS effects (M1-5)
- ***Quaternary***:
  - Low lipid solubility → Limited peroral absorption (should be administered in larger doses)
  - Do not cross BBB → No CNS effects (M1-3)

Quarternary parasympatholytics:

- Divided into non-selective and selective
- Quarternary parasympatholytics are **mainly nonselective**, so they are acting on all 3 muscarinic peripheral parasympathetic receptors; **M1**, **M2**, **M3**
- We have also a newer group of **selective quarternary parasympatholytics** which exhibit some kind of **higher selectivity** to the individual receptor

Non-selective

- Non-selective quarternary parasympatholytics, a group with **limited lipophilicity**, is used **mainly for influencing the GIT** and **smooth muscles**
- We can simply therapeutically divide these non-selective quarternary parasympatholytics to the:

GIT subgroup

- **Clinical use:**
  - ***Cholelithiasis***, ***diarrhea***, ***painful hypertonia*** and ***dyskinesia***
    - **Used for the same reasons as the atropine**; so, **any painful spasm**, or **movement disorders in GIT** that should only be suppressed, **dyskinesia**, **hypertonia** and so on…
- **Drugs:**
  - ***Butylscopolamine***

Respiratory subgroup

- **Clinical use:**
  - **Bronchial asthma, COPD, allergic rhinitis, bradyarrhythmias**
- **Drugs:**
  - ***Ipratropium***, ***thiotropium***
- Ipratropium is mostly used for treatment of ***asthma*** (fast onset of effect)
  - Also alternative to atropine in management of vagal originated bradyarrhythmias
  - B2 agonists = 1st line
- Thiotropium is mostly used for ***COPD*** (has slower onset of effect)
  - B2 agonists = 2nd line

Urogenital subgroup

- **Clinical use:**
  - Treatment of bladder spasms (inflammation, surgery),
  - overactive bladder diseases (detrusor instability, spastic neurogenic bladder, children enuresis
- **Drugs:**
  - ***Oxybutynin***

Selective

Selective antagonists of parietal cells M1 receptors:

- **Clinical use:**
  - Decrease of gastric acid secretion (peptic ulcer, GERD, ZE syndrome)
  - M1 **selective agents** are used as an **alternative treatment** of the **increased gastric acid secretion**, that can be due to **peptic ulcer disease**
    - The inhibition of M_1 receptor is weaker in proton pump inhibition than the effect of the proton pump inhibitor itself
    - This is the reason why this is only existing alternative treatment
  - **Drugs:**
    - ***Pirenzepine***, ***telenzepine***

Selective antagonists of M3 receptors:

- **Clinical use:**
  - Cholelithiasis (results of trials were good), painful hypertonia and dyskinesia of gall and urinary bladder
  - Darifenacine is the drug which was evaluated in clinical trials for the treatment of **cholelithiasis**
  - We are waiting for the approval, because the results were very good, and it is already approved for the treatment of **hypertonia** and **dyskinesia** of **urinary bladder**
- **Drugs:**
  - ***Darifenacine***

10. Agonist of adrenergic receptor (3)

Intro – Nervous system:

- Nervous system is divided into **CNS** and **PNS**
  - PNS → is divided further into **Somatic nervous system** and **ANS**
- **ANS:**
  - Controls involuntary movement of smooth mm. and glands of our organs
  - **PSNS** + **SNS**
    - Have the opposite effect on body

Sympathetic nervous system:

- Sympathetic neurons originate from CNS T1-L5 spinal segments (***thoracolumbar***)
- Preganglionic and postganglionic neurons release different neurotransmitters:

1 **Acetylcholine**:
  - NTs **released by Preganglionic** neurons which binds to **nicotinic receptors** on **Postganglionic** neurons

2 **Epinephrine + Norepinephrine + Dopamine**
  - NTs **released by Postganglionic** neurons which bind to **adrenergic receptors** on **Target organs**

Adrenergic receptors:

- They are G protein coupled receptors (***metabotropic***)

Classification:

- 2 Main groups → **Alpha and Beta**
  - Which have their subtypes

Alpha Receptor

α1

- **Gq receptor**
- Will cause ↑ IP_3 + DAG
- NTs = NE, Epi, Dopamine

Location:

1. **Smooth muscles** (**Blood vessels, urinary sphincter, Eye**)
2. Heart, glands, Liver, adipose tissue

Effects:

- Most dominant effect are ***peripheral vasoconstriction***
  - Arterioles → ↑ ***afterload***
  - Veins → ↑ ***preload***
- Bladder sphincter contraction → Urinary retention
- Mydriasis
- Metabolic effect:
  - ↑ Glycogenolysis + Gluconeogenesis

α2

- **Gi receptor**
  - Will cause ↓ cAMP
- NTs = NE, Epi

Location:

1. **Presynaptic membrane**
2. **Pancreas**

Effect:

Pre-synaptically:

- They are **auto-regulatory receptors**
  - They cause ↓ release of NE
  - This will lead to:
    - **↓ of sympathetic tone** (Centrally ↓ vasomotor center activity on peripheral vessels)
    - ↓ contractility
    - ↓ vasoconstriction

Post-synaptically:

- **↓ *Insulin release***
- ↓ Aqueous humor production in eye

Beta Receptor

β 1

- **Gs receptor**
  - Will cause ↑ cAMP
- NTs = NE, Epi, Dopamine

Location:

- **Heart**
- Macula densa
- Stomach mucosa

Effect:

- **Cardiac excitation:**
  - ↑ HR (chronotr.)
  - ↑ conduction velocity (dormotr.)
  - ↑ force of contraction (inotr.)
- **↑ Renin release**

β 2

- **Gs receptor**
  - Will cause ↑ cAMP
- NTs = Epi

Location:

- Smooth mm. (**Brood vessels, Bronchioles, GIT, uterus)**
- Liver, pancreas, skeletal mm.

Effect:

- **Smooth mm. Relaxation:**
  - Vasodilation (In skeletal mm)
  - **Bronchodilation**
  - Relaxation of uterus
  - GIT relaxation
- **Metabolic effect:**
  - ↑ glucagon release
  - ↑ gluconeogenesis

β 3

- **Gs receptor**
  - Will cause ↑ cAMP
- NTs = Epi

Location:

- Bladder
- Adipose tissue

Effect:

- **↑ Lipolysis**
- **Detrusor relaxation**

Agonists of adrenergic receptors → Sympathomimetic agonists:

❖ *Substances that mimic or modify the action of endogenous catecholamines of sympathetic nervous system*

Classification:

A. Direct acting:	B. Indirect acting:
1 Nonselective → ***Norepinephrine***, ***epinephrine***, ***dopamine*** 2 Alpha agonist ➢ **Selective:** ▪ Alpha 1 selective + alpha 2 selective 3 Beta agonist: ➢ **Selective:** ▪ Beta 1 selective + beta 2 selective	1 **Releasers** (↑ release of catecholamines) 2 **Reuptake inhibitors** (⊖ reuptake of catecholamines) 3 **⊖ breakdown of NTs**

A. Direct acting

1. Nonselective agonist

❖ Group of drugs that stimulate both α and β receptor

Norepinephrine	Epinephrine	Dopamine
• Agonist of **α1 > α2 > β1 receptors** - In contrast to epinephrine → no β2 affinity! **Effect:** • **Vasoconstriction** (***α1***) → ↑ PVR → ↑ BP • **↓ HR** - **Very strong ↑ PVR stimulates baroreceptors → ↑ vagal tone → ↓** HR (reflex bradycardia) - Reflex activation of vagus tone + α2 **Indication:** • = ***drug of choice during hypotension state*** • Used as Vasopressor agent = ↑ BP • Prophylaxis + therapy of ***acute hypotension***, shock condition, sepsis, acute renal impairment	• Agonist of **α 1+2 and β 1+2 → (β > α)** **Effect:** • Stimulation of myocardium (β1) → **↑ *HR*** • ***Bronchodilation*** (β2) • Vasoconstriction (α1) • Vasodilation in skeletal mm. (β2) • α1 - Vasoconstriction (↑ BP) + β2 vasodilation (↓ BP) = ***minimal change in BP*** • Hyperglycemia (β2) **Indication:** • ***Drug of choice for anaphylactic shock*** (β1 + β2) - *Epi is physiological antagonist of histamine* • Bronchospasm (β2 → bronchodilation) • Cardiac arrest (β1 → ↑ HR) • Vasoconstrictor in local anesthesia (α1) • Epistaxis (α1) Epipen → autoinjector (i.m.)	• Agonist of **D1, β1, *α1*** **Effect:** • Agonist of D1: - **Vasodilation of splanchnic and renal vessels → *mild diuretics*** • Agonist of β1: - **Chronotropic**, **dromotropic**, **inotropic** effects • Agonist of α1: - **Vasoconstriction** **Indication:** • Complex therapy of acute heart failure → most commonly used as ***stimulant drug in treatment of cardiac arrest*** • ***Vasodilatory shock associated w. bradycardia = "gold" indication*** of dopamine administration
Norepinephrine and epinephrine – Side effects: 1 CNS → Restlessness, anxiety, nausea, vomiting, 2 CVS → arrhythmia, tachycardia, hypertension (most common side effect) 3 Necrosis of skin (local infiltration) **Norepinephrine and epinephrine – Contraindications:** • Pheochromocytoma, hypertension, thyrotoxicosis…		**Side effect:** • CVS disorders • Hypoprolactinemia - Long term therapy ⊖ prolactin secretion • Hypothyroidism ⊖ conversion of T4 → T3

2. Selective alpha agonist – topic 11

3. Selective beta agonist – topic 12 + 13

B. Indirect acting

❖ They agonist in 3 ways

- ➢ 1. They can increase the release of catecholamine from the nerve endings
- ➢ 2. They can inhibit the reuptake
- ➢ 3. Or they can be selective inhibitors of monoaminoxidase (MAO) or COMT enzyme

↑ release of Catecholamine	↑ release + ⊖ reuptake of Catecholamine	Inhibitors of degradation of Catecholamine (MAO + COMT inhibitors)
A. ***Pseudoephedrine*** (p.o.) • It's an α 1 agonist + has effect in ↑ release of catecholamines • <u>Indication:</u> - Nasal mucosa membrane decongestion ○ It's a very strong vasoconstrictor • <u>Side effect:</u> - CVS disturbances, hypertension, ↑ PVR **B.** ***Ephedrine*** (i.v.) • ↑ release of catecholamines • <u>Indication:</u> - Narcolepsia (irregular sleep cycle)	**A.** ***Methylfenidate*****:** (amphetamine derivative) → **Ritalin** • Inhibits the reuptake + increases release of norepinephrine and dopamine • <u>Indication:</u> - ADHD, narcolepsy, obesity	**A. MAO – A inhibitor** • Inhibits breakdown of NE + serotonin (RIMAs) • Antidepressant **B. MAO – B inhibitor** • Inhibits breakdown of dopamine • Parkinson disease **C. COMT inhibitor** • Inhibits breakdown of L-DOPA • Parkinson disease

Catecholamines metabolism

- There are 2 most important enzymes that destroy catecholamines
- 1. First is **<u>monoaminoxidase</u>** (**MAO**)
  - Monoaminoxidases are a family of enzymes that catalyze the oxidation of monoamines
  - They are bound to the outer membrane of the mitochondria in most cell types of the body
  - In human, there are 2 types of monoaminoxidases:
  - Monoaminoxidase A and monoaminoxidase B
    - Both of them are found in the neurons
  - **<u>Monoaminoxidase A</u>**
    - Has higher activity on **norepinephrine** and **serotonin**
  - **<u>Monoaminoxidase B</u>**
    - Has higher selectivity to **dopamine** destruction
- 2. The second one is **<u>COMT</u>**
  - There are 2 isoforms of COMT
    - First one is the **<u>soluble, short form</u>** (**S-COMT)**
    - And the other one, **<u>membrane-bound, long form</u>** (**MB-COMT**)

11. Alpha – sympathomimetics (16)

Intro – Topic 10!!

Selective alpha agonist

- ***Selective alpha 1 agonists*** = *very strong vasoconstrictions*
- ***Selective alpha 2 agonist*** = control pre-synaptic auto-receptors

Alpha Receptor			
α1		**α2**	
• **Gq receptor** - Will cause ↑ IP_3 + DAG • NTs = NE, Epi, Dopamine **Location:** 1. **Smooth muscles** (**Blood vessels, urinary sphincter, Eye**) 2. Heart, glands, Liver, adipose tissue	**Effects:** • Most dominant effect are ***peripheral vasoconstriction*** - Arterioles → ↑ ***afterload*** - Veins → ↑ ***preload*** • Bladder sphincter contraction → Urinary retention • Mydriasis • Metabolic effect: - ↑ Glycogenolysis + Gluconeogenesis	• **Gi receptor** - Will cause ↓ cAMP • NTs = NE, Epi **Location:** 1. **Presynaptic membrane** 2. **Pancreas**	**Effect:** **Pre-synaptically:** • They are **auto-regulatory receptors** - They cause ↓ release of NE - This will lead to: ○ **↓ of sympathetic tone** (Centrally ↓ vasomotor center activity on peripheral vessels) ○ ↓ contractility ○ ↓ vasoconstriction **Post-synaptically:** • ***↓ Insulin release*** • ↓ Aqueous humor production in eye

A. Selective alpha 1 agonists

❖ α1 receptor most dominant action is **vasoconstriction**!

Phenylephrine

❖ Mostly used as symptomatic treatment for nasal decongestion

❖ Known as ***nasal decongestant*** → dominant indication is ***vasoconstriction of mucus membrane***

Indication:

❖ **Symptomatic** treatment of:

- ➢ **Nasal congestion**
- ➢ **All types of rhinitis** (acute, chronic, allergic, vasomotoric)
- ➢ **Sinusitis**

❖ Hypotension

❖ Ophthalmological procedures (if mydriasis is needed)

Administration:

❖ Nasal spray, eye drops, p.o.

Limitation of use:

❖ ***Tolerance → Long-term stimulation of alpha1 receptor*** reduces the number of alpha1 receptors → loss of effect

- ➢ Maximal time of administration = 7 days

Side effects:

❖ Very strong vasoconstriction of mucus membrane → bleeding from mucous membranes

Contraindication:

❖ Hypertension (due to α1 stimulation), heart disease, hyperthyroidism, BPH (α1 stimulation increases urinary retention)

B. Selective alpha 2 agonists

❖ Stimulation of pre-synaptic alpha2 receptors → inhibition of release of norepinephrine (***negative feedback***)

❖ Alpha2 receptors are localized in the vasomotor center in medulla → controls contraction of vessels

- ➢ Stimulation causes:
  - ▪ Decreased sympathetic tone
  - ▪ Decreased vasoconstriction = Reduced peripheral vascular resistance
  - ▪ Decreased contractility

Drugs:

Selective alpha 2 agonist		
Clonidine	***Methyldopa***	***Tizanidine***
• It activated α 2 receptors in nucleus of solitary tract (**cardiovascular center**) • Has long T ½ (12-16 h) **Indication:** • **Hypertension** (3rd line therapy) – ***only*** resistant form • **"off-label" therapy of opioid withdrawal syndrome** - Most common use of clonidine - ↓ sympathetic symptoms (e.g., tachycardia, anxiety)	• It's a prodrug of a false precursor of norepinephrine (methyl-norepinephrine) - NE is released from terminal but ***cannot stimulate alpha receptors*** **Indication:** • **Hypertension** (3rd line therapy) – resistant form Can be given during pregnancy!	• Centrally acting α2 agonist with a **muscle relaxant** effect - Stimulates alpha 2 receptor in spinal cord and has additional ↓ glutamate + ⊖ NMDA receptor **Indication:** • Used as a ***muscle relaxant*** → Muscle spasm → Multiple sclerosis → Cerebral palsy

Side effect of centrally acting α2 agonist:

- ❖ They are usually relatively safe, but can have some **CNS** side effects:
  - ➢ Anxiety, sedation, depression, sleepiness

Selective α2 agonist – Local application (post-synaptic):

- ❖ Post-synaptic alpha agonists exist in clinical practice for local application
- ❖ ***Brimonidine + apraclonidine***
  - ➢ They ↓ Aqueous humor production → ↓ Intra ocular pressure
  - ➢ Indication:
    - ▪ **Open-angle glaucoma**

12. Sympathomimetics – Agonist of Beta receptors (55)
+ 13. Beta2 sympathomimetics (22)
Intro – Topic 10!!

Beta Receptor					
β 1		**β 2**		**β 3**	
• **Gs receptor** - Will cause ↑ cAMP • NTs = NE, Epi, Dopamine **Location:** • **Heart** • Macula densa • Stomach mucosa	**Effect:** • **Cardiac excitation:** - ↑ HR (chronotr.) - ↑ conduction velocity (dormotr.) - ↑ force of contraction (inotr.) • **↑ Renin release**	• **Gs receptor** - Will cause ↑ cAMP • NTs = Epi **Location:** • Smooth mm. **(Blood vessels, Bronchioles, GIT, uterus)** • Liver, pancreas, skeletal mm.	**Effect:** • **Smooth mm. Relaxation:** - Vasodilation (In skeletal mm) - Bronchodilation - Relaxation of uterus - GIT relaxation • **Metabolic effect:** - ↑ glucagon release - ↑ gluconeogenesis	• **Gs receptor** - Will cause ↑ cAMP • NTs = Epi **Location:** • Bladder • Adipose tissue	**Effect:** • **↑ Lipolysis** • **Detrusor relaxation**

a. Nonselective Beta agonist:

❖ ***Isoprenaline*:**
- ➢ **Short acting β1 and β2 agonist**
- ➢ Effects:
  - ▪ **β1 receptor** (dominant) → positive inotropic, chronotropic, dromotropic effects
    - **↑ Heart rate**
  - ▪ **β2 receptor** → bronchodilation + ↓ PVR (vasodilation in skeletal mm)
- ➢ Indication:
  - ▪ Mainly to ↑ HR + ↑ CO, so used in **severe bradycardia** (= emergency cardio-stimulant)

b. Selective β1 agonist:

❖ **β1 action → positive inotropic, chronotropic, dromotropic effects + ↑ renin release**
- ➢ ↑ HR + ↑ CO → ↑ BP

❖ **Indication**:
- ➢ Inotropic agent → increases heart contractility
- ➢ = Used for ***acute heart failure***, ***BB overdose*** (+ glucagon), ***acute decompensation of ischemic heart disease***

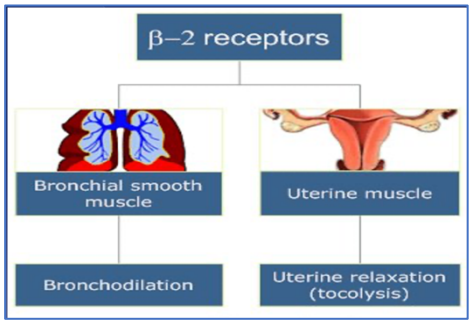
❖ **Drugs**:
- ➢ ***Dobutamine*:**
  - ▪ **β1 (dominant) + β2 and α1 agonist (weak → clinically insignificant)**
    - Has weak or no effect on BP (clinically insignificant)
- ➢ ***Dopexamine***:
  - ▪ Has additional **D1** effect
  - ▪ Rarely used

c. Selective β2 agonist:

❖ Selective agonists of beta2 receptors cause ***smooth muscle relaxation*** (→ ***relax all types of smooth muscles***)
- ➢ Primarily used to treat bronchial asthma or COPD
- ➢ They are also used to treat uterine smooth muscle (tocolytics)

Bronchial effect of beta2 agonists:

❖ Tonus of bronchial smooth muscle is controlled by:
- ➢ **Parasympathetic**: M3 receptors → bronchoconstriction
- ➢ **Sympathetic**: β2 receptors → bronchodilation



Effects:

1 **Primary effect:**
- ➢ **Bronchodilation**

2 **Secondary effects:**
- ➢ **Improve function of rep epithelium**
- ➢ **Mucokinetic effect** (⊕ ciliary movement)

Indication:

1 **Asthma** (1st line therapy)

2 **COPD** (2nd line therapy, parasympatholytics are 1st line)

3 **Anaphylactic shock + other bronchospasms**

- ➢ Drug of choice for anaphylactic shock is adrenaline (but it is short-term therapy), then airway is dilated by using beta2 agonists

4 **Treatment of hyperkalemia** (they ↑ entering of K into cells)

- ➢ Remember, drug of choice to treat hyperkalemia is insulin covered by glucose

❖ β2 agonists are taken with inhaled corticosteroids

- ➢ after long term administration of β2 agonist, there will be downregulation of receptor → ↓ β2 agonist effect
  - Corticosteroids have an effect to ↑ expression of β2 receptors → ↑ β2 agonist effect

❖ β2 agonists are classified according to duration of action:

Short acting beta2 agonist (SABA)	Long acting beta2 agonist (LABA)	Ultra-Long acting beta2 agonist (u-LABA)
• Onset of action = 1-5 min, duration = 4-6 h • Recommended adm → inhaled - Quick local effect + ↓ side effects **Indication:** • Used as Asthma **relivers** **Drugs:** • ***Salbutamol*** (p.o., inh.) • ***Fenoterol*** (inh.)	• Onset of action = 1-5 min, duration = 8-15 h • Recommended adm → inhaled - Quick local effect + ↓ side effects **Indication:** • Used as Asthma **Controllers** **Drugs:** • *Salbutamol* w. prolonged effect (p.o.) • ***Formoterol*** (inh.)	• New type w. ultra-long effect • Recommended adm → inhaled - Quick local effect + ↓ side effects **Indication:** • **ONLY** for COPD ❖ Don't have long-term data for asthma **Drugs:** • *Indacaterol* • *Vilanterol*

β2 agonist – Side effects:

1 **Tremor of skeletal mm.**

2 **↑ lactate**

- ➢ Due to contraction of skeletal mm.

3 **Tachycardia**

- ➢ β1 + β2 receptor have similar structure → β2 agonists can stimulate β1 receptors (↑ HR)

4 **Hypokalemia**

- ➢ ↑ K into cell, recommended to take drugs that improve hypokalemia

5 **Other rare side effect:**

- ➢ Hyperglycemia, lactate acidosis, allergic reaction

Uterine effect of beta2 agonists (tocolytics):

❖ β2 agonist cause **uterus smooth mm relaxation**

❖ **Tocolytics** = anti-contraction medication which are ***used to suppress premature labor***

❖ Used as 2nd line therapy for tocolysis (NSAIDs or CCB are 1st)

❖ Drug – ***Terbutaline*** (SABA)

- ➢ Only used ***only for short-term therapy*** because of risk of side effects
  - Maternal side effects → cardiac arrhythmias, MI, pulmonary edema
  - Fetal side effects → tachycardia, hypoglycemia, MI…

d. Selective β3 agonist:

❖ β3 agonist cause → **relaxation of detrusor mm. + ↑ lipolysis**

❖ These drugs are mainly used to treat **overactive bladder + bladder inflammation**

❖ Drug:

- ➢ ***Mirabegron***
  - Has the benefit over other bladder medication, it lacks anti-M side effects

α1	
• **Gq receptor** - Will cause ↑ IP_3 + DAG • NTs = NE, Epi, Dopamine **Location:** 1. **Smooth muscles (Blood vessels, urinary sphincter, Eye)** 2. Heart, glands, Liver, adipose tissue	**Effects:** • Most dominant effect are ***peripheral vasoconstriction*** - Arterioles → ↑ ***afterload*** - Veins → ↑ ***preload*** • Bladder sphincter contraction → Urinary retention • Mydriasis • Metabolic effect: - ↑ Glycogenolysis + Gluconeogenesis

14. Alfa-sympatholytics (7)

Intro – topic 10

Intro – Sympatholytics:

❖ *Agents that inhibit the activity of SNS*

α_1	α_2
Vasoconstriction	**Inhibition of norepinephrine release**
Increased peripheral resistance	**Inhibition of insulin release**
Increased blood pressure	
Mydriasis	
Increased closure of internal sphincter of the bladder	

Alpha Receptor antagonist (alpha blockers)

❖ They are classified according to selectivity:
- ➢ **A. Non-selective**
- ➢ **B. Selective**

❖ Main indications of Alpha blockers:
- ➢ ***Benign prostatic hyperplasia***
- ➢ ***Hypertension***
- ➢ ***Post-traumatic stress disorder***

A. Non-selective alpha antagonists:

❖ They block both **α1 + α2 receptors**
- ➢ = broader spectrum of side effects – inhibition α2 = ↑ NE → stimulation of β receptors

❖ They can be reversible or irreversible antagonists

Drugs:

❖ **Reversible antagonist** → ***Phentolamine, tolazoline***

❖ **Irreversible antagonist** → ***Phenoxybenzamine***

Effect:

1 **After inhibition of α1 + α2 receptors → very strong vasodilation → ↓ PVR → ↓ BP**
- ➢ **Orthostatic hypotension + reflex tachycardia**

2 **Edema, flashing, redness of face**

3 **Miosis**

4 **Congestion of nasal mucosa**

5 **Relaxation of urethral sphincter → ↑ urination**

6 **Relaxation of prostate smooth muscle, impotence (erection impairment), inability to ejaculate**

Clinical use:

1 Persistent pulmonary hypertension of newborns (→ tolazoline)

2 **Pheochromocytoma**

Currently there are no selective α2 blockers

B. Selective alpha antagonist – Alpha1 antagonist:

❖ Main indication is → **Hypertension, benign prostatic hyperplasia (BPH)**

Effect:

1 ↓ Vasoconstriction → ↓ PVR → ↓ BP
2 Relaxation of bladder neck muscles → easier urination
3 ↓ gluconeogenesis + glycolysis
4 ↓ α1 mediated CNS stress response → ↓ nightmares secondary to PTSD

❖ We can classify selective α1 antagonist according to indication:

Drugs for **Hypertension**	Drugs for **BPH**
• These drugs have very strong vasodilatory effect → ↓ BP • They are **NOT** first line therapy of hypertension (**2nd line**) - They can cause reflex tachycardia - Only used for resistant hypertension - But are ***good for patient w. hypertension and BPH*** → treats both! **Drugs:** • ***Prazosin, Doxazosin, Terazosin*** - *Prazosin* has additional indication → nightmares secondary to PTSD, scorpion poisoning, symptomatic treatment of alcohol withdrawal	• These drugs are more specific → work on **α1A receptor** - Makes them have less effect on blood vessels • **Drug of choice** for BPH • They only have **symptomatic effect** by causing relaxation of bladder neck → easier urination • They have minimal side effects, due to less effect on blood vessels **Drugs:** • ***Tamsulosin***

Other α1 antagonist – *Urapidil:*

❖ Drug with **α1 and 5-HT$_{1A}$ antagonism**
❖ Has very strong vasodilatory effect without reflex tachycardia
  ➢ Both peripheral and central action on blood pressure
❖ **Indication** → 2nd line therapy of **Hypertension, Hypertension crisis**
  ➢ P.o. for hypertension, i.v. for hypertension crisis (fast onset = 2-5 min)

Classification:
1 **1st Generation – Nonselective beta blockers**
2 **2nd Generation – Cardio-selective (β1 selective blocker)**
3 **3rd Generation – Vasodilatory beta blockers**

15. Beta-adrenergic receptors antagonists (63)

Intro – Topic 10

Beta antagonist/Beta blockers

- *= Drugs that inhibit the sympathetic activation of β receptors*
- Beta blockers are competitive antagonists of epinephrine + norepinephrine (they block their receptors sites)

Pharmacokinetics:

1 Almost all have very **high first pass metabolism** → limited bioavailability
2 They have different **plasma protein binding**, and thus have to keep in mind **drug interaction** of those with high binding (*Propranolol, carvedilol*)
3 They differ in T ½
   - E.g., *Esmolol* T ½ = 15 min, *Nadolol* T ½ = 24 h
4 Almost all are metabolized in liver
5 Some are **lipid soluble and can cross BBB** (*metoprolol, propranolol*) → have CNS effect

Effects:

- **Beta1 blocker effect:**
  - ↓ inotropic, chronotropic, dromotropic effects + ↑ renin release
    - ↓ HR + ↓ CO → ↓ BP
  - Those that can cross BBB → ↓ sympathetic tone from central vasomotor center
- **Beta2 blocker effect:**
  - ↓ vasodilation in skeletal mm
  - ↓ bronchodilation → ↑ airway resistance
  - ↑ GIT motility
  - ↓ aqueous humor production → ↓ IOP
  - ⊖ glucagon release + ⊖ gluconeogenesis

Indication:

1 **Hypertension**
   - Chose BB according to disease (e.g., asthma, peripheral vascular resistance)
     - To minimize the side effect
   - They are used w. diuretics and CCB
2 **Ischemic heart disease** (Vasodilatory BB)
   - Ischemia is most often due to obstruction or spasm of coronary aa.
     - Then we chose vasodilatory BB to ↑ the blood supply to heart
3 **Tachyarrhythmias** (MSA BB)
4 **Chronic heart failure** (BB without ISA or vasodilatory)
   - Heart failure is characterized by number of effects e.g., ↑ oxygen demand, by using BB we ↓ the activity of heart → ↓ oxygen demand of the heart
   - BB without ISA are important because we don't want to ⊕ myocardium strongly
   - BB are part of 1st line therapy w. ACE-I
5 **Thyrotoxicosis** (non-selective BB)
   - It's a condition when there is high amount of thyroid hormone (hyperthyroidism) → leads to ⊕ of myocardium → tachycardia, tremor, hypertension
   - BB are **symptomatic treatment of thyrotoxicosis**
6 **Other rare indication:**
   - **Pheochromocytoma** (non-selective), **↓ portal hypertension in cirrhosis** (*propranolol*), **anxiety** (*propranolol*), **migraine prophylaxis** (*propranolol*), **Glaucoma** (nonselective)

Side effects:

1 **Beta 1 blocker:**
   - **Bradycardia**

2 **Beta 2 blocker:**
   - **Bronchoconstriction**
   - **Metabolic syndrome** (⊖ lipolysis, glycogenolysis, gluconeogenesis, Hypoglycemia)
   - **Transient rise peripheral resistance** → ↑ sensitivity to cold

3 **Lipophilic BB**
   - **CNS disturbance** → sedation, bad mood, depression, insomnia, nightmares

4 **Vasodilatory BB:**
   - Have additional $\alpha 1$ blocker side effects (e.g., orthostatic hypotension)

Drugs:

1 **1st Generation – Nonselective**
   - ***Propranolol, Nadolol, Sotalol, Pindolol***

2 **2nd Generation – Cardio-selective (β1 selective)**
   - ***Atenolol, Metoprolol, Esmolol, Acebutolol***
     - Esmolol has ultra-short onset of action (3-5 min)

3 **3rd Generation – Vasodilatory BB**
   - ***Labetalol, Carvedilol***
     - They have additional ***α*1 blocker effect**
     - ***Carvedilol*** has also additional antioxidant effect

ISA: (*Intrinsic sympathomimetic activity*)
- Beta blockers can be with or without ISA
- ISA beta blocker have dual effect
  → Partial agonist and antagonist effect
- This will create less effet but also less side effect
- Drugs:
  - ***Pindolol, Acebutolol, Labetalol***

MSA:
- *Membrane stabilizing activity*
- BB w. MSA are used as Class ⊖ antiarrhythmics
- Drugs:
  - ***Propranolol, Pindolol, Metoprolol, Labetalol, Carvedilol***

3. Gastrointestinal tract

1. **Treatment of peptic ulcer disease – drugs inhibiting HCl production (11)**
2. **Inhibitors of proton pump – treatment of peptic ulcer disease (3)**
3. **Peptic ulcer disease - mucoprotective drugs (48)**
4. **Antacids (20, 45)**
5. **Emetics and antiemetics (30)**
6. **Spasmolytics** (Centrally acting muscle relaxants) **(36)**
7. **Laxatives, treatment of diarrhea (12)**

1. Treatment of peptic ulcer disease – drugs inhibiting HCl production (11)

Intro – Peptic ulcer:

- *A circumscribed ulceration of GIT mucosa occurring in areas exposed to acid and pepsin, and most often caused by H. pylori infection*
- Peptic ulcer = a distinct breach in the mucosal lining of the stomach or first part of small intestine:
  - **Gastric ulcer + Duodenal ulcer** (more common)
- ***Causes***:
  - Imbalance between **aggressive factor** and **protective factors**
    - Either ↑ of aggressive factors or ↓ of protective factors
  - Genetic factors
  - Stress
- ***Symptoms:***
  - Epigastric pain (*after eating in gastric, empty stomach in duodenal*), heartburn, indigestion, nausea + vomiting, weight loss

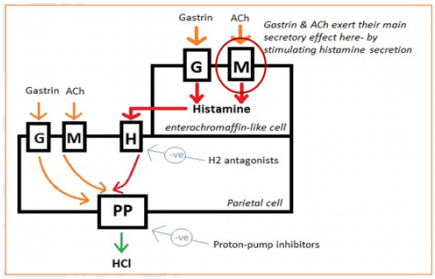
Protective factors:
- Mucus, bicarbonate, mucosal blood flow, ↓ prostaglandins

Aggressive factors:
- HCL, pepsin, drugs, H.pylori, stress, alcohol

Intro - Treatment of peptic ulcer:

1 Non-Pharmacological (have minor role):
- Diet, ↓ risk factors

2 **Pharmacological:**
- A. **Antisecretory agents** = ↓ HCL production and secretion
- B. **Antacids** = Neutralization of pH
- C. **Mucous membrane protection**
- D. **Antibiotics** = Eradication H. pylori



Antisecretory agents		
Proton pump inhibitors	**H_2 antagonist**	**Antimuscarinics**
• Most effective drugs against Peptic ulcer **Mechanism of action:** • Irreversible inhibition of H^+/K^+-ATPase in parietal cells → ↑ stomach pH • Complete ⊖ of gastric acid secretion **Drug:** • ***Omeprazole, Esomeprazole, Lansoprazole***	• Mostly for maintenance or in combination w. PPIs if needed **Mechanism of action:** • Competitive inhibition of H_2 receptors in parietal cells → ↓ cAMP → ↓ ⊕ H/K ATPase → ↑ Stomach pH **Drugs:** - ***Ranitidine***, ***Famotidine***, *Cimetidine* (not used anymore)	• Not recommended for patient w. Gastric ulcer - Due to slower gastric emptying + promote duodenal-gastric reflux **Mechanism of action:** • ⊖ of M_{1+3} receptors in parietal cells → ↓ ⊕ H/K ATPase → ↑ stomach pH **Drugs:** • ***Pirenzepine, Telenzepine***

Antisecretory agents – Indication:

1 **Peptic ulcer**
2 **GERD**
3 **Prevention of peptic ulcer**

Antisecretory agents – Side effects

- Gastric disturbances (diarrhea, constipation), Allergic reaction, hepatic complication, Muscle pain, Anticholinergic effect (dry mouth...)

Treatment plan in HP+ peptic ulcers

- Therapy of helicobacter positive peptic ulcers must contain also **antibiotic compound**
- **Triple therapy** → ***proton pump inhibitor*** + ***2 antibiotics*** (*clarithromycin combined with amoxicillin*) for 10-14 days
- **Quadruple therapy** → ***bismuth, 2 ATBs*** and ***PPI*** **or** ***H2-blocker*** **for 14 days**

2. Inhibitors of proton pump – treatment of peptic ulcer disease (3)

Intro – Peptic ulcer:

- *A circumscribed ulceration of GIT mucosa occurring in areas exposed to acid and pepsin, and most often caused by H. pylori infection*
- Peptic ulcer = a distinct breach in the mucosal lining of the stomach or first part of small intestine:
  - **Gastric ulcer + Duodenal ulcer** (more common)
- ***Causes***:
  - Imbalance between **aggressive factor** and **protective factors**
    - Either ↑ of aggressive factors or ↓ of protective factors
  - Genetic factors
  - Stress
- ***Symptoms:***
  - Epigastric pain (*after eating in gastric*, *empty stomach in duodenal*), heartburn, indigestion, nausea + vomiting, weight loss

Protective factors:
- Mucus, bicarbonate, mucosal blood flow, ↓ prostaglandins

Aggressive factors:
- HCL, pepsin, drugs, H.pylori, stress, alcohol

Intro - Treatment of peptic ulcer:

1 Non-Pharmacological (have minor role):
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  - B. **Antacids** = Neutralization of pH
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  - D. **Antibiotics** = Eradication H. pylori

Proton Pump Inhibitors:

- Most effective drugs against peptic ulcers
- They are a part of **antisecretory agents**
- Prodrug that requires activation in acid environment

Mechanism of action:

- After rapid absorption into systemic circulation, the prodrug diffuses into parietal cells (in acidic secretory canaliculi) and gets activated → after activation they are able to **irreversibly inhibit H^+/K^+ ATPase in parietal cells → ↑ stomach pH**
  - ↓ H secretion in intestinal lumen to form HCl → **Completely blocks HCL secretion**
    - Until new proton pumps are synthesized (because its irreversible) → Long-acting drug (24-48 h)
  - PPIs inhibit the last step in acid secretion, which makes them really effective
- They ↓ conversion of pepsinogen to pepsin (↓ degradation of proteins)

Drugs:

- ***Omeprazole, Esomeprazole, Lansoprazole***
  - *Esomeprazole* has longer T ½
- Applied in **coated tablets** (enteric coated) to prevent their degradation by acid in the gastric lumen

Indication:

1 **Active Gastric/Duodenal ulcer**
2 **Treatment and prevention of recurrences NSAID associated gastric ulcer**
3 **GERD**
4 **Zollinger-Ellison syndrome**

Side effects:

- ***GIT disturbances*** (abdominal pain, diarrhea, constipation…)
  - Most commonly occurring side effects
- ***Allergic reaction***
- ***Hepatic complication*** (interference w. CYP450 metabolism)
- ***Hypomagnesemia***
  - Damage of proton pump inhibitors induce damage of the intestinal magnesium absorption
- ***Hypergastrinemia***

3. Peptic ulcer disease - mucoprotective drugs (48)

Intro – Peptic ulcer:

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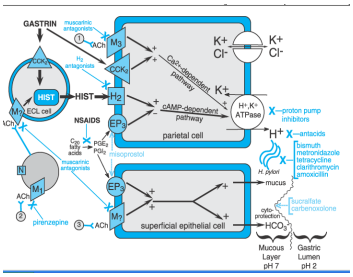
Protective factors:
- Mucus, bicarbonate, mucosal blood flow, ↓ prostaglandins

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Intro - Treatment of peptic ulcer:

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  - D. **Antibiotics** = Eradication H. pylori



Mucosal protective Agents:

- Are ***drugs that protect the mucosal lining of the stomach from gastric acid***

Sucralfate	Colloidal bismuth compounds	*Misoprostol*
Mechanism of action: • **In acidic pH → forms a viscous gel that adheres to ulcer + stimulates prostaglandin production** - It forms a protective film at the site of the mucosal lesion → prevents further digestion of lesion - Secondary mechanism: stimulation PG synthesis → it improves blood flow and mucosal regeneration to injured site + ⊕ mucus and bicarbonate production **Indication:** • Prophylaxis of stress ulcer (taken 1h before meal) **Side effects/risk of therapy:** • Kidney disease - It contains small amount of aluminum → can cause kidney disease • ↓ Phosphate absorption (Hypophosphatemia)	**Mechanism of action:** • **Coat ulcers, ⊕ Mucus + bicarbonate secretion** - Bind to peptic lesion and form protective film • ⊕ Regeneration of epithelium + **Bactericidal effect on Helicobacter pylori** **Side effects:** • Bismuth toxicity (long term use) **Disadvantages:** • They need 4-8 weeks to form their lining • Color of stool + tongue turns black - Sometimes mistaken to melena	• = synthetic ***PGE_1 analogue*** **Mechanism of action:** • Bind EP_3 receptor on parietal cells (G_i pathway) which leads to: - ⊖ ***Gastric acid secretion*** - ⊕ ***mucus + bicarbonate secretion*** - ⊕ ***mucosal blood flow*** **Indication:** • Prevention of NSAID induced ulcer → Because NSAIDs ⊖ PGE_2 synthesis **Side effect:** • Diarrhea + abdominal pain (30% of cases) **Contraindications:** • Pregnancy → Prostaglandins increase uterine contractility = can lead to abortion

4. Antacids (20, 45)

Intro – Peptic ulcer:

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Antacids

- It produces neutralization of pH in GIT (↑ pH)
- Mainly used as additional acid suppression for rapid symptom relief
  - Provide fast acting effects, which patient use for quick relief of symptoms
- They should be taken between meals when the period of food neutralization of gastric acid ends and maximal HCL secretion begins
- They are admitted, especially in the beginning of therapy when the peptic ulcers are the most painful

Classification

- According to the mechanism of action, we talk about colloid and reactive antacids
  - The main difference between them is that colloid antacids are able to bind gastric acid, and reactive, they are inactivating gastric acid by simple chemical reaction

Colloid antacids		Reactive antacids	
Aluminum salts: (most commonly used!) • Formation of insoluble aluminum-phosphate complexes • Most commonly used **Effects:** • In addition to their neutralizing ability, they are able to increase the defense and regenerative abilities of the mucosa - ⊕ epidermal growth factor effect (⊕ synthesis of PG and NO) **Side effects:** • Constipation, hypophosphatemia, osteomalacia, renal insufficiency	**Magnesium Salts:** • $MgCl_2$ production **Side effects:** • Diarrhea, hypermagnesemia, kidney + heart disease	**Calcium salts:** **Side effect:** • Due to excessive calcium absorption: → Hypercalcemia, kidney stones	**Sodium bicarbonate ($NaHCO_3$):** • Quick onset + short duration **Side effect:** • Due to excessive calcium absorption: → Metabolic alkalosis, risk of hypertension

5. Emetics and antiemetics (30)

Intro - Vomiting

- *Forceful oral expulsion of stomach contents*

Vomiting center:

- → located in medulla oblongata
- Not only 1 nucleus and not limited to 1 area → it is several nuclei and complex of neurons

Systems connected to vomiting center:

1. **Vestibular system** (H_1 + M_1)
   - Involuntary ⊕ of these receptors will lead to vomiting
2. **Chemoreceptor trigger zone – CTZ** (D_2, NK_1, 5-HT_3, Chemoreceptors)
   - Contain thinner BBB than other parts of brain → substances in blood may stimulate CTZ activity which can lead to vomiting
3. **GIT** (mechanoreceptors, Chemoreceptors, 5-HT_3)
   - Mechanoreceptors → overdistension can stimulate these receptor and lead to vomiting
   - Vomiting can be caused by any condition which causes slowing down of motion of GIT
     - Constipation, gastric stasis, obstruction…
4. **CNS**
   - Emotions, pain, smell and some more effects can lead to ⊕ of vomiting center → vomiting

- By looking at these systems, the cause of vomiting can be:
  - **Physiological** (e.g., constipation, ↑ ICP), **Metabolic** (e.g., electrolyte imbalance), **Treatment** (e.g., chemotherapy), **Emotional**, **vestibular system** (motion sickness)

Menier's syndrome
= Disorder within vesibular system

Antiemetics

- = Drugs used to inhibit vomiting

Therapeutic use:

- ***Motion sickness*** (Meniere's syndrome)
- ***Postoperative emesis***
  - 2 reasons: anesthetics + reduced motility of GIT
- Kidney failure + hepatitis
- **M*igraine*** (very often associated with vomiting)
- ***Chemo- and radiotherapy***
- *Antiemetics are **not** recommended for pregnancy, use non-pharmacological therapy*

Classification of receptors of vomiting center

1. **Antihistaminics (H_1+H_3 antagonist)**
2. **Phenothiazines (D_2 antagonist)**
3. **Antagonists of 5-HT_3**
4. **Antimuscarinics**
5. **Antagonist of NK_1**
6. **Agonists of Cannabinoids**
7. **Other:**
   - Are those that ⊖ vomiting caused by CNS
   - E.g., Benzodiazepines (↓ anxiety → no vomiting)

- In case of serotonin, neurokinin and dopamine, histamine and acetylcholine, to inhibit vomiting center, we use **antagonists**
- All these receptors should be **blocked** to inhibit vomiting center

- In case of cannabinoid receptors, to inhibit vomiting center, we use agonists
  - → Anorexia can be treated by cannabinoid agonists
  - **Stimulation** of cannabinoid receptor with cannabis and some metabolites and analogs can lead to increased activity of hunger center and inhibition of vomiting center

Antihistaminics (H_1)	Antihistaminics (H_3)	Phenothiazines (anti-D_2)
• Main indication of H_1 antihistaminics is anti-allergic effect but some can be effective in vomiting • Mainly effect receptors in Vestibular system **Indication:** • Motion sickness, migraine, Meniere's syndrome **Drugs:** • They are divided into 3 generation - **1st** being able to **cross** the **BBB** easily, thus have the **antiemetic effect** - **2nd + 3rd** do **NOT cross BBB**, thus have **NO antiemetic effect** • Most common: - ***Mephenhydrinate + Diphenhydramine***	**Indication:** • Vestibular system disturbances (Meniere's synd.) **Mechanism of action:** • Indirect antiemetic effect • ↑ blood flow to the vestibular system **Drug:** • ***Betahistine***	• Anti-D_2 are a group of antipsychotic drugs, but D_2 receptors are also found in **CTZ** - So, by blocking them → antiemetic effect **Mechanism of action:** • Centrally action (block D_2 in CTZ) • Peripheral acting = **Prokinetic** - ↑ GIT motility, resting Esophageal sphincter → allows food to move quicker to the intestine **Indication:** • Cancer therapy, Meniere's syndrome, Postoperative emesis **Drugs:** • ***Thiethylperazine*** (very common), ***Promethazine*** (has additional antihistaminic effect) - These drugs are more centrally acting • ***Metoclopramide*** (Afipran) - Prokinetic effect, anti-H_3 in higher doses

5-HT_3 antagonist	Antimuscarinic	NK_1 antagonist	Cannabinoids
• Also known as Setrons **Mechanism of action:** • Central and peripheral effect - Strong central effect on CZT - Peripheral effect through ⊖ of vagus nerve **Indication:** • Very effective in cancer treatment - Radiotherapy, chemotherapy, or after operation **Drugs:** • ***Ondansetron***	• Only ***Scopolamine*** - Can penetrate BBB - often given in patches **Mechanism of action:** • They will affect vestibular system, CZT, directly vomiting center **Indication:** • Major indication is prevention and treatment of motion sickness **Side effects** → anticholinergic effect	• Antagonist of substance P on Neurokinin-1 receptor **Indication:** • Delayed emesis induced by chemotherapy and postoperatively **Drug:** • ***Aprepitant***	• Pure synthetic isomer of THC • Partial agonist at CB receptors **Indication:** • Treatment of anorexia in AIDS patients, as well as for refractory nausea and vomiting of patients undergoing chemotherapy **Risk:** • Considered to be non-narcotic and have low risk of physical or mental dependence **Drug:** • ***Dronabinol***

Emetics:

- = Substances that induce vomiting when administered orally or by injection
- Indication:
  - Used in intoxication
    - But are usually not recommended, rather stimulate gag reflex (conscious) or gastric lavage (unconscious)
- Drug that is used → ***Apomorphine***
  - It has multiple effect:
    - **Non-selective dopamine agonist, 5-HT_2 antagonist, α antagonist,** partial opioid antagonist
  - Dosing → 15 ml (adult), 5-10 mil (children)
- **Ipecacuanhae syrup**
  - Was used in old days but is not used anymore due to high risk of side effects

6. Spasmolytics (Centrally acting muscle relaxants) (36)

Spasmolytics:

- Also called antispasmodics, are drugs used to suppress muscle spasm (opposite to prokinetics)
  - If gastric modality is increased, it usually leads to pain → then we use spasmolytics
- It can be smooth mm relaxant or skeletal muscle relaxant
- They are used to ↓ spams in → **GIT and urinary bladder**
- Drugs representing spasmolytics are group of:
  - **Antimuscarinic**, **Selective inhibitors of PDE-4**, **L-type Ca channel blocker**

Antimuscarinics:

- They are group of anticholinergic drugs that competitively inhibit postganglionic muscarinic receptors
- They are divided into Tertiary and Quarternary antimuscarinic
  - **Tertiary parasympatholytics** are lipid soluble → cross BBB
  - **Quarternary parasympatholytics** are less lipid soluble → do not cross BBB

Muscarinic receptors:

1. **M1, M4, M5**
   - Influence the **CNS**
2. **M2**
   - Work on the **heart** (↑ HR)
3. **M3:**
   - Work on **smooth mm**. In:
     - GIT, UT, Airway, eye, blood vessels (little effect)
   - Also influence Exocrine glands
     - ↓ secretion

Antimuscarinic drugs used as spasmolytics:

1 ***Butylscopolamine*** (BUSCOPAN)
  - Quarternary antimuscarinic
  - Peripherally acting antimuscarinic used to treat pain and discomfort caused by GIT spasm + prevent bladder spasm

2 ***Otilonium*** often known as spasmomen

3 ***Fenpiverine + pitophenone***

Side effects:

- Can lead to anticholinergic side effects (dry mouth…)

Selective inhibitors of PDE-4:

- Drug that ⊖ degradation of cAMP → ↑ cAMP → ↑ smooth mm. relaxation
- PDE-4 receptors are mostly in smooth mm.
  - Often used for asthma and COPD, but also as spasmolytic
- **Drug → *Drotaverine***
- **Side effects** of PDE inhibitors:
  - Headache, dyspepsia, nasal congestion

L-type Ca channel blocker:

- By inhibiting Ca channel → less Ca for smooth mm contraction
- **Drug → *Pinaverine*, *Alverine***
- **Side effects** of Ca channel blockers:
  - Edema, headache, gingival hyperplasia

So, as **antispasmodics**, we use drugs with:

- **Antimuscarinic action**
  - → **Butylscopolamine**
- **Selective inhibition of phosphodiesterase** (increasing cAMP)
  - → **Drotaverine**
- And **blocking of calcium channels**
  - → **Pinaverine** and **alverine**
  - Less calcium in smooth muscle = less contraction
  - Contraction is not possible without calcium
  - So, that's why blocking of these calcium channels will lead to relaxation of smooth muscles

7. Laxatives, treatment of diarrhea (12)

Intro – Diarrhea:

- Diarrhea is mostly associated:
  - Net fluid accumulation + ↑ propulsive contraction + ↓ mixing contraction
  - There is ↑ flow through the intestine
- Many things can cause diarrhea:
  - E.g. Ingestion of poorly absorbed material, infection, drugs
- Clinical features → Fever, abdominal pain, blood in stool, nausea + vomiting, **dehydration**

Treatment:

1. Elimination of causative agent (e.g., ATB to kill bacteria)
2. **Rehydration**
3. **Absorbents or hydroscopic agents**
4. **Antimotility, antisecretory drugs**
5. **Antidysmicrobial agents** (probiotics)

2. Rehydration:

- Rehydration is important in severe cases, we have to monitor electrolyte levels and give according to need.
- **Solution for rehydration:**
  - 1L water
  - 3.5 g NaCl
  - 20 g Glucose
  - 2.5 g $NaHCO_3$
  - 1.5 g KCl

3. Absorbents:

- Used in case there is toxin
- Effect:
  - They are not absorbed in GIT, and they will bind to toxin and water → than that complex goes out with feces
- Agents:
  - ***Diosmectid, carbo adsorbens***
- Side effects:
  - They may cause ↓ absorption of other drugs

4. Antimotility, Antisecretory drugs:

Opioids:	Antimuscarinic agents – *Atropine*	Other agents:	
Mechanism of action: • ⊖ propulsive peristalsis, ↑ sphincter tone, ⊖ intestinal fluid secretion **Mostly used opioids for diarrhea are:** • ***Diphenoxylate + Loperamide*** - *Loperamide* cannot cross BBB → no CNS effect - *Diphenoxylate* partially crosses BBB → little CNS effect • Opioids are often combined with *atropine* **Side effects:** • Constipation (very common), CNS effects	**Mechanism of action:** • ↓ propulsive contraction + ↓ cholinergic secretion **Side effects:** • Anticholinergic effects (dry mouth…)	A. ***Octreotide*** • Somatostatin analogue - ⊖ secretion induced by serotonin and GI peptidase (gastrin, VIP, insulin, secretin) • Used in severe diarrhea - e.g., HIV **Long-acting somatostatin analogue:** • ***Lanreotide, Pasireotide*** Those drug ⊖ secretion and activity of GIT peptides	B. ***Clonidine*** • A presynaptic $\alpha 2$ agonist → inhibits the release of secretory neurotransmitters and stimulates absorption - Substances causing other substances to be secreted • ↑ fluid and electrolyte absorption • Not used in Slovakia for diarrhea - Used for hypertension • SE → hypotension

5. Antidysmicrobial agents – Probiotics

- Group of agents that are usually given to patients taking ATB
  - To prevent dismicrobia and superinfection
- It's a group of normal bacteria's present in our GIT pharmacologically combined
  - To make normal/good bacterial flora in GIT
- Agents:
  - **Hylak** → concentrate of metabolic product of bacteria (E.coli + strep faecalis + lactobacillus)
  - **Lacidofil** → combination of Lactobacillus rhamnoses + Lactobacillus Helvetius
  - **Enterol** → Saccharomyces boulardii

Constipation - Laxatives

- *Infrequent passage of stool*
- Generally, best recommendation is to make some dietary changes
  - Only when that is ineffective, **Laxatives** are used
- Number 1 cause of constipation is **laxative abuse**
- Laxatives are divided into 4 groups:

1. **Bulking agents**
2. **Osmotic Laxatives**
3. **Stimulant drugs**
4. **Stool softeners**

<table>
<tr><th>Bulking Agents</th><th>Osmotic Laxatives</th></tr>
<tr><td>
• They are considered relatively safe
- They are not absorbed → no systemic effect
• Have delayed onset of action
- Need to be used for long time and regularly
Mechanism of action:
• ↑ Bowel content volume → ⊕ stretch receptors in intestinal wall → ⊕ peristalsis
Natural Agents:
• Agar, Gelatin, Plant cereals
</td><td>
• They are commonly used, not only for constipation, but also when we need to empty the bowel (e.g., before colonoscopy)
Mechanism of action:
• Bring water into GIT → ↑ volume in GIT → ⊕ stretch receptors → ⊕ peristalsis
Agents:
• Epsom salt, milk of magnesia (magnesium medic), Glauber's salt
Nondigestible sugars and alcohols:
• Lactulose, Sorbitol, mannitol
Side effects:
• Impairment of kidney, electrolyte imbalance, dehydration, spasms of GIT
</td></tr>
<tr><th>Stimulant drugs</th><th>Stool Softeners</th></tr>
<tr><td colspan="2">
• They work either on small intestine or large intestine acc. agents
Mechanism of action:
• They ⊕ neurons and smooth mm directly → ↑ peristalsis
• ⊕ secretion in intestine
</td><td rowspan="2">
• These agents lubricate the stool → easier passage of stool through GIT
• Safe for children and pregnancy
Agent:
• Glycerol (suppositories)
Other effects:
• They can cause ↓ absorption of lipophilic substances (e.g., vitamins) BAD
• Treatment of intoxication w. lipophilic substances
</td></tr>
<tr><td>
Small intestine agents:
• Caster oil
- Not used often because its relatively toxic → fast dehydration
- Small amount can lead to severe side effects
</td><td>
Large intestine agents:
• Bisacodyl, Picosulphate, Antarquinones
- These agents are frequently used before diagnostic procedures (e.g. colonoscopy)
</td></tr>
</table>

4. Endocrine

1. **Insulin and insulin analogues (1)**
2. **Peroral antidiabetics (54, 59)**
3. **Glucocorticosteroids (34)**
4. **Mineralocorticosteroids – and antagonists (53)**
5. **Estrogens and antiestrogens (2)**
6. **Gestagens and antigestagens (39)**
7. **Contraception (14)**
8. **Androgens (17)**
9. **Antithyroidal drugs (51)**
10. **Thyroid hormones and treatment of hypothyroidism (43)**
11. **Therapy of osteoporosis (40)**

1. Insulin and insulin analogues

Intro – Insulin:

- Insulin = *Peptide hormone that is produced and secreted from **ß cells** in pancreas.*
  - Preproinsulin → proinsulin → insulin
- **Process of secretion:**
  - Plasma glucose level is the main regulator of insulin secretion
  - Glucose goes into β cells of pancreas through **GLUT 2** glucose transporters→ ***glycolysis increases ATP concentration*** and ***closes ATP-dependent potassium channels in the membrane → high amount of K^+ will cause depolarization of the membrane → influx of Ca^{2+}*** through voltage gated Ca^{2+} channels → Ca^{2+} will ***stimulate exocytosis of insulin vesicle*** → insulin release!
- **Insulin receptor:**
  - It's a **tyrosine kinase type**
  - Mechanism: Insulin binds insulin receptor → phosphorylation of tyrosine kinase → activation of insulin-receptor-substrate (IRS) → cellular responses

Insulin effects:

Cell survival, cell proliferation, **translocation of GLUT 4 to cell membrane**

Stimulation ⊕	Inhibition ⊖
Glucose uptake in muscles + adipose tissue	Lipolysis
Glycolysis	Gluconeogenesis
Glycogen synthesis	Glycogenolysis
Protein synthesis	Proteolysis
Uptake of ions (especially K^+ + PO_4^{-3})	Ketogenesis

Insulin deficiency:

- ↓ glucose utilization, hyperglycemia, hyperlipemia, glycosuria, ketonemia, ketoacidosis

Pharmacokinetics:

- P.o. destroyed in GIT → ***given subcutaneously*** (*i.m.* → *painful*, *i.v.* → *only acute states*)
- T ½ = 7-10 min
  - Inactivated by insulinase + proteinase (in liver + kidney)
- Sources of insulin = recombination DNA technology (E. coli), human insulin, insulin analogues

Indication:

- **DM 1** (long term treatment)
- **DM 2** (short term treatment)
- **Diabetic ketoacidosis**
  - → Short-acting insulins
- **Hyperkalemia**
  - Insulin covered with glucose is used for the treatment of hyperkalemia

Insulin delivery system

a. Standard:
   - Conventional disposable needles and syringes

b. Portable pen injectors:
   - Insulin pens
   - 1 basal, 1 prandial

c. Insulin pumps:
   - With glucose sensor

Insulin therapy:

- Insulin can be divided into:
  - **Prandial**: (administered before meals)
    - **Short acting** (**Regular**)
    - **Rapid/ultra-short acting** (**Rapid insulin analogs**)
  - **Basal**: (control daily (or basal) concentration of insulin)
    - **Intermediate acting** (**NPH**/**Lente**)
    - **Long acting**

Prandial Insulins		
Rapid/ultra-short acting	**Short acting – Regular insulin**	**Inhaled insulin**
• Onset of action = 15 min • Duration = 90 min • S.c. **Drugs**: • ***Aspart (NOVORAPID), Lispro, Glulisine***	• Onset of action = 30-60 min • Duration = 2-4 h • S.c. and i.v. - ***Only type which is given i.v.*** in acute sates (e.g., Diabetic ketoacidosis or Somogyi phenomenon) **Drugs:** • **ACTRAPID**	• Onset of action = 15 min • For adults • Side effects/contraindications: – Has increased resp. side effects (e.g., Asthma, COPD) **Drugs:** • **AFREZZA**

Basal insulins		
Intermediate acting	**Long acting**	**Long acting insulin analogues**
• Onset of action = 2 h • Duration = 12-16 h • Delayed onset of action • ***Only subcutaneous*** administration! **Drug:** • ***NPH*** - Insulin + protamine • ***Lente L*** - Insulin + Zn (zinc)	• Onset of action = 3-4 h • Duration = 26-36 h **Drug:** • *Ultralente* (very rare use)	• Onset of action = 1-4 h • Duration = 24 h **Drug:** • *Degludec* • *Glargine* • *Detemir* → MEST NOTAÐ

INSULIN REGIMENS

Side effects:

- **Hypoglycemia** (→ the most serious adverse effect of insulin therapy!)
- **Weight gain**
- Insulin allergy
- Insulin resistance
- Lipodystrophy
- Disorder of adipose tissue at sites of insulin injection (hypo/hypertrophy)
  - → Change injection sites!

Treatment of hypoglycemia

- **Conscious patient**
  - Early symptoms
    - Consuming 15 to 20 grams of a fast-acting carbohydrate (glucose tablets, gel, fruit juice, regular soft drinks, and sugary candy)
  - Recheck blood sugar levels after 15 minutes
    - If blood sugar levels are still under 3,9 mmol/L – repeat!
- **Unconscious patient**
  - Glucagon 0,5-1 mg i.m., s.c.
  - 40-60 ml 40% glucose i.v. during 3 min – subsequently 10-20% glucose infusion
  - Or 25-50 ml. 50% dextrose (D50) i.v.

Antidiabetic agents:

1 **Insulin sensitizers – Biguanide**
- ***Metformin*** (1st line therapy)

2 **Substances influenced incretins metabolism**
- GLP-1 agonists
- DPP4-inhibitors

3 **Drugs control glucose absorption**
- α-glucosidase inhibitors
- SGLT 2 inhibitors

4 **Insulin secretagogues**
- Sulfonylureas
- Meglitinides

2. Peroral antidiabetics (54, 59)

Intro – Antidiabetic drugs:

- Peroral antidiabetics are used to control diabetes 2 (non-insulin dependent)
- The goal in the therapy of diabetes type 2 is to **stimulate the insulin receptors**
  - We do this by using hypoglycemic agents
- Drugs that are used for hyperglycemia in DM type 2 (insulin resistant type)
  - When DM type 2 patient cannot manage it by diet alone

1. Insulin sensitizers

A. *Metformin*

- **First line therapy for DM type 2**

Mechanism of action:
- Insulin sensitizer = ↑ Sensitivity of peripheral tissues to insulin **(↑ insulin binding to insulin receptor**)

Effect:
- **Euglycemic effect**
  - **↑ hepatic uptake of glucose**
  - **↓ hepatic gluconeogenesis**
  - **↓ glucagon**
- **↓ plasma lipid levels** (through PPAR α pathway)
- **↓ of food intake**
- **↑ GLP1 pathway** → ⊕ insulin secretion from pancreas
- **Modest weight loss in obese people**

Pharmacokinetics:
- Remains unmetabolized in the body + excreted in kidney

Side effects: *(metformin has excellent safety profile)*
- GIT disturbances (e.g., nausea + vomiting), Lactic acidosis (rare), folic acid + B12 deficiency, allergy

B. Thiazolidinediones (TZD)

- Less used insulin sensitizer due to high risk of side effects

Mechanism of action:
- Selective agonist of peroxisome proliferator activated receptor gamma (PPAR-γ) → ↑ insulin sensation

Effects:
- Facilitate ↑ glucose uptake in adipose tissue, muscle and liver
- Diminution of free FA metabolism
- ↓ inflammatory cytokines
- ↑ adiponectin levels + improvement of insulin resistance

Side effects:
- **Weight gain**, **fluid retention**, **edema**, ↓ mineral bone density (Fracture)…

Drugs:
- ***Pioglitazone, Rosiglitazone***

2. Substances influenced incretins metabolism:
(Incretins = hormones which stimulate decrease in blood glucose levels after meals by increasing insulin secretion)

A. GLP-1 analogs *(Incretin mimetics)*

Mechanism of action:
- Meal → intestinal **GLP-1 + GIP** released and activated
  - → they **stimulate insulin secretion**
- GLP-1 analogs have the same effect → **↑ insulin secretion**

Benefits:
- Modest weight loss, ↑ satiety and delayed gastric emptying

Side effects:
- Black box warning (**Risk of thyroid tumors**), **GIT disturbances…**

Drugs:
- ***Exenatide (= the first member – derived from Gila monster)***
- ***Liraglutide***

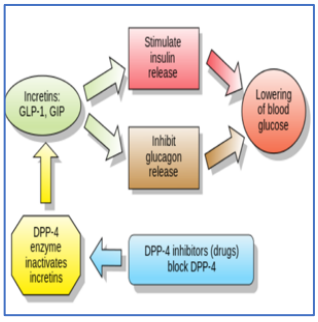
B. DPP-4 inhibitors (Gliptins) *(Inhibit destruction of incretins)*

Mechanism of action
- DPP-4 = the enzyme that breaks down Incretins (GLP-4, GIP)
- Thus, gliptins ***inhibit the enzyme which degrades incretins***

Benefits:
- Weight neutral, low risk of hypoglycemia, **no GIT disturbances**

Side effects:
- Upper resp tract infection, acute pancreatitis

Drugs:
- ***Sitagliptin, Linagliptin, Saxagliptin***



3. Drug which control glucose absorption

A. α-glucosidase inhibitor
(Inhibit glucose reabsorption from GIT)

Mechanism of action:

- Competitive inhibitors of intestinal α-glucosidase → **delay** + **↓ glucose absorption**

- α-glucosidase = an enzyme which converts carbohydrates to monosaccharides

- By inhibiting this enzyme = ↓ absorption of carbohydrates

Advantages:

- **No risk of hypoglycemia, no systemic effect, no weight gain**

Disadvantages:

- **Low effectiveness**, **GIT side effects** (diarrhea)

Drugs:

- ***Miglitol, Acarbose***

B. Sodium-glucose co-transporter (SGLT-2) inhibitors (gliflozins)
(Inhibit glucose reabsorption from kidney)

Mechanism of action:

- **Inhibits SGLT-2 in kidney → ↓ glucose reabsorption → glycosuria + polyuria**

- They inhibit the transporters responsible for reabsorption of glucose → glycosurie

Indication:

- People with high glucose level, despite being on antidiabetic medication

Benefits:

- Modest weight loss, low hypoglycemic effect

Side effects:

- UT infection, risk of diabetic ketoacidosis, ↓ BP, **kidney disturbances**

Drugs:

- **Canagliflozin, dapagliflozin, empagliflozin ("-flozins")**

4. Insulin Secretagogues
(older members of anti-diabetic agents)

A. Sulfonylureas

Mechanism of action:

- Block ATP-sensitive K channel in β cells → Ca influx → **insulin secretion**

Side effects:

- **Hypoglycemia, weight gain**, headache, allergic reaction

Contraindication:

- Liver + kidney disease, pregnancy…
- Absolutely not recommended for obese patients

Drugs:

- 1st Generation → ***Chlorpropamide, Tolbutamide***
- 2nd Generation → ***Glyburide, Glipizide***
  - 2nd generation has less risk of hypoglycemia + less weight gain

B. Meglitinides

Mechanism of action:

- Block ATP-sensitive K channel in β cells → Ca influx → **insulin secretion**

Side effects:

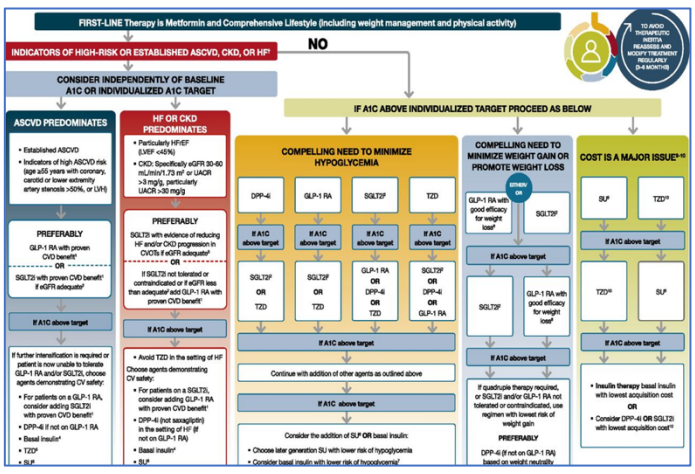
- Hypoglycemia, weight gain
  - Less than Sulfonylureas

Drugs:

- ***Nateglinide***

Why do we need so many hypoglycemic agents?

- Understand that there exist different combinations to treat DM2 according to what the main problem is:
- If we need to ***minimize hypoglycemia***:
  - We can combine **metformin** with **DPP-4 inhibitors** with drugs that **inhibit the reabsorption of glucose in the kidney**, **incretin agonists** and others
- If we need to ***minimize weight gain*** or ***promote weight loss***:
  - **GLP-1** (incretin mimetics) have very good effect on weight loss, **SGLT2 antagonists** have very good effect to promote weight loss
- Or we can solve the ***cost of therapy*** for some low-cost countries:
  - **Derivates of sulfonylurea** and **thiazolidinediones** have some limitation but their prize is low



Adrenal steroids intro: (3 layers of adrenal cortex + products)
- Outermost layer – zona glomerulosa → mineralocorticoids (aldosterone)
- Middle layer – zona fasciculata → glucocorticoids (cortisol)
- Innermost layer – zona reticularis → androgens (testosterone + estrogen)

3. Glucocorticosteroids (34)

Glucocorticoids – intro:

- Glucocorticosteroid = a hormone of the adrenal cortex (zona fasciculata)
- They have ***anti-inflammatory***, ***anti-proliferative*** and ***immunosuppressive activates***
- Glucocorticoids are under the control of adrenocorticotropic hormone (ACTH)
  - The hypothalamus secretes corticotropin releasing hormone (CRH) which stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH)
  - ACTH then stimulates the adrenal cortex to release glucocorticoids
  - Glucocorticoids have negative feedback effect on the hypothalamo-pituitary-adrenal (HPA) axis
    - Excess corticosteroids suppress the release of both CRH and ACTH into the circulation

Pharmacokinetics:

Ways of administration

Systemic	Topical/local
Peroral (p.o.) **Intravenous (i.v.)** **Intramuscular (i.m.)**	**Skin – creme…**
	Join (intra-articular) → Rapid resolution of synovitis
	Inhaled – aerosol → Cornerstone of asthma therapy
	Nose – drops → 1st line therapy for allergic rhinitis
	Eye's conjunctiva – drops → Control intraocular inflammation
	Ears – drops
	Colon – enema
	Epidural space
	Join (intra-articular)

- Topical agents generally provide ***higher anti-inflammatory effect*** with ***lower incidence of systemic side effects***

→ Absorption • Glucocorticoids are small, ***lipophilic molecules*** which are transported easily by passive diffusion across membranes	**→ Metabolism** • Natural glucocorticosteroids ***undergo extensive metabolism*** in the gut and liver • Synthetic glucocorticosteroids are metabolized slower in the liver • Prednisone is administered perorally to become active in the liver, as it is delivered as a prodrug form
→ Distribution • Endogenous glucocorticoids (cortisol) bind to ***corticosteroid binding globulin*** • Synthetic corticosteroids bind to albumin	**→ Elimination** • Via kidney

Mechanism of action

- Glucocorticosteroids are lipophilic molecules, so they readily cross the cell membrane, enter inside the cell and bind to cytoplasmic receptor proteins (glucocorticoid receptor)
  - Glucocorticoid receptor are members of the steroid hormone receptor superfamily (includes receptors also for; **mineralocorticoids**, **estrogens**, **androgens**, in addition to **vitamin D3** and **thyroid hormones**)
- Generally, glucocorticoid receptor is present in the **cytoplasm** in **inactive state**, as multimeric complex with different chaperone proteins, or **heat shock proteins** (Hsp)
  - After binding → **conformational change** in the receptor → **heat shock proteins dissociate** → **receptor becomes active** → glucocorticoid receptors **translocate to the nucleus**, where they **bind directly to specific sites of the DNA**, called **glucocorticoid-responsive elements**
  - This leads to the **activation of genes encoding anti-inflammatory proteins**
- In the nucleus, again, glucocorticoid receptors, exerts its transcription activity, either **transactivation** (↑ synthesis of anti-inflammatory proteins), or **transrepression** (↓ expression of pro-inflammatory genes)

Effects of glucocorticoids

Anti-inflammatory:	**Inhibit inflammation by blocking the action of inflammatory mediators (transrepression)** Or, by **inducing anti-inflammatory mediators (transactivation)**
Immunosuppressive:	Suppress delayed hypersensitive reactions by **directly affecting T-lymphocytes**
Anti-proliferative:	**Inhibition of DNA synthesis** and **epidermal cell turnover**
Vasoconstrictive:	**Inhibit the action of histamine** and **other vasoconstrictive mediators** + upregulation of alpha1 receptors

Replacement therapy

Anti-inflammatory/immunosuppressive

- **Slower metabolism**
- **Longer half-time ($t_{1/2}$)**
- **Higher affinity at GR than MR**
- **= Minimal mineralocorticoid response**

Cushing's diagnosis + relieve cerebral edema

Classification:

Natural glucocorticoids	**Synthetic Glucocorticoids**
• **Hydrocortisone (cortisol)** • = major natural glucocorticosteroid • Has some mineralocorticoid properties – affecting fluid balance	→ **Short acting** • **Hydrocortisone** → **Intermediate acting** • **Prednisone** • **Prednisolone** • **Triamcinolone** → **Long acting** • **Dexamethasone**

Clinical use of glucocorticoids

1. Endocrine indications

→ Used in treatment of **adrenal conditions** which are characterized be ***low corticosteroid*** levels in the body

• Primary adrenal insufficiency – ***Addison disease*** - Underlaying problem: damage to the adrenal gland	• To treat these conditions, we use short-acting glucocorticoids (replacement therapy) • ***Hydrocortisone*** = agent of choice due to its shot onset of action (→ minimal HPA axis suppression • Due to short duration of effect – multiple dosing - Replacement therapy should mimic the normal physiologic diurnal pattern (patient should receive the largest dose in the morning – later in the afternoon, a smaller dose)
• ***Congenital adrenal hyperplasia*** - Underlaying problem: genetic defect that prevents the synthesis of enzymes which make cortisol	

→ Dexamethasone test

- Dexamethasone is the most potent glucocorticoid – it causes marked suppression of HPA axis
  - It will lower the production of endogenous cortisol due to negative feedback
  - Due to this, it is used in the *overnight dexamethasone suppression test*, where it is used to diagnose Cushing's syndrome (and endocrine disorder caused by ↑ cortisol production)
  - A low dose of dexamethasone is given which suppresses ACTH production in the pituitary gland → normally that should cause a ↓ in serum cortisol levels
    - If ↑ Cortisol levels = positive test = diagnosed Cushing syndrome
- Also, dexamethasone is commonly used to **relieve cerebral edema** due to strong anti-edemic properties

2. Non endocrine indications

→ Anti-inflammatory/immunosuppressive therapy

- For asthma
- Autoimmune disease (rheumatoid arthritis, chon's disease, ulcerative colitis…)
- Inflammatory conditions of skin, eye ear or nose (eczema, allergic conjunctivitis, rhinitis…)
- Hypersensitivity states (severe allergic reactions
- Betamethasone can be given to pregnant women before birth to speed up fetal lung maturation

→ Hematological diseases

- Due to their anti-lymphocytic effect (↓ expansion of B and T cells) they are effective in hematopoietic cancers (such as leukemia)

Side effects

- Risk of side effects increases in individuals receiving high doses for prolonged period of time
- Iatrogenic Cushing's syndrome:
  - Iatrogenic Cushing's syndrome is more common than "regular" Cushing's syndrome (because of the frequent use of glucocorticoids)
  - Redistribution of fat → where the extra adipose tissue tends to build up:
    - Between the shoulders → buffalo hump
    - And in the face → moon face
- Fluid and electrolyte disturbances
  - Fluid retention, hypertension and hypokalemia

- Endocrine side effects:
  - Suppression of HPA axis → can lead to adrenocortical atrophy
  - Hyperglycemia and diabetes can result from the increased gluconeogenesis and insulin resistance
- Since they cause immunosuppression, they are associated with ↑ risk of infections and impaired would healing
- Musculoskeletal side effects
  - Myopathy + avascular necrosis of femur
  - Osteoporosis → because they decrease the activity of osteoblasts and increase activity of osteoclasts
- Psychiatric disturbances
  - Depression, insomnia, psychosis and mood swings
- Glucocorticoids cause inhibition of growth in children

(Local) Side effects

- **<u>Inhaled steroids</u>**
  - **Dysphonia**
  - **Oropharyngeal candidiasis**
  - **Throat irritation**
- **<u>Nasal steroids</u>**
  - **Nose irritation**
  - **Dry nose**
  - **Headache**
  - **Nose bleeding**
- **<u>Local steroids</u>**
  - **Epidermal atrophy**

Long-term glucocorticoid therapy

- Remember the additional "stress doses", commonly used before or after surgery or during severe illness – to prevent adrenal crisis
- Also remember, "alternate-day therapy" to prevent suppression of HPA axis (→ adrenocortical atrophy)
  - = Double daily dose every other day

Adrenal steroids intro: (3 layers of adrenal cortex + products)
- Outermost layer – zona glomerulosa → mineralocorticoids (aldosterone)
- Middle layer – zona fasciculata → glucocorticoids (cortisol)
- Innermost layer – zona reticularis → androgens (testosterone + estrogen)

4. Mineralocorticosteroids – and antagonists (53)

a. Aldosterone

❖ The main endogenous mineralocorticoid, aldosterone, binds to the **aldosterone receptors** in the **cells** of the **collecting duct** → ***stimulates sodium reabsorption*** by **increasing the number of open sodium channels** and **increasing the number of sodium/potassium ATP-ase pumps**

❖ Aldosterone is made from cholesterol and its production is controlled by renin-angiotensin system

Mechanism of action

- Generally, Aldosterone receptor is present in the **cytoplasm** in **inactive state**, as multimeric complex with different chaperone proteins, or **heat shock proteins** (Hsp)
  - After binding → **conformational change** in the receptor → **heat shock proteins dissociate** → **receptor becomes active** → glucocorticoid receptors **translocate to the nucleus**, where they **bind directly to specific sites of the DNA**
  - This leads to the activation of genes **enhancing expression of Na/K ATPases** and **Na+ channels**

Effects

- ↑ Na resorption → increase in blood volume → ↑ blood pressure
- ↑ K excretion → alkalosis + hypokalemia

Fludrocortisone

❖ A Synthetic analog of aldosterone

❖ A powerful mineralocorticoid along with some additional, but very weak glucocorticoid properties

❖ **Clinical use:**

➢ Generally used in the management of primary adrenal insufficiency (replacement therapy)

b. Antagonists of mineralocorticoid receptor

Spironolactone, ***Eplerenone***

Mechanism of action

- Competitively bind to aldosterone receptors in the collecting duct → **inhibition of aldosterone effects**
  - = **Decreased Na+ reabsorption** and **decreased K+ excretion** → **diuresis**
- ↑level of potassium is corrected by proton/potassium ATPase → ↑ proton in blood → **metabolic acidosis**

Spironolactone

❖ *Non-specific mineralocorticoid antagonist* → has affinity for progesterone and androgen receptors

➢ = Side effects: gynecomastia, diminished libido and menstrual irregularities

❖ It is effective against hyperaldosteronism (Conn's syndrome).

Eplerenone

❖ *More specific mineralocorticoid antagonist* → fewer side effects but less potent

❖ Binds to the mineralocorticoid receptor → aldosterone antagonist.

❖ It is approved as an antihypertensive.

- Spironolactone decreases both systolic and diastolic blood pressure and can be used in resistant hypertension in combination with other anti-hypertensive agents
- Mineralocorticoid receptor antagonists are protective against left ventricular dysfunction
- They are especially indicated for hypertension with chronic heart failure

- If the diagnosis of subtype of primary aldosteronism is confirmed, we have to choose appropriate therapy, it is either:
  - Surgical therapy → For unilateral adrenal hyperplasia

Or medical therapy with mineralocorticoid receptor antagonists → For the management of bilateral

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EN HINIR ANTAGONISTS

5. Estrogens and antiestrogens (2)

Estrogens – intro

- Estrogens are important hormones for sexual and reproductive development (especially in women)

Synthesis

- Synthesis of estrogens is initiated by same pathways as synthesis of glucocorticoids and mineralocorticoids
- Synthesized in ovarian granulosa cells in women and in Sertoli + Leydig cells in men
  - Estrogen is also synthesized in adipose tissue, bones and brain

Estrogen receptors

Estrogen Receptor α (BAD)	Estrogen Receptor β (GOOD)
• Localization: - ***Endometrium***, ***breast***, ovarian stromal cells, and the hypothalamus • 70% of breast cancers → ER-α positive	• Localization: - Epithelial cells of kidney, ***bone***, heart, intestine and lungs, mononuclear blood cells, some areas of brain • ER-β oppose the actions of ER-α in reproductive tissue

Effects of estrogens

- Maximal importance during **puberty**, **reproductive age**
  - Lack of them is manifested is **post-menopausal** age (osteoporosis…)
- Estrogens generally are required for the **normal sexual maturation** and **growth of female**
- Liver: **regulate cholesterol metabolism → suppress the process** of **atherogenesis**
- Bone: important to **maintain bone density → promote apoptosis of osteoclasts** = ↓ rate of bone resorption
- **Metabolic effects**: mostly positive (↑ HDL, ↓ LDL, slightly ↑ TAGs)
- Estrogens have **pro-thrombotic effects**

Classification of estrogen

1. Steroidal-natural
- ***Estrone***, ***estradiol***, ***estriol***
- Natural hormones
- Administration**:**
  - **Almost complete first pass effect** when administered **orally** → recommended **intravaginal** or by **transdermal** administration
- ***Conjugated estrogens***
  - mixture of estrogenic compounds extracted from the urine of mares or plants (↓ first pass)

2. Semi-synthetic esterified estrogen
- ***Benzoate, dipropionate, valerate, pipate***
- Conjugation of esters → ↑ half-life
- Administration:
  - Only **intramuscularly**
- Clinical use:
  - ***Hormone replacement therapy***
- Effect: several days (half-life: 3-7 days**)**

3a. Synthetic – Steroidal
- ***Mestranol → Ethinylestradiol***
- Administration:
  - More resistant to the first-pass effect = increased bioavailability
  - available for peroral administration
- ***Mestranol*** – prodrug converted to ***ethinylestradiol*** in enterocytes and during the first pass through the liver

3b. Synthetic – Non-steroidal
- Some of them are harmful
- **Limited use…**

Pharmacokinetics (typical steroids pharmacokinetics!)

Absorption:
- Strongly lipophilic → absorbed promptly regardless of administration (p.o., parenteral & transdermal)
- Natural → high first pass metabolism
- Esterified forms - i.m. admin. slowly absorbed & prolonged action

Transport:
- Strongly bound to plasma proteins (Sex hormone binding globulin (SHBG), albumin)

Metabolism:
- Elimination by liver CYP450 enzymes
- Significant entero-hepatic circulation
- Excretion by urine after conjugation
- Their hepatic effect is responsible for ***increased synthesis of clotting factors*** (→ pro-thrombotic effects)
  - ↑ risk of deep venous thrombosis

Therapeutic use of estrogens

- **Replacement therapy:**
  - ***Primary hypogonadism***
    - Estrogens are the drug of choice for management of primary hypogonadism
    - The treatment begins very early, between 11 – 13 years of age (↑ sex characteristics + menstrual cycle)
  - ***Postmenopausal syndrome***
  - ***Hysterectomy***
- **Treatment of amenorrhea, dysmenorrhea**
- **Atrophic vaginitis**
- **Contraception** → Estrogens combined with progestins suppress ovulation

Adverse effects

- **Most common**: *nausea*, *breast tenderness*, *disturbances of the menstrual cycle*, *impacts of sexual desire*…
- **More severe but less frequent:**
  - Stimulation of endometrial proliferation → ↑ risk of endometrial carcinoma (estrogen-only therapy)
    - The problem of "estrogen-only" therapy is ***increased risk of breast + endometrial cancer***
      - Progestins antagonize this risk related to higher incidence of cancer in sex tissue
  - Pro-thrombotic effects → ↑ *risk of venous thromboembolism*
  - Due to their intensive enterohepatic circulation → ↑ *risk of gall bladder stones*

Anti-estrogens

- Antiestrogens are agents which poses opposite effects of estrogens
- This action can be achieved by:
  - **Modulation estrogen receptors** (agonist on β ER receptors, antagonists on α ER receptors)
    - They are so-called selective estrogen receptor modulators (**SERM**)
  - The **inhibit of estrogen synthesis**
  - They can act **directly on the receptors as antagonists (SERD)**

A. SERM – Selective modulators of estrogen receptors

- They act as partial agonist/antagonists on estrogen receptors
- ***Agonists on β receptors – antagonists on α receptors***

Tamoxifen

- Agonist on β receptors → bone, liver and endometrium
  - Agonist in bones → preventing osteoporosis
  - Agonist in endometrium → ↑ endometrial proliferation
    - Side effects: endometrial polyps, hyperplasia and ↑ risk of endometrial cancer
  - Agonist in liver → ↑ synthesis of clotting factors
    - Side effects: ↑ risk of venous thromboembolism
- Antagonist on α receptors → breast tissue
- **Clinical use:**
  - Used to treat estrogen receptor (ER) positive breast cancers
  - Also, primary prophylaxis of high-risk women for breast cancer
  - 2nd line treatment of post-menopausal osteoporosis

Raloxifen

- Agonist of β receptors in bones
- Antagonist of α receptors in breast tissue
  - Raloxifen has no estrogenic effects on endometrium (does not ↑risk of endometrial cancer)
- **Clinical use:**
  - 1st line therapy for post-menopausal osteoporosis
- Side effects
  - ↑ risk of thromboembolism

Clomiphene

- Acts as estrogen antagonist in the hypothalamus (preventing negative feedback → ↑ FSH and LH)
  - → stimulation of ovulation
- **Clinical use:**
  - To induce ovulation and treat infertility in women who have anovulatory cycles

B. **Inhibitors of estrogen synthesis**

- They act on the **earlier steps** (**Danazol** and **gestrinon**)
- Or they act on the **final step of synthesis**
  - This can be achieved by the **inhibition of the enzyme aromatase**

Aromatase inhibitors

- Clinical use:
  - Treatment of estrogen-depended tumor in post-menopausal women
  - Or the **treatment of breast cancer** after failure in treatment of **Tamoxifen**
  - Thus, reversible non-steroidal aromatase inhibitors are the **drug of choice** for the treatment of **tamoxifen-resistant cancers**
- Side effects:
  - Serious estrogen-lacking side-effects (e.g., osteoporosis), androgenic effects
- Drugs: (reversible non-steroidal aromatase inhibitors)
  - ***Letrozole*** + ***anastrozole*** (ekki nógu gott, veit ekki hvernig á að gera þetta)

C. **SERD – Selective estrogen receptor degrader**

- ***Fulvestrant → Full estrogen receptor antagonist***
  - Basically, destroys estrogen receptors
- Unlike SERMs, full antagonists have anti-estrogenic effects in all tissues
- Clinical use:
  - Breast cancer that is resistant to tamoxifen
- Advantage: only administered monthly (i.m.)

6. Gestagens and antigestagens (39)

Gestagens (progestins) – intro

- Natural gestagens = progesterone
  - = a natural hormone secreted by corpus luteum and placenta
  - Also, an important intermediate in steroid genesis
    - → Progesterone is a precures of estrogen, androgens and adrenocorticoids
      - So, they are not only present in the ovaries, but also testes and adrenal cortex
  - It is **synthesized from the circulating cholesterol** (the precursor)
  - It has complementary action along with estrogens, on development of primary and secondary sex characteristic development
- Gestagens = drugs which mimic the actions of progesterone

Mechanism of action

- Generally, Aldosterone receptor is present in the **cytoplasm** in **inactive state**, as multimeric complex with different chaperone proteins, or **heat shock proteins** (Hsp)
  - After binding → **conformational change** in the receptor → **heat shock proteins dissociate** → **receptor becomes active** → glucocorticoid receptors **translocate to the nucleus**, where they **bind directly to specific sites of the DNA**

Physiological effects of gestagens

- Cervix → thickened cervical lining
- Endometrium: → proliferative endometrium changed to secretory
- Breast → proliferated lobuli and alveoli
- Pregnancy → decrease number of estrogen receptors
  - This way, maintains low density of oxytocin receptors synthesis (to prevent premature contraction)
- CNS → mild depression of CNS and increased body temperature
- Metabolic effects: → not pleasant, ↑ lipoprotein lipase activity + ↑ synthesis of insulin
  - This increases appetite → most frequent side effect gestagens = weight gain

Natural gestagens

- **Typical steroidal pharmacokinetics (short half-life, first pass metabolism, etc.)**
  - **Rapidly absorbed** following any route of administration (due to high lipophilicity)
  - It is distributed bound the **corticotropin binding globulin**, it is **lower affinity to sex hormone binding globulin**
  - The plasma **half-life** is **very short**, maximally 5 minutes (due to complete 1st-pass metabolism in liver)
- = not suitable for oral administration (administered parenterally or locally)
- **Clinical use:**
  - The major use of the progesterone is **hormonal replacement therapy** and **hormonal contraception**
  - **Also used in treatment of polycystic ovarian syndrome**
  - And to prevent preterm labor

Synthetic gestagens – clinical use

- **Treatment of endometriosis**
- **Transgender women** → feminizing hormone therapy for transgender women
- **Suppression of anovulatory irregular bleeding**
- **Therapy of premenstrual syndrome?**
- **Contraception → *Levonorgestrel***

Controversial indications

- **Hormonal replacement therapy (E+G)**
  - studies suggest that **combining synthetic progestin and estrogen**, in terms of replacement therapy in post-menopausal women may **significantly enhance risk for breast cancer**

Side effects

- **Adverse effects:**
  - **Weight gain** (most frequent)
  - **Hepatal disorders**
  - **Gastrointestinal disturbances**
  - **Unfavorable influence on lipid levels**, **salt-retaining effect**, **edema**
  - **Combination with estrogens – breast cancers?**
  - **Androgenic activity of synthetic derivates – acne**, **hirsutism**

Anti-gestagens (anti-progestins)

Mifepristone (key representative of anti-gestagens)

- **Dual action – anti-glucocorticosteroidal + anti-progestin**
- **Clinical uses:**
  - Major use: ***termination of early pregnancies***
    - It is used in **combination with prostaglandins**
    - The doses for the abortion that are recommended, are between 400-600 mg for 4 days, followed by increase of the dose at the level 80 mg for the next 2 days
    - The 6-day treatment with prostaglandins successfully terminates pregnancy in over 85% of women
  - Treatment progesterone-dependent breast cancers

Selective – progesterone receptor modulators – SPRM

Ulipristal

- = selective progesterone receptor modulators → Dual effect, partial agonistic/antagonistic action
- It is represented by **Ulipristal**
- Clinical use:
  - ***Emergency contraceptive agent*** (taken within 5 days after intercourse)
  - Inhibits ovulation by suppressing luteinizing hormone release, leading to premature follicular rupture

7. Contraception (14)

Intro

- **= Drugs that decrease fertility**
- **Classification:**
  - **1. according to route of administration:**
    - **Oral, parenteral (TTS), implants, etc.**
  - **2. according to composition:**
    - **Estrogen + gestagen** (most frequently used)
    - **Gestagen-only = minipills**

Mechanism of action

- The contraceptive agent effectiveness is evaluated by the pearl index
- The mechanism of action, how these drugs can suppress the chance of ovulation is based on the ***activation of negative feedback loop***
  - **Sustained level of Progestin:**
    - → Suppression of gonadotropin release hormone (GnRH) pulse
    - → Decreased release of LH and FSH from pituitary
  - **Sustained level of Estrogen:**
    - → Decreased FSH from pituitary
- So, both progestins and estrogen are able **activate the negative feedback** (↓ FSH, ↓ LH), which leads to the **failure of the maturation of follicles** → this way they **prevent ovulation**

Combined peroral contraceptives

- The peroral combined contraceptive pills are divided to 2 basic categories
  - As **monophasic** and **phased**

→ 1. Monophasic

- **Monophasic** contains the **same levels of hormones** in **each tablet**
  - One package usually contains **28 tablets**, which is the classical duration of normal menstrual cycle
  - **21 pills contain therapeutic compound** followed by **7 tablets** which **represent the placebo**

→ 2. Phased

- The number of the tablets is the same (28) also in the phased preparations
- The phased contraceptives differ in the tablet's composition, according to different levels in each tablet, we talk about bi-, tri- and four-phasic contraceptive pills
- **Biphasic E/G ratio = 10 (8, 7)/11 (12, 14)**
  - In **bi-phasic**, has the most common ratio between estrogenic and gestagenic dominance is 10:11
  - 10 days "↑estrogen" tablets
  - 11 days "↑ gestagen" tablets → then placebo up to 28 tablets
- **Triphasic E7/ E+G7/ G7**
  - In **tri-phasic**, the typical ratio is 7:7:7
  - Estrogen-alone (7), combined (7) or gestagen-alone (7) → then placebo for up to 28 days
- **Fourphasic contraceptive pills**
  - **Contains 4 phases of doses for estrogen or combined estrogen/progestin**
  - No gestagen-only pills
  - Four-phasic are the most recent type of phased contraception
  - They were evaluated many studies; however, we can conclude that both effectiveness and the incidence of side effects from which the metrorrhagia, acne and weight gain were mainly reported, are very similar to older version of the phased pills
  - So, there were no differences found between phased pills in terms of efficacy as well as in terms of effectiveness

Side effects of combined contraceptives

- The most common side effects of all combined hormonal contraceptive pills are:
  - ***Nausea***, ***menstrual irregularities***, ***breast tenderness*** and ***decreased sexual desire***
- From the more severe side effects:
  - ***↑ Incidence of deep venous thrombosis***, ***hypertension***, ***myocardial infarction***
- Also ***increased frequency of migraine attacks***, and the ***worsening or induction of depression***

Contraindications

- **Cardiovascular diseases, thromboembolic disease, liver disease, migraine, smoking, estrogen - dependent cancer**

Gestagen-only peroral contraceptives

- Progestogen-only pills or progestin-only pills (POP) known as "mini-pills"
  - They are taken continuously without any break
- They are less efficacious than the combined oral contraceptive pills
- **Clinical use:**
  - Only for women which are at ***high risk of estrogen-related contraindications***
  - Or for breastfeeding women (because mini pills don't affect milk production)
- **Side effects:**
  - Amenorrhea (over a few months)
  - Light spotting at irregular intervals or heavy bleeding
  - Breast tenderness and mood swings, anxiety, depression.

Gestagen-only parenteral contraceptives

- ***Intrauterine device*** or ***ministicks*** are mostly preferred
  - ***Injectable*** progestin is less used (excessive bleeding + slow return to fertility)

Post-coital contraceptive pills

- The **postcoital contraceptive pills (emergency pill)** also belong to the **gestagen-only group**
- They act by **preventing implantation of the blastocyst** or they can **destroy the implanted blastocyst**
- **Indicated for emergency condition only**
  - **Contain higher dose of steroids → side effects**
  - **Less effective than standard regimens**
- **Probably acts by:**
  - **Effects on gametes function and survival**
  - **Effects on implantation**
  - **May dislodge a just implanted blastocyst or may interfere with fertilization/implantation**

- **REGIMEN**
  - **Two pills regimen:**
    - ***Levonorgestrel*** – 2 doses with 12 hours apart within 72 hours after unprotected sex
  - **One pill regimen:**
    - ***Levonorgestrel*** + ***Ulipristal***
      - Less preferred

Testosterone secretion regulation:

- Synthesized in Leydig cells in testis
- Regulation of secretion:
  - **FSH** → ⊕ Sertoli cells to release androgen-binding protein → ⊕ testosterone binding
  - **LH** → ⊕ Leydig cells to secrete testosterone
  - **Inhibin** (produced in spermatogenic cells) → inactivate **activin** + ⊖ **hypothalamus**
    - **Activin** ⊕ FSH effects
      - Negative feedback loop

8. Androgens (17) (Antianemics topic)

Intro – Androgen:

- Androgens = steroid hormones that regulate the development and maintenance of male characteristics
- Bind to Androgen receptors
- Main androgen is **Testosterone**
  - Testosterone is converted in Dihydrotestosterone (DHT) by **5α reductase**

Mechanism of action

Effects:

1. Effects according to age:
   - **Fetus → promotes development of male reproductive tract**
   - **Puberty → promotes development of primary + secondary sexual characteristics**
     - E.g., Adam's apple, ↑ muscle mass
   - **Adult → Baldness, BPH, Prostatic cancer**
2. **Promotion of spermatogenesis + maturation of sperm**
3. **Anabolic effect:**
   - ↑ Muscle building + bone growth, ↑ appetite + weight, ⊕ ***erythropoiesis*** (↑ RBCs)
4. ↑ Libido
5. Influences behavior

1+2. Androgens:

- They are used in **androgen replacement therapy**
- Indication:
  - **Hypogonadism**:
    - Primary → testicular disease
    - Secondary → pituitary disease
  - To ↑ weight + recovery after injury

Classificaiton of Androgens drugs:

1. **Natural Testosterone**
2. **Synthetic testosterones**
   - ***Fluoxymesterone*** (p.o.)
   - ***Methyltestosterone*** (p.o.)
   - ***Testosterone cypionate*** (i.m.)
3. **Anabolic Steroids:**
   - ***Oxandrolone***
   - ***Nandrolone***

3. Anabolic Steroid

- *Group of androgens with **higher anabolic effect***
- Have higher risk of Side effects
- Indication:

1. **Catabolic states:**
   - E.g., Severe trauma, major surgery, malnutrition
2. **Osteoporosis**
3. **Suboptimal growth in children**
4. **Anemia**
5. **Renal failure** (↓ production of urea + frequency of dialysis)
6. Abuse (↑ Strength)

Androgens – Side effects:

1. **In female → Virilization** (where woman develops male characteristics)
   - Occurs after high doses for long time
2. **In males →** development of female characteristics (e.g., gynecomastia)
3. **Other:**
   - Cholestatic jaundice + Hepatic carcinoma, Priapism (prolonged erection), Oligospermia + infertility, edema, acne, ↑ weight

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9. Antithyroidal drugs (51)

Intro – Thyroid gland:

- Gland that secreted thyroid hormone
- **Thyroid hormone secretion regulation:**
  - TRH (hypothalamus) → TSH (ant. Pituitary gland) → TSH receptor (thyroid gland) → ⊕ organification of iodine + production of TH
  - Negative feedback loop (T3 + T4 ⊖ both TRH + TSH)
  - Other regulators → glucocorticoids ⊖ TSH, Estrogens ⊕ TSH

Thyroid hormone synthesis:

- The membrane of follicular cells contains **Na^+/I^- symporter** which transports iodine into the follicular cell
  - It moves 2 Na^+ + I^- into thyroid (from blood)
- Then iodide is moved into the colloid where it undergoes oxidation by the enzyme ***thyroid peroxidase***
  - ($I^- \rightarrow I^0$) – this is the ***peroxidase*** step
- Iodine is then attached to tyrosine (this step is called ***organification***) to create **mono-iodotyrosine** (MIT)or **di-iodotyrosine** (DIT) on the molecule of **thyroglobulin**
- After this, there is a process of **conjugation** so, T2+T2 = T4 and T1+T2 = T3
- And then, the whole structure is joined with lysosomes → cutting of bonds of thyroglobulin into **T4** or **T3**, ready to be **released into plasma**

Thyroid hormone - Effects		
Growth + Development	**Metabolism**	**Clinical effect**
Growth: - Required for normal growth in children • Thyroid deficiency → Growth retardation **Development:** - Required for development of fetal + neonatal brain Thyroid deficiency → impaired mental function	**General**: - ⊕ metabolism in most tissues - ↑ basal metabolic rate **Lipid metabolism**: - ↑ TH → ⊕ fat mobilization → ↑ FA in blood - TH → ↑ oxidation of FA in many tissues - TH → ↑ CH + TAG plasma concentration • ↑ LDL receptors **Carbohydrate metabolism**: - TH → ⊕ sensitivity of peripheral to insulin • ⊕ entry of glucose into cells - ↑ gluconeogenesis + ↑ glycogenolysis in liver	**CVS:** - ↑ HR + ↑ cardiac contractility + ↑ CO + ↓ PVR - ⊕ vasodilation - ↑ number of β receptors (SNS) **CNS**: - TH leads to alternation of mental state - ↓ TH → mentally sluggish ppl - ↑ TH → anxiety + stress **Reproductive system**: - Normal reproductive behavior and physiology - Effect on menstrual cycle **Kidney**: - ↑ renal blood flow → ↑ GFR + GFP - ↑ RAAS - β receptors are ⊕

Intro - Thyroid Hormone disorder

1 **Hyperthyroidism:**
   - = Overproduction of Thyroid horomone

2 **Hypothyroidism:**
   - Underproduction of Thyroid hormone

Antithyroid drugs:

1 **Thioamides**
2 **Iodides**
3 Iodinated contrast media
4 Radioactive iodine – ^{131}I
5 Anion inhibitors
6 Adrenoceptor blocking agents

Antithyroidal drugs:

- Drugs indicated for **Hyperthyroidism**
- Drugs that ↓ thyroid hormone effect in 3 ways:

1 **Interfere with thyroid hormone synthesis:**
- We can inhibit hormone synthesis at different levels
  - E.g., inhibition of **organification** of iodine, inhibition of **oxidation** of iodine or inhibition of **ionization**
- Or we can inhibit the conversation of T4 → T3 (by inhibiting 5-deiodinase)

2 **Destruction of thyroid gland with radiation + surgery:**
- Radio therapy, using radio labeled iodine→ will ↑ iodine concentration → impairment
- Removal of thyroid gland

3 **Modify tissue response to thyroid hormones**
- We may also use some peripherally acting agents which are modifying the tissue response
- For example, ***β blockers*** are typical drugs used to modify the peripheral activity, they can protect the heart

Antithyroid Drugs:	
1. Thioamide	**2. Iodides**
Mechanism of action: • Competitive ⊖ of Thyroid peroxidase → ⊖ iodine oxidation → ↓ thyroid hormone synthesis • ⊖ Peripheral deiodination of T4 + T3 (Only *Propylthiouracil*) **Indication:** • Hyperthyroidism, Thyrotoxicosis **Side effects:** • Allergic reaction (most common), agranulocytosis (reversible) **Drugs:** • ***Propylthiouracil*** (PTU)**,** ***Carbimazol, Methimazole*** - *Methimazole* is most potent (dose related SE) **SLOW onset of action (3-4 weeks)**	• Should be initiated after onset of thioamides **Mechanism of action:** • ⊖ proteases → ⊖ T3 + T4 cleavage from thyroglobulin → ⊖ **TH release** • ⊖ Organification → ⊖ **TH synthesis** **Indication:** • ***Thyrotoxic crisis***, before thyroidectomy • **NOT a long-term therapy** **Side effects:** • Iodism: (E.g., mucus membrane ulceration, bleeding disorders) **Agents:** • **Potassium iodide, Lugol's solution** (KI in aqueous solution) **FAST onset of action (2-7 days)**

3. Iodinated contrast media	4. Radioactive Iodine ^{131}I	5. Anion inhibitors	6. Adrenoceptor blocking
Mechanism of action: • ⊖ **T4 → T3** - ⊖ 5'-deiodinase **Indication:** • Used mainly in acute situations (**Thyrotoxic crisis**) • Diagnostic purpose • When Thioamides + iodides are contraindicated	**Mechanism of action:** • Go into thyroid follicle → β-rays therapy application → cytotoxic effect in follicle **Indication:** • Diagnosis of thyroid dysfunction • Radioiodine ablation - Remove remnants of thyroid gland	**Mechanism of action:** • **Competitive inhibitors of iodide transport** **Indication:** • **Not used due to SE** **Side effect:** - Toxicity, Hypotension, Aplastic anemia **Agents:** - Thiocyanate, Perchlorate, Pertechnetate	**β blockers** (***propranolol***) • in symptomatic therapy of thyrotoxicosis **Indirect sympatholytic** (***Guanethidine***): • eye drops for exophthalmos **Glucocorticosteroids**: - Rapid ⊖ of T4 → T3 - For thyrotoxic crises

10. Thyroid hormones and treatment of hypothyroidism (43)

INTRO – Topic 9!!

Thyroid Hormones – General Indication:

1 **Replacement therapy** (substitution):
- Maintain physiological concentration of TH w. Low doses of TH
- Low risk of side effects

2 **Suppressive therapy:**
- High doses by negative feedback induced suppression of of TSH
- Used in **Cancer of thyroid gland + thyroditis**
- High risk of side effects

Thyroid hormone – Drugs:

1 ***Levothyroxine*** **(T4)**
- **Synthetic form of T4 → peripherally converted to T3 + inactive T3 (rT3)**
- Indication:
  - Used as lifelong relpacement thyroid hormone therapy
  - **First line therapy** of Hypothyroidism
- Pharmacokinetics:
  - Slow onset of action (3-5 days), maximal effect after 2-4 weeks
  - Dose → 1x daily
  - Metabolism → 50% deiodinized to T3 (active), 50% to rT3 (inactive)
  - Excretion → kidney + feces
- Side effects:
  - Rare
  - Tachycardia, weight loss

2 ***Liothyronine*** **(T3)**
- **Synthetic form of T3**
- Indication:
  - **In emergency situation**
  - **NOT** long term therapy
- Pharmacokinetics:
  - Rapid onset of action (4-8), maximal effect after 2-3 days, duration only few days
  - Dose → 2-3x daily
  - Metabolism → in liver, deiodinated and canjugate metabolites (inactive compounds)
- Side effects:
  - Has higher risk of side effects
  - **Hyperthyrosis symptoms, cardiotoxicity, osteoporosis** (due to loss of Ca in hyperthyroidism)

Monitoring:
- Check T4 +T3 levels, TSH

11. Therapy of osteoporosis (40)

Intro – Osteoporosis:

❖ *Systemic skeletal disorder characterized by low bone mass, leading to bone fragility and ↑ risk of fracture*
- ➢ Imbalance between **bone resorption** and **bone formation**

❖ Types:

1 **Primary osteoporosis** (most common)
- ➢ Type 1 → in postmenopausal women (due to low level of estrogen)
  - ▪ Estrogen ⊕ osteoblasts + ⊖ osteoclasts
- ➢ Type 2 → gradual loss of bone mass as patient gets older

2 **Secondary osteoporosis**
- ➢ Drug induced (most commonly long-term **corticosteroid** therapy)
- ➢ Endocrine dysfunction, cancer, immobilization

❖ Risk factors → smoking, malnutrition, family history

Parathyroid Hormone:
- ⊕ Bone formation (low [c])
- ⊕ Bone Resorption (high [c])

Calcitonin:
- ⊖ osteoclast activity → ↓ bone resorption
- ⊕ Osteoblasts → ↑ Bone

Osteoporosis Therapy:

❖ They are divided into 2 groups

1 **Non-Hormonal medication:**
- ➢ **Bisphosphonates!!!**
- ➢ **Densumab**

2 **Hormonal modulators** (alterative drugs):
- ➢ **Teriparatide, Calcitonin, Raloxifene**

Hydroxyapatite
= Mineralized form of Calcium in bones

Non-Hormonal Medication

A. Bisphosphonates

- **First line therapy** of osteoporosis

Drugs:

1st Generation (non-nitrogen-containing)
- *Etidronate*

2nd + 3rd Genreation (nitrogen-containing)
- *Alendronate* (2nd), *Risedronate* (3rd)

Mechanism of action:

1. Non-nitrogen containing
- They are **pyrophosphate**, which gets added to **ADP** → formin **non-functional ATP** (no source of energy)
- Bind to **Hydroxyapatite** on bone surface → When osteoclast break down bones they take up bisphosphonates → no energy for osteoclast → apoptosis → ↓ Bone resorption

2. Nitrogen-containing:
- ⊖ **Osteoclast mevalonate pathway** → ↓ synthesis of CH → Inactivate osteoclasts
  - CH is important for cell membrane + enzymes

Side effects:
- GIT disturbances (ulcers, esophagitis...)
- Osteonecrosis of jaw

Due to toxicity, Must be taken on empty stomach w. Full glass of water → has to go quickly through esophagus to stomach!!!

B. Densumab (*not in lecture*)

- Human monoclonal antibody

Mechanism of action:
- Bind to osteoclast receptors → ⊖ osteoclast activity

Side effects:
- Hypocalcemia, hypophosphatemia, infection, Osteonecrosis

Hormonal Modulators

Teriparatide

- **Parathyroid hormone** analog (s.c. 1x day)

Mechanism of action:
- Just like parathyroid hormone = ⊕ **Osteoblast** → ↑ **Bone formation**

Side effects:
- Hypercalcemia, ↑ risk of bone cancer

Calcitonin

- Peptide hormone (physiologically synthesized by thyroid gland)

Mechanism of action:
- **Directly ⊖ osteoclast → ↓ Bone resorption**
- **⊕ Osteoblast → ↑ Bone formation**
- ↑ excretion of Ca + Phosphate in kidney

Adm → s.c., i.m., i.n.

Raloxifene

- Selective estrogen receptor modulator (**SERM**)

Mechanism of action:

1. Partial agonist of estrogen receptors in bones → ⊕ osteoblast + ⊖ osteoclasts

2. Antagonist of estrogen receptors in breast tissue → prevention of breast cancer

Side effects:
- Hot flashes, ↑ risk of venous thrombosis

Anabolic steroids (androgens) → sometimes used for osteoporosis

5. Respiratory system

1. **Antitussives (25)**
2. **Expectroants, mucolytics (5)**
3. **Antiasthmatics** (Overview, mechanism of action) **(38)**
4. **Antiasthmatics with anti-inflammatory effect (24)**

Cough reflex:
Consist of:
- Cough receptors
- Afferent pathway (vagus n.)
- Cough center (brain stem)
- Efferent pathway (phrenic n., spinal motor nn., recurrent laryngeal nn.)
- Effectors (diaphragm, intercostal mm., laryngeal mm., abdominal mm.)

Process:
- Receptor → afferent nerves → cough center → efferent nerves → expiratory mm.

Afferent fibers:
- ***C-fibers***, ***RAS fibers***

1. Antitussives (25)

Intro – **Pathologic cough:**

- Cough = is reflex action to **clear airways of mucus and irritants** (e.g., dust or smoke)
- **Pathological cough** = Excessive and non-productive, irritating and potential harmful to mucosa of airways
- Therapy of pathological cough can be divided into:
- **1. Inhibition of the cough reflex**
  - **Antitussive therapy → Antitussives**
    - Aim: to **reduce the frequency** or **intensity of coughing**
- **2. Increase the efficiency of cough reflex**
  - **Pro-tussive → Expectorants**
    - Aim: to **enhance the cough effectiveness** and **promote the clearance of airway secretion**

Antitussives

- Antitussives = medicines that **suppress coughing** (also known as "cough suppressants")
  - → they inhibit the cough reflex
- Divided into **central** and **peripheral**

Antitussive with central mechanisms of action: (opioid and non-opioid agents)

1. Opioid receptor agonists: Codeine and its derivatives

→ A. *Codeine*:

- **Codeine is the first-line of the treatment of cough**
- Clinical use: (only):
  - ***Dry chronic cough***, ***dry painful cough*** and as a ***cough suppressant*** before some ***invasive diagnostics procedure*** (for example bronchoscopy)
- **Mechanism of action:**
  - **Direct agonist of opioid receptor** (central + peripheral) → mainly stimulates ***mí (μ) receptors***
    - 2 subtypes of mí receptors
    - **μ_1 – Typical effects of opioids (Analgesia, miosis, euphoria...)**
      - Responsible for "other" effects of codeine → raises threshold of pain perception (= good analgesia)
    - **μ_2 – Antitussive effects → (= dominant effect)**
- **Metabolism:**
  - *Codeine* is metabolized into → ***morphine*** (5-15%), codeine-6-glycuronide (50-70%), Nor-codeine (10-15%)
  - It is Metabolized to morphine by CYP450 system
  - Patients with ↑ activity of CYP450 → ↑ formation of morphine with opioid effects → ↑ risk of morphine side effects
- **Side effects:**
  - Rarely, (people with ↑ κ receptors in CNS) codeine can cause **dysphoria**, **distress** and **physical discomfort** due to **stimulation of the kappa (*κ*) *receptor***
  - Nausea + vomiting, suppression of breathing (don't combine with other CNS depressors!), hypotension, bradycardia, constipation, miosis
  - *Long-term administration of codeine provokes **tolerance**, which is the reason for **increasing doses***
    - *This, together with slight **euphoric** effect, are the **risk of addiction or dependence***
      - *Remember, no tolerance in miosis + constipation (miosis = good diagnostic feature)*
- **Contraindications:**
  - Asthma + COPD (because codeine increases the viscosity of mucus!)
  - Paralytic ileus (due to constipation → opioid decrease gastric motility)
  - Pregnancy + lactation

2. Non-opioid: *dextromethorphan*, pentoxyverine

→ B. *Dextromethorphan* (DXM)

- Another type of ***centrally acting antitussive*** – **inhibits the cough center** in CNS and has antitussive activity
- Cough suppressant in over-the-counter cold and cough medicine (syrup, tbl.)
- **Mechanism of action**: (not an opioid agonist like previously thought!)
  - ***Non-selective serotonin reuptake inhibitor*** → increases serotonin concentration in synaptic cleft
    - ↑ in serotonin levels in the brain has a depressant influence on cough reflex
    - → Do not combine with SSRIs or MAO-I → can lead to serotonin syndrome
  - The second mechanism of action is that Dextromethorphan is an **antagonist of NMDA receptor**
    - Dextrorphan (active metabolite of dextromethorphan) blocks NMDA glutamate receptors at high doses
      - At high doses → acts as dissociated hallucinogen (similar to ketamine)
  - Sum up → *non-selective serotonin reuptake inhibitor* (SRI) and *antagonist of NMDA receptors*
- **Metabolism:**
  - Dextromethorphan, like codeine, is metabolized with ***cytochrome P450***
  - But here it is **opposite** activity to codeine → in persons with **reduced activity** of cytochrome P450, dextromethorphan will be accumulated in higher concentrations → hallucinations
- **Side effects:**
  - Common side effects are **confusion**, **insomnia**, **seizures, hyperactivity, angioedema, urticaria, abdominal pain, nausea** + **vomiting**
- Not recommended for children under 4 years of age

→ C. *Pentoxyverine*

- A weak agonist of opioid receptors + antagonist of muscarinic receptors
  - = atropine-like side effects (dry mouth, mydriasis, tachycardia…)

Other centrally acting drugs with antitussive activity – *masking of respiratory disease*

- **Cough reflex** is described as the "**watch dog**" of the **respiratory tract and keeping the airway in order**
  - It is the **first symptom** of **serious respiratory diseases**
- Many other centrally acting drugs can reach the cough suppressing activity
  - However, **they can also mask serious respiratory diseases**
- Example of drugs with this affect can be for example
  - **Benzodiazepines**, **anxiolytics** they are **GABA agonists,** and they **inhibit the cough reflex**
  - Some **antihistaminics** that cross the **blood-brain-barrier** (H1 1st generation)

Antitussive with peripheral mechanisms of action:

- **Do NOT cross blood-brain barrier → suppress the cough through the following peripheral mechanisms:**
  - By inhibiting **rapidly adapting receptors** (RARs) or **C fibers**
  - Inhibition of the **conduction of afferent fibers** – local anesthetic effect
  - Or they can **modulate the activity of the effector muscles** (mainly bronchodilation)
- **Clinical uses:**
  - *Irritant cough*, *allergic cough*, *cough associated with infectious respiratory disease*
- **Drugs:**
  - ***Butamirate citrate***
  - ***Oxeladine***
  - ***Dropropizine***

Mucopathology:

- 2 reasons why mucociliary clearance is impaired:
  - Disorder of movement of cilia + mucus layer is changed

1. ↑ **Production** (hypercrinia)
   - ↑ activity of secretory cells
2. ↑ **Viscosity** (dyscrinia)
   - impaired acitvity of secretory cells
   - ↑ number of S-S bridges and mucopolysaccharides → dehydration of epithelium

This will ↑ risk of infection

2. Expectorants, mucolytics (5)

Intro – **Pathologic cough:**

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    - Aim: to **enhance the cough effectiveness** and **promote the clearance of airway secretion**

Pro-tussive agents (expectorants):

- Mucociliary clearance (MCC) is the **primary innate defense mechanism of the lungs** (along with cough reflex)
- **The aim of therapy with pro-tussive agents:**
  - **Increase production of sol (water) layer** or **decrease the viscosity of mucus**
  - **Stimulation of ciliary beat frequency**

❖ Mucus consists of 2 very important layers:
- ➢ **Gel or viscous layer**
  - This layer is **produced by goblet cells**
- ➢ **Sol, watery layer**
  - This layer is **produced by serous cells of submucosal gland**

- And by this, we **improve the expectoration**
  - Expectoration = removing of mucous from the respiratory tract by mucociliary clearance or coughing out from the airways

Drugs modifying mucociliary clearance:

1. Secretolytics

- Stimulate the secretion of the serous glands to **increase the water content** in periciliary fluid layer

Drugs:

→ A. Reflex secretolytics

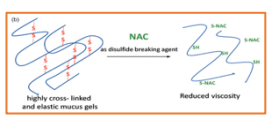
- They **irritate receptors in the stomach** with **vago-vagal reflex** → increase secretion of mucus in airways
- By this way they **increase the secretion of water layer in mucus of the airways**
- **Drugs**: ***Emetine*** and ***Saponines***
  - Side effects: nausea + vomiting

→ B. Guaifenesin

- **Stimulates the activity of serous glands → Increases amount of water** and **reduces viscosity**
  - = Guaifenesin modulates the mucociliary clearance
- Other effects of guaifenesin → **myorelaxant effects**, **reduces psychological** and **emotional tension**, feeling of **anxiety** and has **mild sedative effects** (can be used for stage fright or anxiety!)
- Guaifenesin is often a part of combined over-the-counter drugs containing paracetamol or NSAIDs

2. Mucolytics

- **Reduce viscosity of mucus** by influencing the chemical composition and physical properties of mucus
  - → So, they don't stimulate the serous glands or modify the goblet cells
    - → They only change the chemical composition of the mucus!
- Mechanism of action
  - They change the composition of secretion by **degrading the mucin polymers**, **DNA**, **fibrin** or **F-actin** in the airway secretion → **decreasing the viscosity of the mucus**



- We have **2 groups** here, the **classic mucolytics** and **peptide mucolytics**
  - 1. Classic mucolytics:
    - **N-Acetylcysteine**, **Erdosteine**, **Bromhexine** and **Ambroxol** (classic mucolytics)
    - Recommended for common microbial upper and lower respiratory tract infections
  - 2. The second type are **peptide mucolytic** and **Dornase alpha**
    - They are **only used for management of cystic fibrosis** (1st line drugs for cystic fibrosis)

3. Mucokinetics

- Stimulate the frequency of movement of respiratory cilia
- β2-agonists (LABA)

4. Mucoregulators

- Indirectly affect the quality and effectiveness of the mucus clearance
  - By anti-inflammatory effect or by bronchodilation
- Glucocorticoids, macrolide ATBs…

Classic mucolytics – Mechanism of action

- They are able to **depolymerize mucus glycoproteins** by **hydrolyzing the di-sulphate bonds** that link the **mucin monomers** and thus, reduce the mucus viscosity

Classic Mucolytics - Drugs					
N-Acetylcysteine		***Erdosteine***		***Bromhexine, Ambroxol***	
Other effect:	**Indication:**	**Other effect:**	**Indication:**	**Other effect:**	**Indication:**
• Anti-inflammatory - ↓ synthesis of inflammatory cytokines • Bactericidal • Antiviral	• Infectious disease of respiratory tract - Bronchitis, sinusitis, laryngitis… - COPD	• Mucokinetic • Antioxidant • Anti-inflammatory • Anti bacterial	• Infectious disease of respiratory tract	• Secretolytic • Mucokinetic • Local anesthetics - *Ambroxol* • Anti-inflammatory	• Treatment of infectious disease in respiratory tract *Bromhexine* is precursor of *Ambroxol*

Therapy of Cough – Basic principles

1. Central antitussive are recommended only in **short term**
   - And just for **irritable** or **painful cough**
2. Opioid antitussive ↑ viscosity of mucus
   - They are **not recommended in productive cough**
3. Post-infectious cough last several days-weeks
   - Removal of mucus can be facilitated w. short term administration of bronchodilators
4. A cough induced by treatment w. ACE-I and psychogenic cough **cannot** be suppressed w. antitussives
5. Viscosity of mucus has to be evaluated before expectorant administration
6. Administration of expectorants is indicated only in case of cough w. ↑ production of viscous mucus
7. Expectorants are NOT needed in moist cough w. ↑ production of watery mucus
8. Antitussive + expectorant has no rational justification
   - Are not used together
9. Mucolytics, secretolytics → are contraindicated in patients w. primary dyskinesia

3. Antiasthmatics (38)
+ Antiasthmatics with anti-inflammatory effect (24)

Intro – Bronchial asthma

- Bronchial asthma = **inflammatory disease of airways** (= crucial point for therapy)
  - Of course, there is obstruction of airways, but the **background is an inflammation**
- The disease usually occurs in **attacks**, with a typical symptomatology which can be **wheezing**, **cough**, **dyspnea** and **chest pain** etc.

Pathogenesis

- Allergens reach the respiratory tract, are picked up by dendritic cells which present them to Th2 cells which produce cytokines (IL-4, IL5) → leading features of asthma
  - IL-4 lead to the production of IgE antibodies → which stimulate mast cells to release histamines, leukotriens and prostaglandins
  - IL-5 activate eosinophils → which promote an immune response by releasing more cytokines and leukotriens
- This leads to 2 series of events:
  - 1. Minutes after exposure to the allergen, smooth muscle around the bronchioles start to spasm + increased mucus section → this narrows the airways, making it difficult to breath
  - 2. There is also an increase in vascular permeability → recruitment of additional immune cells from the blood → immune cells (especially eosinophils) release chemical mediators that damage the endothelium of lungs

Symptoms

- Cough, dyspnea, wheezing, increased mucus…

Phenotypes of asthma

1. Allergic asthma	2. Eosinophilic asthma	3. Non-eosinophilic asthma
• ↑ IgE → allergic asthma • It is important to distinguish this phenotype because of therapy • As an add-on therapy for 5th level allergic asthma – use biological treatment – **anti-IgE** → ***Omalizumab***	• ↑ Eosinophils (both in blood + sputum) • Usually not evoked by antigens → due to other stimuli, viruses etc. • As an add-on therapy for 5th level eosinophilic asthma – **anti-IL 5** → **mepolizumab**	• Absence of elevated eosinophil numbers in induced sputum • Similar to COPD • May respond to LABA, LAMA, theophylline or macrolides

Pharmacotherapy

- In terms of medications, we have 3 classes of medications:

Bronchodilators	Anti-inflammatory medications	Mast cell stabilizers
Short-acting β-agonists (**SABA**) → e.g., Salbutamol	**Inhaled corticosteroids** → e.g., budesonide or fluticasone	**Cromoglycates**
	Leukotriene antagonists → Montelukast + zafirlukast	
Long-acting β-agonists (**LABA**) → e.g., Formoterol	**Oral corticosteroids** → e.g., Prednisolone	

Asthma controllers according to severity

- 1. level → **Mild intermittent asthma** → *symptoms less than 2x a month*
  - *As-needed low dose* **inhaled corticosteroids** (IHC) + **formoterol** (LABA)
- 2. level → **Mild persistent asthma** → *Symptoms more than 2x a month but less than daily*
  - As-needed low dose ICS + formoterol or daily low dose of inhaled corticosteroids (IHC)
- 3. level → **Moderate persistent asthma** → *Symptoms most days*
  - Low dose inhaled corticosteroids (ICS) + LABA
- 4. level → **Severe persistent asthma** → *Symptoms daily*
  - Medium dose inhaled corticosteroids (ICS) + LABA
- 5. Level → 4. Level treatment + Add-on therapy according to phenotype!

e. Biological treatment
- → Omalizumab (anti-IgE)
  - Monoclonal antibodies used to treat allergic asthma,
  - Used as add-on treatment for step 5 allergic asthma
- → Reslizumab (anti-IL5)
  - Monoclonal antibodies used to treat eosinophilic asthma
  - Used as add-on treatment for step 5 allergic asthma

Relievers – therapy of acute symptoms in bronchial asthma

Short-acting β2-agonists (SABA) – with inhaled corticosteroids

- SABA should always be administered **<u>with</u> inhaled corticosteroids**
- Drugs: ***Salbutamol***

Controllers – long-term treatment of bronchial asthma

a. Long-acting β2-agonists (LABA)

Beta1 receptors → heart (so in high doses of β2 agonists = cardiac side effects)
Beta2 receptors → vasodilation + <u>bronchodilation</u>

- **Effects of β2 agonists on lungs:**
  - ***Bronchodilation*** via bronchial smooth muscle relaxation
  - ***Inhibition of mediators releasing*** from mastocytes, eosinophiles and basophiles
    - Beta blockers increase cAMP in inflammatory cells → stabilization → inhibition of mediator release
  - Increasing of ***mucociliary transport*** via increase of cilia motion frequency
  - Smaller ***permeability of capillaries***, relieving of mucous membrane **edema** caused by inflammatory mediators
  - Stimulation of epithelial cells to enhanced secretion of Cl^- and H_2O to bronchi
- **Tolerance of β2 agonists**
  - This is why we coadminister them with inhaled corticosteroids
- **Side effects:**
  - Side effects are mostly related to the activation of beta1 receptors
  - Tremor, tachycardia, metabolic changes, anxiety, headache…
- Drugs:
  - ***Formoterol***

b. Corticoids

- They are **<u>muscle relaxants</u>**, but not direct → indirect relaxants through reduced secretion of edema
  - They will lead to **bronchodilation**, by **lowering amounts of mediators**, they also **reduce the overactivity of smooth muscle**
- What is important, they are one of the few groups of drugs which have **<u>anti-proliferative activity</u>**
  - They **reduce hypertrophy** and **hyperplasia** of **airway smooth muscle,** and they also prevent **fibrosis**
- Corticoids **<u>increase sensitivity</u>** of **<u>β-adrenergic receptors</u>** of **smooth muscles** to **<u>β2 agonists</u>**
  - This is the reason why they should be **<u>co-administered</u>** also with **relievers** and also at **step 1 therapy** of bronchial asthma
- Corticoids are always used in the smallest possible amount
- **Inhalatory corticosteroids:**
  - **Inhalation route** of **administration** is **<u>preferred</u>**
  - They have only local effects
    - It means that the **adverse effects** will be **limited** → only local side effects (dysphonia, cough…)
  - Drugs: ***budesonide***, ***fluticasone*** (longest deposition time in lungs, best affinity to corticoid receptors)
- **Systemic corticosteroids:**
  - Systemic corticosteroids are **not generally recommended**, **<u>only</u>** in **step 5 treatment** of **asthma**
  - Drugs: ***prednisone***
- Side effects:
  - Hypertension, Corticosteroids induced diabetes mellitus, reduce wound healing, osteoporosis, moon face, redistribution of fat (buffalo hump), thrombosis…

c. Cromoglycates

- = ***mast cell stabilizers*** →Anti-inflammatory effects → inhibition of inflammatory cells activity
- **Advantages** → **safe for children**
- **Disadvantages**
  - Their effect can only be **observed after longer period** → So, many patients stop their medication
  - Currently they are not recommended as 1st of 2nd line treatment
    - But only used as **add-on treatment**

d. Antileukotriens (LT modifiers)

- Drugs: ***Montelukast***, ***zafirlukast***
- We may divide them into 2 major groups:
  - 1. Those which are **inhibiting lipoxygenase**
    - By inhibition of lipoxygenase, you **reduce production of leukotriens**
  - 2. Those which are **antagonists of leukotriens receptors**
    - By antagonizing of receptors, you block the receptors, so even if the production is still the same, the receptors are blocked
    - And if they are blocked, then the **effect will not be present**
- Why do we use them?
  - Especially in **aspirin-induced asthma**, because **aspirin blocks cyclooxygenase**
    - If you **block cyclooxygenase**, **lipoxygenase** will be **working more**
    - This is why in aspirin-induced asthma, their benefit is to block this pathway

e. Biological treatment

- → **Omalizumab (anti-IgE)**
  - Monoclonal antibodies used to treat **allergic asthma**,
  - Used as add-on treatment for step 5 allergic asthma
- → **Reslizumab (anti-IL5)**
  - Monoclonal antibodies used to treat eosinophilic asthma
  - Used as add-on treatment for step 5 allergic asthma

6. Autacoids

1. **Treatment of anaphylactic shock (36)**
2. **Antagonists of H_1 receptors (4)**
3. **Antagonists of H_2 receptors (15)**
4. **Antagonists of serotonin receptors (59)**
5. **Treatment of migraine (19)**
6. **Prostaglandins (58)**

1. Treatment of anaphylactic shock (36)

Intro

- Anaphylactic shock is an *acute life-threatening syndrome*
- It is due to the release of inflammatory mediators and cytokines from mast cells and basophils, typically due to an immunologic reaction but sometimes non-immunologic mechanism

Mediators

- Symptoms associated with allergy and anaphylaxis result from the release of certain mediators from the storage sites → ***Histamine***, ***serotonin***, ***leukotrienes***…
- Under some conditions these mediators may produce a local response, while in other cases systemic reaction (anaphylactic shock).
    - If release of histamine is fast it will be unable to inactivate it before entering bloodstream which may result in a full-blown anaphylactic reaction.

Etiology

- Drugs: Any medication may potentially trigger anaphylaxis
    - The most common are β-lactam ATBs (penicillin), followed by aspirin and NSAIDs
- Insect bites/sting (ants, bees, wasps)
- Foods (e.g., peanuts, wheat, seafood, milk, eggs)
- Typically caused by IgE-mediated release of vasoactive mediators – like histamine and bradykinin from mast cells and basophils in response to various allergens

Symptoms

- It typically causes more than one of the following: an ***itchy rash***, ***throat or tongue swelling***, ***shortness of breath***, ***vomiting***, ***lightheadedness***, and ***hypotension***.

Treatment

- As soon as anaphylaxis is suspected, the first and most important thing to do is to inject:
    - ***0,5 mg of 1:1000 epinephrine intramuscularly*** (1 gram of epinephrine in 1000 ml)
        - (i.v. route → risk of dosing error, which can cause ventricular arrhythmias
            - Therefore, the intramuscular route is preferred)
    - Injection may be repeated every 5-15 minutes if there is insufficient response

Epinephrine increases cardiac output, relaxes the smooth muscle of airways and causes vasoconstriction → all these effects lead to increased blood pressure and reduced movement of intravascular fluid into the interstitial space → this reduced mucosal edema

Additional medications which help with symptom relief

- Oral or i.v. ***antihistamines*** (like diphenhydramine or ranitidine) may be given
- Sometimes, a less severe episode of anaphylaxis can recur within 72 hours after the initial episode → biphasic reaction → ***Glucocorticoids*** (like methylprednisolone) have a delayed onset of action – they can reduce the risk of a biphasic reaction
- In addition, because massive amounts of fluid shift to the interstitial compartment, it's also important to give IV crystalloid fluids

Interactions

- Patients on β blockers may be resistant to the effects of epinephrine
    - If epinephrine is not effective, i.v. glucagon can be administered
        - Glucagon does not rely on beta receptors and can potentiate the effect of epinephrine

- You have to treat systemic anaphylactic reaction immediately
- Here is the scheme of the therapy
  - Drug of choice is adrenaline (epinephrine) – don't forget the 1:1000 solution in recommended for intramuscular
  - You can use intravenous administration, but it is recommended for experienced physicians
- Then you have to control the late phase of the reaction with anti-histaminics, administration of corticosteroids
  - You have to control the tonus of airways with inhaled β2-agonists such as salbutamol
  - And crystalloid infusion is recommended
- Don't forget, very important, some drugs can block the effect of adrenalin, especially β-blockers
  - Then you have to use higher doses of adrenaline

2. Antagonists of H1 receptors (4)

Autacoids – intro

- Autacoid definition:
  - = ***locally produced modulating mediators*** – influencing locally the function of cells or tissues which are produced on demand → subsequently metabolized by the same cells
  - Sometimes also called "*local hormones*" – because they primarily act in their place of production
    - In large quantities, they can be moved into circulation and reach systemic effects

Classification of autacoids:

- A. Biogenic amines:
  - ***Histamine*** + ***Serotonin***
- B. Prostanoids:
  - ***Prostaglandins*** (PGs), ***thromboxane***, ***leukotriens***
  - Inflammatory mediators that control many physiological and pathophysiological processes in the body
- C. Polypeptides
  - Kinins (bradykinin), tachykinins (substance P, NKA, NKB), CGRP

Histamine - intro

- Histamine is a biogenic amine formed from histidine
- = mediator of anaphylactic and allergic reactions

Function of histamine

- It is involved both in regulation of physiological and pathological processes
  - Pathological → mediator of allergy, inflammation, mastocytosis, carcinoid, urticaria pigmentosa

Histamine receptors

Receptor	G-protein	Localisation	Effects
H_1	G_q-protein	Smooth muscle, Endothelium, CNS, mastocytes	↑ Vascular permeability Vasodilation, Edema Bronchoconstriction, GIT, Uterus contraction CNS neurotrasmission
H_2	G_s-protein	Gastric mucosa, Myocardium, CNS	↑ GIT secretion ↑ Secretion of airways Stimulation heart contractility

Antihistamines

- Antihistamines are medications that work by blocking histamine receptors
- Depending on the type of receptors they affect, antihistamines are subdivided into 2 main groups:
  - **H1 blockers → *used to treat allergies***
  - H2 blockers → primarily used to treat gastric problems like heart burn

Histamine and allergic reactions

- Histamine is a small molecule that is mainly produced by mast cells and basophils
  - Once released, they cause ***local inflammation*** and ***vasodilation***
- They are also present in the brain as neurotransmitters, and they are also produced by enterochromaffin cells in the stomach to increase gastric acid secretion
- In order to develop allergic reaction, an allergen (e.g., pollen) needs to enter the body and cause the activation of B-cells → activated B-cells produce IgE antibodies that get released into the bloodstream and bind to mast cells → the mast cells are now "primed", meaning that if pollen enters the body again in the future, the mast cells degranulate and release their histamine into the local tissue

H1 receptor

- H1 receptors: → ***stimulatory Gq protein***
- Predominantly found on ***endothelial cells***, ***smooth muscle cells***, ***sensory nerve endings*** and in the ***brain***
  - On endothelial cells, stimulation of H1 receptors causes blood capillaries to dilate and become leaky
    - Eventually leading to redness and edema
  - On smooth muscle cells in the lungs → stimulation of H1 receptors results in bronchoconstriction
  - On sensory nerve endings, → stimulation of H1 receptors leads to pain and itching
  - In the brain → H1 receptors promote wakefulness and appetite suppression

H1 blockers (H1 antihistaminics)

- Antihistamines for allergies, also known as H1 blockers, are medications that are primarily used to treat allergic reactions, such as urticaria, angioedema and allergic rhinitis
  - These conditions are related to an increased release of histamine

Mechanism of action

- H1 blockers work by reversible inhibiting H1 receptors → blocking the effects of histamine in tissues that have H1 receptors, thereby relieving symptoms of allergic reactions

H1 blockers - classification

- H1 blockers are categorized into 3 generations which differ in their ***lipophilicity***

1st generation H1 blockers

- ***Diphenhydramine***, ***Bisulepine*** and ***Dimenhydrinate***
- Primarily used to treat allergic reactions, such as urticaria, angioedema and allergic rhinitis
- They have **high lipid solubility** → able to easily cross the BBB and block H1 receptors in the brain
  - This way, 1st generation H1 blockers can cause cognitive side effects like **sedation**
    - Therefore, they can also be used as short-term treatment for sleeping problems!
  - ***Diphenhydramine*** → can be used to treat *nausea*, *vomiting* and *motion sickness*
- **Common side effects of H1 blockers:**
  - ***Anti-histaminic effects***: sedation, increased appetite (+ weight gain)
  - ***Antimuscarinic effects*** (atropine-like): dilated pupils, dry mouth, blurry vision…
  - ***Anti-α-adrenergic effects***: orthostatic hypotension and dizziness
- Specific indication of 1st generation H1 blockers → antiemetics (motion sickness)
  - 2 mostly used are: **mephenhydrinate** and **diphenhydramine**
  - Indications: motion sickness, migraine, Meniere's syndrome
  - Remember the 1, 2, 3 rule of antiemetic drugs (H1, D2 and 5-HT3)

2nd + 3rd generation H1 blockers

- Fexofenadine, desloratadine, ***loratadine*** and cetirizine
- Just like 1st generation, 2nd generation H1 blockers are primarily used to treat allergic reactions
- But since they have **far less lipid solubility** than the 1st generation, they cause less cognitive side effects
- In addition, the anti-muscarinic side effects also tend to be less severe
- So, the 2nd generation is preferable to the 1st generation H1 blockers
- Due to the fact that they don't cross the BBB – they cannot be used as antiemetics
  - Drugs of 2nd generation H1 blockers are often called antiallergics

3. Antagonists of H2 receptors (15)

Autacoids – intro

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Suppressors of gastric acid secretion – Antisecretory drugs

- **1. Inhibitors of proton pump** (golden standard)
- **2. Antagonists of H_2 receptors**
- **3. Antagonists of muscarinic receptors**

H2 receptors

- Stimulatory Gs protein (↑ cAMP)
- Found in gastric mucosa and myocardium
- In GIT → ↑ ***gastric acid (HCl) secretion***, in the heart → ↑ ***contractility*** + ↑ ***heart rate***

Antagonists of H_2 receptors (H2 blockers)

❖ H_2 blockers are antagonist acting on H_2 receptors on the parietal cells in stomach
  ➢ This blockage inhibits CAMP-dependent pathway involved in the stimulation of gastric acid production

❖ **= They reduce the secretion of HCl in the stomach by blocking H2 receptors**

Drugs:

- **Cimetidine**
- **Ranitidine – t1/2 6-8h**
- **Famotidine – t1/2 10-12h**

- In clinical practice these are mostly used H2 blockers are Ranitidine, Famotidine (available p.o., i.v. and i.m.)
- The first H_2 blocker, Cimetidine, is NOT used anymore because these newer agents compared to cimetidine, have much more favorable safety profile and have fewer drug interactions
  - The half-life of crimidine was too short (more than 2x daily dosing)
  - Famotidine → 1x daily dosing

Therapeutic uses

- H2 blockers are mostly used as alternatives to proton pump inhibitors
  - They are used when treatment by PPIs is too intensive
- They are preferred in **long-term maintenance treatment after the healing of uncomplicated peptic ulcers**
- Also, H2 blockers are the ***drug of choice for stress-related ulcers***
- **Promote healing of gastric and duodenal ulcers**

Side effects

- Low incidences of side effects
- Mainly gastrointestinal → **Diarrhea, constipation**
- **Muscular pain**
- Their transport through BBB is mostly seen in older patients and can cause:
  - **CNS (confusion, delirium, hallucinations, slurred speech) mostly elderly patient**
- **Tolerance – rebound effect**
- **CIMETIDINE!!!**
  - Cimetidine was withdrawn from clinical practice, not only because of its pharmacokinetics and its potential to produce pharmacokinetic interactions, but also because of its steroidal structure which poses anti-androgenic effect
    - **Anti-androgenic effect, inhibits estradiol hydroxylation**
    - **Galactorrhea in women**
    - **Gynecomastia, reduced sperm count, impotence in men**
  - **Inhibits CYPs (e.g., CYP1A2, CYP2C9 and CYP2D6)**

- So, this drug is not in clinical use anymore

4. Antagonists of serotonin receptors (59)

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Serotonin

- Serotonin or 5-hydroxytryptamine (5-HT), is synthetized from tryptophan, an amino acid derived from dietary protein.
- It is an important CNS transmitter which regulates ***mood***, is involved in ***sleep***, ***appetite***, ***thermoregulation***, ***pain perception***, ***BP*** etc.
- Serotonin deficiency can be responsible for development of depression and anxiety
  - Serotonin agonists (SSRIs for depression, buspirone for anxiety) are used
- Approximately 90% of the body's total serotonin is located in enterochromaffin cells in GIT, where it regulates intestinal movements.
- However, it is also produced in the CNS (3%), specifically in the Raphe nuclei in the brainstem.
- It binds to serotonin membrane receptors (7 classes, 14 known receptors)
  - → Pharmacology of serotonin is very complicated due to all these receptors…

Effects

CVS - Contraction of smooth muscle (5-HT2) - Vasodilation in skeletal muscle and heart (EDRF) - Reflex tachycardia (5-HT3) - ↑ Platelet aggregation (5-HT2)	**CNS** - Stimulation of peripheral sensory nerve endings - Central stimulation of pain - Migraine - Precursor of melatonin - Regulation of mood, hallucination, schizophrenia, depression, anxiety - Regulation of appetite
GIT - Contraction of smooth muscle (5-HT2) → ↑ tone, peristalsis - ↑ AcH release – prokinetic effect (5-HT4)	**Respiratory system** - Small direct simulant effect of smooth muscle - Hyperventilation – chemoreceptor reflex, ↑ nerve endings

Serotonin antagonists

- A serotonin antagonist is a drug used to inhibit the action at serotonin (5-HT) receptors

Classifications of serotonin antagonists:

Atypical antipsychotics

- Serotonin antagonists can be used as ***atypical antipsychotics***
  - (In contrast to typical antipsychotics which are purely dopamine)
  - **SDAs** (**S**erotonin, **D**opamine **A**ntagonists)
    - ***Risperidone***
    - SDAs interact with dopamine, but they also manage some serotoninergic pathways
  - **MARTAs** (**M**ulti **A**cting **R**eceptor **T**argeted **A**gents)
    - ***Clozapine***, ***quetiapine***, ***olanzapine***
    - Remember the side effect of MARTAs → weight gain
      - Because MARTAs inhibit serotonin receptors 2C – which regulates appetite and satiety

Cyproheptadine

- Cyproheptadine is a blocker of serotoninergic 2A receptor and H1 receptor
- Cyproheptadine = antidote for serotonin syndrome
  - Serotonin syndrome = after administration of very high doses of serotonin agonist
  -
- It is very useful for the treatment of states where it is necessary to block serotonin and histamine
- For example, with carcinoid tumor, treatment of chronic urticaria and treatment of some complicated skin allergies

Setrons (5-HT3 antagonists)

- Remember the "1, 2, 3" rule of antiemetic drugs (H1, D2 and 5-HT3)
- **Ondansetron (ZOFRAN) – both central and peripheral receptors**
- **Granisetron (KYTRIL)**
- **Palonosetron (ALOXI) – both central and peripheral receptors**
- **Indications:**
  - **Vomiting induced by radiotherapy, chemotherapy or after operation**

5. Treatment of migraine (19)

Definition of migraine:

- ***Throbbing headache***, pain is typically localized on one side of the head (moderate to severe), lasts for a long time (4-72 hours)
- Migraine is frequently accompanied by nausea and vomiting
- *POUND (P = pulsatile headache, O = one day, U = unilateral, N = nausea, D = disabling)*

Pathomechanism

- The pathomechanism of migraine is not fully understood
  - Concentration of serotonin increases during the "aura" → triggering vasoconstriction
  - Then concentration of serotonin decreases during migraine attack → triggering vasodilation
- These changes of the tonus of blood vessels may be a trigger for pain receptors, causing the headache
- The initial vasoconstriction also triggers cortical spreading depression (CSD)
  - A phenomenon when the brain becomes hypersensitive to certain stimuli, like lights, sounds and smells

Pharmacotherapy of migraine

- There are 2 treatment approaches for migraine
  - Acute treatment → to help manage the pain
    - NSAIDs, opioid analgesics
  - Preventative treatment → to keep headaches happening in the first place

Acute treatment of migraine attacks

- Common analgesics drugs
  - For people with mild to moderate symptoms
  - ***NSAIDs*** (aspirin, ibuprofen) or ***opioid analgesics*** (codeine, oxycodone)
- For severe pain, we use ***serotonin agonists***, **triptans** or **ergotamine**
  - They are useful because they mimic serotonin to cause vasoconstriction
- **Triptans**
  - Drugs: ***sumatriptan, zolmitriptan, naratriptan, rizatriptan***
    - These drugs can be taken perorally – but for people who have nausea they can be taken by s.c. injection of nasal spray
  - Triptans are agonists of ***5-HT1B*** and ***5-HT1D serotonin receptors***
    - Agonistic effect on **postsynaptic 5-HT_{1B}** receptors in meningeal blood vessels
      - → Causing their constriction
    - Agonistic effect on **presynaptic 5-HT_{1D}** receptors cause subsequent **inhibition** of **pro-inflammatory neuropeptides** (tachykinins, CGRP...) release in trigeminal nerve terminals
  - A limitation of the clinical use of triptans is <u>vasoconstriction</u>
    - Except for meningeal vessels, they constrict other vessels in periphery
  - Contraindications:
    - In patients with cardiovascular diseases (hypertension, angina…) → because they ↑ blood pressure
  - Interactions: SSRIs and MAO-I increase the concentration of serotonin and will increase side effects of triptans (and induce serotonin syndrome)
- **Ergot alkaloids**
  - Ergotamine (sublingual) + dihydroergotamine (injected or nasal spray)
  - Non-specific agonists of 5-HT receptors = more side effects compared to triptans
    - For example, when they stimulate 5-HT3 receptors in the vomiting center → vomiting

Preventative treatment

- For people who have multiple episodes of migraines each year
- Multiple drugs can be used: ***β blockers***, ***calcium channel blockers*** and ***antiepileptics***
- Anti-CGRP antibodies
  - A new group of drugs developed specifically for prophylactic treatment
  - Erenumab, Fremanezumab and Galcanezumab
  - They are monoclonal antibodies that block either calcitonin gene-related peptide or its receptor
    - This peptide is involved in the transmission of sensory nerve impulses throughout the trigeminal nerve → which is the key to migraine headache (no nerve impulses = no pain)

6. Prostaglandins (58)

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Eicosanoids

- Eicosanoids are metabolites of arachidonic acid
- They can be categorized into:
  - Cyclooxygenase pathway → ***Prostaglandins,*** Prostacyclin and Thromboxane
  - Or lipoxygenase pathway → Leukotriens

Prostaglandins

- **Prostaglandins have many physiological functions in the body**
  - Constriction or dilation of blood vessels
  - Enhancing or inhibiting platelet aggregation
  - Opening or closing up airways
  - Contracting or relaxing smooth muscle in the gastrointestinal (GI) tract
  - Causing uterine contractions in pregnancy and when not pregnant

Prostaglandins in pharmacotherapy

- The trend in pharmacotherapy is to use **synthetic derivates of prostaglandins**

→ Vascular system (*vasodilatory prostaglandins*)

- In the vascular system we use *vasodilatory prostaglandins*
- ***Alprostadil* (PGE1), inj.**
  - Alprostadil causes **very strong vasodilation**
  - Direct effect on vascular smooth muscle
  - Clinical use:
    - The treatment of erectile dysfunction
    - And preventing or reversing the functional closure of ductus arteriosus
- ***Iloprost* (PGI1), inj.**
  - In comparison with alprostadil, Iloprost has wider activity
    - It causes vasodilation, also inhibits platelet aggregation, and has very strong anti-inflammatory effect
  - Clinical use:
    - For patients with serious states of limb ischemia that cannot be treated by surgery
    - For treatment of pulmonary hypertension

→ Uterine smooth muscle contraction (*prostaglandins cause contraction of uterine smooth muscle*)

- ***Dinoproston*** (PGE_2). inj, vaginal tbl., gel
  - Used for ***termination of pregnancy*** from the 12th through the 20th gestational week
  - For evacuation of the uterine contents in the management of abortion or intrauterine fetal death up to 28 gestational weeks
- ***Carboprost*** ($PGF_{2\alpha}$) inj.
  - Same indication as Dinoproston
  - + it also causes very strong contraction of vessels of the uterus
    - So, it is used to treat severe bleeding after childbirth (postpartum) due to atony of uterus

→ **Protection of gastric mucosa**

- **Misoprostol (PGE_1)**
  - A synthetic prostaglandin which increases bicarbonate and mucus production
  - = Has mucoprotective effect
  - Clinical use: Protection of mucous membrane during NSAID therapy

→ **Reduction of intraocular pressure**

- **Latanoprost ($PGF_{2\alpha}$)**
  - Increases the sclera's permeability to aqueous fluid.
  - Increase in prostaglandin activity stimulates the outflow of aqueous fluid
    - = reduces the intraocular pressure
  - Used to treat ***ocular hypertension*** and ***open angle glaucoma***

7. CVS

→ **Hypertension**

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→ **Heart failure**

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1. Treatment of hypertension – general principles, drugs (41)

Hypertension intro:

- Hypertension = blood pressure elevated above **140/90** in 2 out of 3 measurements (white coat sy.)
  - **3 degrees**: grade 1 (140-159/90-99), 2 (160-179/100-109), 3 (≥ 180/≥ 110) and hypertension crisis (≥ 180/120)

Classification of hypertension according to etiology

- 1. **Essential** (primary) – 90-95% of patients
  - When the exact cause cannot be determines – only risk factors
  - Divided according if the risk factors can be affected or not into:
    - Non-susceptive (family, sex, age) and susceptive (obesity, stress, salt intake, smoking…)
- 2. **Secondary** → to some distinct disease (renal, hormonal, pregnancy etc. …)

Hypertensive agents:

- Blood pressure = cardiac output x peripheral resistance
  - → So, to decrease blood pressure, either reduce cardiac output or peripheral resistance
- Drugs which are recommended for the treatment of hypertension are able to:
  - **Reduce systemic vascular resistance** → or **decreasing afterload**
  - **Reduce the volume of circulating fluid** → **decreasing preload**
  - Or they are able to **reduce cardiac function** → **reducing cardiac output**
- **7 Classes of antihypertensives**:
  - **1. Diuretics**
  - **2. Peripheral α1 adrenergic antagonists:**
  - **3. Centrally acting**
    - **α2 agonists, imidazoline receptor agonists**
  - **4. β blockers**
  - **5. RAS inhibitors**
    - **ACE inhibitors**
    - **Antagonists of AT1 receptors (Sartans)**
    - Antagonists of renin receptors
    - Antagonists of aldosterone receptors
  - **6. Calcium channel blockers**
  - **7. Other vasodilators (nitroprusside, hydralazine, nitroglycerine…)**

5 of the represent first-line of antihypertensive treatment

- 1. Diuretics → **Thiazide**
- 2. **Beta blockers**
- 3. ACE inhibitors
- 4. Antagonists of angiotensin1 receptors or sartans as alternatives for ACE inhibitors
- 5. Direct vasodilatory calcium channel blockers

The selection of antihypertensive drugs:

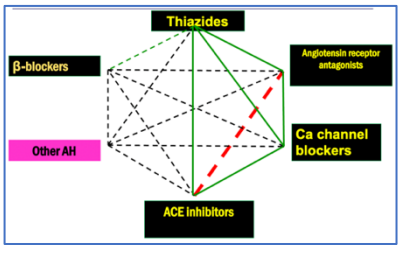
- We need to take into account differences in **mechanism of action** and the presence and **type of adverse effects** → To prevent synergy between adverse effects
- **Total cardiovascular risk** – presence of concomitant disease
- **Risk of cardiovascular adverse events**
  - By evaluating these 3 points, we can select appropriate combination of antihypertensive drugs

Double (or more) combination is recommended

- The recent trend in the treatment of hypertension is the use of combination of 2 drugs in low doses
- The most frequently used **double combination** in clinical practice:
  - Combination of **ACE inhibitors** + **thiazide**, or **ACE inhibitors** + **calcium channel blockers**
  - These are the most effective and safest combinations (sartans can be used as an alternative of ACE-I)
- **Triple combination:** **ACE inhibitors** + **Thiazide** + **calcium channel blockers**

When this combination fails → resistant hypertension → we need to add agents from 2nd line agents

❖ It is estimated that approx. 10-15% of patients suffer from resistant hypertension
  ➢ In these cases, it is strongly recommended to repeat complete diagnostic algorithm in order to exclude secondary hypertensions



2. Treatment of hypertension crisis (30)

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  - → **Hypertension crisis** (≥ 180/120)

Hypertension crisis

- Hypertensive crisis is an acute increase in blood pressure (generally defined as ≥ 180/120 mmHg)
- Hypertension crisis is one of the most common acute escalation of hypertension
- Aim of treatment → Reduce BP by max. 25% within the first hour
  - In order to prevent coronary insufficiency and to ensure adequate cerebral perfusion pressure.
  - It is recommended, during the first 24 hours, to maintain the blood pressure between 150-160 in systolic, 100-120 in diastolic blood pressure
  - And to normalize blood pressure below 140/90 within 2-3 days
- It can be divided to:
  - **Hypertensive urgency** or **hypertensive emergency**

1. Hypertensive urgency → without organ changes

- No imminent risk of target organ damage, not an acute life-threatening condition
- Treatment → use slow adjustments of blood pressure using **peroral** therapy
  - ***Captopril*** (ACE-I) + ***diuretics***

2. Hypertensive emergency → with organ changes

- A life-threating state which is associated with organ changes
- Treatment → **parenteral** antihypertensive drugs (drug selection depends on clinical situations)
- Most commonly used parenteral drugs are:
  - **Loop diuretics**: **Furosemide**
  - **Antiadrenergics**
    - **Esmolol** (selective β1 blocker with no ISA and no MSA) → used when hypertension is associated with severe tachycardia
    - **Labetalol** (non-selective β blocker with α1 antagonism)
    - **Urapidil** (α1 blocker)
  - **Alternative therapy** (in case intravenous treatment is not available) → **sublingual tablets**
    - **Captopril** (ACE-I) **Nitrendipine** (calcium channel blockers) and **nitroglycerine** (nitrate)

5 of the represent first-line of antihypertensive treatment

- 1. Diuretics → **Thiazide**
- 2. **Beta blockers**
- 3. **ACE inhibitors**
- 4. **Antagonists of angiotensin1 receptors** or **sartans** as alternatives for ACE inhibitors
- 5. Direct vasodilatory **calcium channel blockers**

3. Diuretics (23)

Hypertension intro:

- Hypertension = blood pressure elevated above **140/90** in 2 of 3 consecutive measurements (white coat sy.)

Diuretics general:

- Diuretics = substances which promote diuresis (urination) → decrease preload
  - All diuretics increase the excretion of water, although each class does it via different mechanism

General mechanism of action of diuretics:

- The most common mechanism is associated with increased excretion of sodium ions → increased excretion of water into urine → ↓ plasma volume → ↓ cardiac output → ↓ blood pressure
- **Acute response:** (*renal*)
  - **Decrease in preload** due to increased excretion of water → decrease in the necessity of cardiac work
- **Late response:** (*extrarenal*)
  - After several weeks we can also follow decrease in afterload (decreased peripheral resistance)
  - Thought to be cause by increased synthesis of vasodilatory prostaglandins

Classification of diuretics

- Diuretics are divided according to which part of the renal nephron they act on:
  - **Proximal tubule diuretics:**
    - Osmotic → **Mannitol**
    - Carbonic anhydrase inhibitor → **Acetazolamide**
  - **Loop diuretics:**
    - Furosemide + Torasemide
  - **Distal tubule diuretics:**
    - Thiazides + Sulfonamides
  - **Potassium sparing diuretics: (collecting duct)**
    - Amiloride, Spironolactone, Triamterene

- **Distal tubule diuretics** (thiazides + sulfonamides) are considered as **true antihypertensive diuretics**
  - They pose only minor diuretic effect
    - An advantage of distal diuretics is that **they retain the potassium ions**
      - So, they can be used for the compensation of the ionic disbalance that standardly occurs after long-term treatment using diuretics
  - Also, they pose ***antagonistic effect on the aldosterone receptors***, which are presented in higher degree in vessels of patients with hypertension
    - So, their administration can also influence afterload

- The **loop diuretics** (furosemide + torasemide) are the **most powerful diuretics**
  - They are used for more **complicated patients**, suffering from some renal insufficiency
  - They are also suitable for treatment of patients in **acute states** of hypertension (hypertension crisis)

Side effects of diuretics:

- The most serious side effects of the majority of diuretics include **volume depletion** and **excessive changes in serum electrolyte levels** (particularly of sodium and **potassium**), hypokalemia increases the risk for **cardiac arrhythmias.**

Classification of diuretics

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4. Loop diuretics (54)

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  - All diuretics increase the excretion of water, although each class does it via different mechanism

Loop diuretics:

- Action site → Loop of Henle
- Loop diuretics have the **most effective diuretic action** = **most effective diuretic agents**
  - Due to the high amount of sodium and water which is transported from urine to the loop of Henle
- They have fast onset of effect (10 min) but limited duration of effect (2-3 hours)
  - Used *especially for acute states* → e.g., hypertensive emergency!
- **Furosemide** + **Torasemide**

Mechanism of action:

→ Renal effect (early)

- Loop diuretics inhibit the transport of sodium into the ascending limb of loop of Henle
- It does this by **inhibiting** the **cotransport (*reabsorption*) of sodium, potassium and 2 chloride ions**
  - $Na^+ + K^+ + Cl^-$ = lost in urine → water follows = decreased plasma volume
  - **↓ blood volume → ↓ Preload → ↓cardiac output → ↓ blood pressure**
  - **Compensatory responses**:
    - ***Hyponatremia*** → exchange of Na^+ and proton or potassium = **metabolic alkalosis/hypokalemia**
    - ***Hypokalemia*** → K^+ is reabsorbed back into blood → positive charge inside tubule → positively charged calcium (Ca^{2+}) + magnesium (Mg^{2+}) leaks out = **Hypocalcemia** and **hypomagnesemia**

→ Extrarenal effects (late effects 2-4 weeks)

- Increased prostaglandin release → vasodilation = ↓ peripheral resistance → decreased blood pressure
  - **= ↓ Afterload**

Indications of Loop diuretics

- **Acute states** → administered parenterally
  - **Hypertension crisis** (emergency)
  - **Edema** (lung, brain…) + **ascites** (liver cirrhosis, renal failure…)
  - Chronic heart failure
  - Hypercalcemia + hyperkalemia
- **Chronic therapy** → administered perorally
  - Only allowed in patients which have low response to thiazide (distal tubule uretic)

Side effects of loop diuretics

- Side effects of loop diuretics origin from their mechanism of action

- **Ionic disbalance → Hypokalemia, Hypomagnesemia, Hypocalcemia**
- **Hyperuricemia + hyperglycemia →** Furosemide is a weak acid
- When the drug is eliminated it is exchanged with uric acid and glucose → **hyperuricemia + hyperglycemia**
  - = ***Negative metabolic profile***
- **Ototoxicity (dose dependent, reversible, aminoglycoside ATB)**
  - Due to increased penetration of loop diuretics into the fluid of inner ear
  - A very typical side effect of loop diuretics
- **Dehydration**

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    - Furosemide + Torasemide
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    - **Thiazides + Sulfonamides**
  - **Potassium sparing diuretics (collecting duct):**
    - Amiloride, Spironolactone, Triamterene

5. Diuretics act on distal tubule (49)

Hypertension intro:

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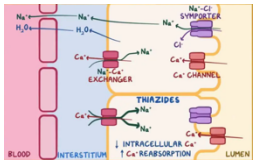
Diuretics general:

- Diuretics = substances which promote diuresis (urination) → decrease preload
  - All diuretics increase the excretion of water, although each class does it via different mechanism

Distal tubule diuretics – General:

- **Distal tubule diuretics** (thiazides + sulfonamides) are considered as **true antihypertensive diuretics**
  - They pose only minor diuretic effect, but are important in treatment of hypertension
    - Because they **retain potassium**

Mechanism of action:



→ **Renal effect (early effect)**

- **Sodium and chloride co-transport** from urine back to blood is **inhibited** → water follows
  - = **↓ blood volume → ↓ preload → ↓ cardiac output → ↓ blood pressure**
  - **Compensatory mechanisms:**
    - Inhibition of Na^+/Cl^- cotransporter leads to ↓ Na ***inside tubular cells*** → compensation: Na into cell from blood and more calcium into the blood in exchange through the Na^+/Ca^{2+} antiporter → hyponatremia + **hypercalcemia** (side effects)
    - Hyponatremia → exchange of Na and proton or potassium = **metabolic alkalosis/hypokalemia**

→ **Extrarenal effects (late effects 2-4 weeks)**

- Increased prostaglandin release → vasodilation = ↓ peripheral resistance → decreased blood pressure
  - **= ↓ Afterload**

Indications

- They are part of **first line therapy of hypertension**
  - Long-lasting **peroral** therapy of hypertension
  - Can be used as monotherapy (grade 1 HTN) or in combination with other antihypertensive drugs (grade II and III)
    - (***Double*** therapy with ACE-I ***or*** CCBs or ***triple*** therapy with ACE-I ***and*** CCBs)
- Additional indications: **chronic heart failure**, **hypercalciuria**, **osteoporosis (***due to hypercalcemia effect!***)**

Side effects

- **Ion disbalance**
  - **Hyponatremia**, **Hypokalemia**, **Hypercalcemia** (in contrast to loops!)
    - Hypercalcemia will not be significant due to action of parathyroid gland (calcitonin)
    - Due to hypokalemia → it's good to combine them w. *ACE-I* or *kalium sparing diuretics*
- **Hyperuricemia, Hyperglycemia, Hyperlipidemia, Allergic reaction**
- When the drug is eliminated, it is exchanged with uric acid and glucose → **hyperuricemia + hyperglycemia**
  - = ***Negative metabolic profile***

Drugs:

- **1. Thiazides**
  - Hydrochlorothiazide + Chlorthalidone
  - Hydrochlorothiazide additionally inhibits the release of insulin
    - metabolic SE
- **2. Sulfonamides**
  - Indapamide + Metipamide
  - Sulfonamides have lower renal effect than thiazides, but they have higher extrarenal effects

Contraindications:

- **Gout** (*because of hyperuricemia*), Hypokalemia, dyslipidemia, uncontrolled DM

Diuretics of distal tubule – summary

- **Good aspects**
  - **Low cost, long-lasting effects, Calcium sparing = good in combination with ACE-I**
- **Bad aspects**
  - **Potassium washout, ↑ in uric acid, adverse effect on lipids, glucose control**

- Here is a summary of diuretics, the first class of basic antihypertensive drugs, we need to mention that the good aspects of these drugs are much more significant than the bad ones
  - It is especially the effectiveness regardless of age of the patient
  - The calcium sparing effects is very important
  - Their combinatory potency is also a very good aspect
- Bad aspect, epically the side effects resulting from the mechanism of action, or metabolic side effects are especially the ionic disbalance (which is relatively well managed by the appropriate combination)
  - And when we use the drugs in low doses, the incidence of metabolic side effects is also relatively low

Classification of diuretics

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  - **Loop diuretics:**
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    - Thiazides + Sulfonamides
  - **Potassium sparing diuretics (collecting duct):**
    - **Amiloride, Spironolactone, Triamterene**

6. Kalium – sparing diuretics (62)

Hypertension intro:

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Diuretics general:

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  - All diuretics increase the excretion of water, although each class does it via different mechanism

General mechanism of action of diuretics:

- The most common mechanism is associated with increased excretion of sodium ions → increased excretion of water into urine
- **Acute response:**
  - **Decrease in preload** due to increased excretion of water → decrease in the necessity of cardiac work
- **Late response:**
  - After several weeks we can also follow decrease in afterload (decreased peripheral resistance)
  - Thought to be cause by increased synthesis of vasodilatory prostaglandins

Potassium-sparing diuretics – general:

- Potassium-sparing diuretics are drugs that do not promote the secretion of potassium into the urine
- Because they act in collecting duct, where amount of water and Na is low, their diuretic effect is very non-significant = never used in monotherapy → always combination
  - However, they have a position in treatment of hypertension due to their compensatory effect on potassium levels → **often combined with loop and distal tubule diuretics**

(Normal function of aldosterone)

- Aldosterone promotes Na+ and water reabsorption (↑ blood pressure)
- And lower plasma K+ concentration

Mechanism of action

1. Aldosterone receptor inhibitors: (**spironolactone**, **eplerenone**)

- Competitively bind to aldosterone receptors in the collecting duct → inhibition of aldosterone effects
  - = **Decreased Na+ reabsorption** and **decreased K+ excretion** → **diuresis**
- ↑level of potassium is corrected by proton/potassium ATPase → ↑ proton in blood → **metabolic acidosis**

2. Epithelial sodium channel blockers: (**triamterene**, **amiloride**):

- Direct inhibition of the epithelial sodium channels in the collecting duct → reduced Na+ reabsorption and reduced K+ secretion → diuresis

Side effects of potassium sparing diuretics:

- **Hyperkalemia (! Do not combine with ACE-I, ARBs or NSAID)**
- **Metabolic acidosis**

Therapeutic use:

– (In therapy of hypertension *only as the combination therapy* → due to compensatory effects)

→ **Main indication**

– **Primary hyperaldosteronism (Diagnosis and therapy)**

– **Secondary hyperaldosteronism (heart failure, ascites, nephrotic syndrome, liver cirrhosis...)**

→ **Other indications**

– Hypokalemia, prevention of hypokalemia

7 Classes of antihypertensives:
- **1. Diuretics**
- **2. Peripheral α1 adrenergic antagonists:**
- **3. Centrally acting**
  - **α2 agonists, imidazoline receptor agonists**
- **4. β blockers**
- 5. RAS inhibitors
  - **ACE inhibitors**
  - **Antagonists of AT1 receptors (Sartans)**
  - Antagonists of renin receptors
  - Antagonists of aldosterone receptors
- **6. Calcium channel blockers**
- **7. Other vasodilators**

7. Agonists of imidazoline receptors and therapy of hypertension (52)

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  - **3 degrees**: grade 1 (140-159/90-99), 2 (140-159/90-99), 3 (≥ 180/≥ 110) and hypertension crisis (≥ 180/120)

Classification of hypertension according to etiology

- Essential (primary) – 90-95% of patients
  - When the exact cause cannot be determines – only risk factors
  - Divided according if the risk factors can be affected or not into:
    - Non-susceptive (family, sex, age) and susceptive (obesity, stress, salt intake, smoking…)
- Secondary → to some distinct disease (renal, hormonal, pregnancy etc. …)

Centrally acting antihypertensives

5 of the represent first-line of antihypertensive treatment
- 1. Diuretics → **Thiazide**
- 2. Beta blockers
- 3. ACE inhibitors
- 4. Antagonists of angiotensin1 receptors or sartans as alternatives for ACE inhibitors
- 5. Direct vasodilatory calcium channel blockers

- Centrally acting antihypertensives are ***2nd line antihypertensives***
  - Can be used in combinations with other antihypertensives in the treatment of **resistant hypertension** (when triple therapy of has failed)
    - Triple therapy = **ACE inhibitors** + **Thiazide** + **calcium channel blockers**
- We divide them into 1st and 2nd generation:
  - 1st generation: **Methyldopa + clonidine**
    - = Non-selective agonists of alpha2 pre-synaptic receptors
  - 2nd generation: **Rilmenidine + Moxonidine**
    - = Agonists of Imidazoline receptor

Mechanism of action

- 2nd generation of selective **imidazoline receptor agonists** are drugs which selective act through imidazoline type 1 receptors
  - This causes inhibition of the sympathetic nervous system activity and results in lowering of blood pressure
- Except for in the CNS, these receptors can also be found in the beta cells of pancreas
  - Here they can regulate and enhance insulin secretion and modulate the resistance to insulin in patients

Results of clinical trials

- **Positive effect on lipid metabolism**
- **↓cholesterol, TG**
- **Adjustment of ins. resistance and glucose tolerance**
- **Biological availability – p.o. 90%**
- **Duration of effect – 24 hours**

Indications:

- **Resistance hypertension**
- **Suitable for management of obese patients with metabolic impairment, suffering from resistant form of hypertension**

The imidazoline receptors have recently been discovered to be involved in central nervous system control of blood pressure (I-1 receptor) and in neuroprotection for cerebral ischemia (I-2 receptor).
A new class of central-acting antihypertensive agents has been developed, the imidazoline receptor agonists (Rilmenidine and Moxonidine), which control blood pressure effectively without the adverse effects of sedation and mental depression that are usually associated with central-acting antihypertensives.
This new generation of central-acting antihypertensive agents are highly selective for the imidazoline receptor, while having a low affinity for alpha 2-adrenergic receptors.

- The treatment of hypertension in pregnancy is still mainly based on methyldopa
  - Methyldopa is the drug of choice (first line), especially within 1st trimester of pregnancy
- Beta blockers and calcium channel blockers are second-line treatment
  - The efficacy and safety of beta blockers was demonstrated in later pregnancy especially

5 of the represent first-line of antihypertensive treatment
- 1. Diuretics → **Thiazide**
- 2. **Beta blockers**
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- 4. Antagonists of angiotensin1 receptors or sartans as alternatives for ACE inhibitors
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8. ACE inhibitors (48)

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Renin-Angiotensin-Aldosterone system

- RAAS = hormone system that regulates *blood pressure* and *fluid electrolytes balance* as well as *systemic vascular resistance*
- **Renin** is secreted from juxtaglomerular cells of kidneys in response to decreased blood flow → renin is released to the blood stream → plasma renin converts **angiotensinogens** (released by liver) to **angiotensin 1** → angiotensin 1 is converted to angiotensin 2 by ***angiotensin converting enzyme*** (ACE)
  - → ACE can be found in vascular endothelial cells, and predominantly in the lungs
- Angiotensin 2 = the strongest vasoconstrictor in the human body = ↑ blood pressure
- Angiotensin 2 also stimulates the **release of aldosterone** by adrenal glands
  - Aldosterone increases the reabsorption of sodium in the kidneys → increases water reabsorption → increases blood volume = ↑ blood pressure

Mechanism of action:

1. Inhibition of angiotensin 2 formation

- Inhibition of ACE → **prevention of angiotensin 2 formation → ↓ vasoconstriction → ↓ blood pressure**
- Inhibition of aldosterone secretion → **↑ Sodium excretion + ↓ potassium excretion → ↓ plasma volume → ↓ blood pressure**

2. Increased amount of bradykinin

- Normally, ACE also breaks down bradykinin to inactive mediators
- With the inhibition of ACE → bradykinin will accumulate (→ ***dry cough*** + ***angioedema***!)
- Benefits of bradykinin accumulation = *Cardioprotection (reduce ventricular hypertrophy + fibrosis), neuroprotection*, *nephroprotection,* vasodilation, inhibition of growth factors, inhibition of Na excretion

3. Angiotensin 1 → Angiotensin 1-7

- We will have excess angiotensin 1 (because it won't be converted into angiotensin 2)
- ***Neprilysin*** converts angiotensin 1 to angiotensin 1-7
  - = Vasodilation, sodium excretion, anti-inflammatory, ↓ oxidative stress

Indications:

- ACE inhibitors are **first-line treatment** in **antihypertensive treatment** as well as for **chronic heart failure**
  - Because ACE inhibitors decrease the peripheral resistance and afterload – so the heart doesn't have to pump as hard against the resistance
- Recommended in hypertensive patients with concomitant chronic heart failure or DM
  - DM → *nephroprotection + neuroprotection*
  - Chronic heart failure → *Cardioprotection*

Combination with other antihypertensives

- A part of the most effective double combination with distal tubule diuretic ***thiazide***
  - Good compensatory combination (ACE-I = hyperkalemia, thiazide = hypokalemia)
- Do not combine ACE (or ARBs) with K+ sparing diuretics due to synergistic effect – hyperkalemia

Side effects

- The most common side effect → **dry cough** (*Due to bradykinin accumulation*)
- More rare side effect → **Angioedema** (*also due to bradykinin accumulation*)
- **Hypotension** (but only after 1st dose)
- **Hyperkalemia** (avoid high potassium diet)
  - Due to decreased aldosterone production → less potassium excretion to urine
  - = Positive combination with thiazides

Drugs:

- **Captopril** (short-acting)
- **Enalapril** (intermediate acting)
- **Ramipril**, **lisinopril** (long-acting

5 of the represent first-line of antihypertensive treatment

- 1. Diuretics → **Thiazide**
- 2. **Beta blockers**
- 3. **ACE inhibitors**
- 4. **Antagonists of angiotensin1 receptors** or **sartans** as alternatives for ACE inhibitors
- 5. Direct vasodilatory **calcium channel blockers**

9. Antagonists of angiotensin receptors (10)

Angiotensin 2 receptor blockers (known as sartans) selectively block the activation of angiotensin receptor type 1 (AT1)

- ❖ They are alternative of ACE inhibitors
- ❖ And logically, they reduce the consequences of angiotensin 2 activity

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  - → ACE can be found in vascular endothelial cells, and predominantly in the lungs
- Angiotensin 2 = the strongest vasoconstrictor in the human body = ↑ blood pressure
- Angiotensin 2 also stimulates the **release of aldosterone** by adrenal glands
  - Aldosterone increases the reabsorption of sodium in the kidneys → increases water reabsorption → increases blood volume = ↑ blood pressure

1. Antagonists of angiotensin receptors type 1 (Sartans)

- ❖ Angiotensin receptor blockers (known as sartans) selectively block the activation of angiotensin receptor type 1 (AT1)
- ❖ Similar pharmacological profile as ACE-I → only ***without bradykinin*** + ***AT 1-7 action***
  - ➢ = *Safer* (fewer side effects) but *less effective*

Mechanism of action

- ❖ Angiotensin receptor blockers bind to ***angiotensin receptor 1*** and ***prevent angiotensin 2 from binding***
  - ➢ **↓ vasoconstriction** (vasodilation) → **↓ BP**, **↓ synthesis in aldosterone → ↓ BP**
- ❖ In contrast to ACE inhibitors, they don't increase bradykinin levels in the blood

Indications

- ❖ The sartans have the same indications as ACE inhibitors
  - ➢ → Also used to treat **hypertension** and **chronic heart failure** = Used as **alternatives for ACE-I**

Advantages vs disadvantages

- ❖ **Good aspect: without cough and angioedema**
  - ➢ Better side effect profile, because they don't cause the bradykinin accumulation like ACE-I do
- ❖ **Bad aspect: smaller protective effects as ACE-I**
  - ➢ Also, because they don't affect bradykinin, the protective effect, especially the cardioprotective effects seen on the remodeling of the heart and vessel wall is much smaller than in the case of ACE inhibitors

Side effects:

- In contrast to ACE inhibitors, they don't increase bradykinin levels in the blood → cause less dry cough and angioedema
  - But like for ACE inhibitors they cause hyperkalemia and hypotension

Drugs - Sartans

- **LOSARTAN, VALSARTAN, CANDESARTAN, TELMISARTAN**

2. ARNI – (dual) Angiotensin Receptor and Neprilysin Inhibitor

- A new group of drugs which has entered clinical practice
- The goal of these drugs is to improve the outcome for patients with **chronic heart failure**
  - These drugs are abbreviated "ARNI", and they are dual angiotensin receptor and neprilysin inhibitors
- ARNI is a combination which consist of:
  - **Angiotensin receptor blocker → valsartan**
    - Angiotensin receptor blockers inhibit the RAAS activity by inhibiting angiotensin receptors
  - And **neprilysin inhibitor → Sacubitril**
    - Sacubitril is an inhibitor of neprilysin = *increased bradykinin*, *increased ANP* and *BNP*
  - Atrial natriuretic peptides promote sodium and water excretion and cause vasodilation, decrease aldosterone secretion, inhibits the fibrotic changes in the failing myocardium
  - The effects of natriuretic peptide system are antagonistic to those of sympaticus and RAAS
- **Combination therapy with ACEI (or ARB) and ARNI is contraindicated** due to ***synergistic effects***
- **Side effects:**
  - **Hyperkalemia, hypotension, angioedema (less than ACE-I)**

Intro – Antihypertensives

1 **Diuretics**
2 **Peripheral α1 antagonists**
3 **β Blocker**
4 **Centrally acting** (α2 agonists, imidazoline receptors agonists)
5 **RAAS:**
- ACE inhibitor
- Antagonists AT1 receptors, Renin receptors, aldosterone receptors

6 **Ca Channel blockers**
7 **Other vasodilators**

10. Calcium channels blockers (14)

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Calcium Channel Blocker

- They are widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias and other specific disorders
- Structurally divided into:
  - **Dihydropyridines (DHP)** → more selective of inhibition of vascular L-types of calcium ion channels
  - **Non-Dihydropyridines (NDHP)** → more selective of inhibition of cardiac L-types of calcium ion channels

Mechanism of action

- **Bind L-type Ca channels** (in cardiac and vascular muscles) → **↓ Ca influx:**

1 Vascular smooth mm. relaxation → vasodilation → ↓ PVR → ↓ BP
2 ↓ cardiac mm. contraction → ↓ CO → ↓ BP
3 ↓ SA + AV node activity → ↓ HR
  - ↓ AV conduction → termination of supraventricular tachycardia

Indication – Both DHP and NDHP:

- **Arterial hypertension** (part of 1st line therapy)
- **Angina Pectoris** (part of 1st line therapy)

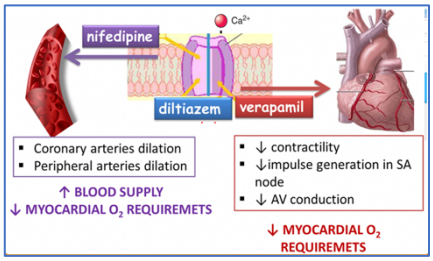
Side effects – Both DHP and NDHP:

- **Hypotension, dizziness, flushing**
- **Fast ↓ blood pressure → reflex tachycardia**
- **Gingival hyperplasia**

Contraindication:

- Tachycardia, chronic heart failure
- **Don't combine beta blockers with non-DHP derivates** (especially verapamil)
  - Due to synergistic effects on myocardium
-

Dihydropyridine	Non-Dihydropyridine
• Act mainly on **vascular smooth mm.** **Effects:** • Strong Vasodilators • Minimal myocardial depressant activity **Additional Indication:** • Raynaud phenomenon • Alternative therapy of Hypertension crisis (emergency) **Drugs:** 1. Short acting → ***Nifedipine*** 2. Intermediate acting → ***Nitrendipine, Nicardipine, Lercanidipine*** 3. Long acting → ***Amlodipine*** **Side effects:** • Reflex tachycardia (due to fast ↓ BP), Headache, edema	• Act mainly on the **Heart** **Effect:** • Moderate Vasodilators • Strong myocardial depression **Additional indication:** • Supraventricular arrythmia (Atrial fib + flutter, PSVT) • Migraine **Drugs:** • ***Diltiazem + Verapamil*** ▪ *Verapamil* is more cardiac selective + *Diltiazem* is more effective on coronary vessels **Side effects:** 1. ***Diltiazem*** → same are DHP, but milder 2. ***Verapamil*** → Constipation, hyperprolactinemia, Heart block



Differences between DHP and Non-DHP calcium channel blockers

- Here are summarized differences between **dihydropyridine** (nifedipine) and **non-dihydropyridine** (diltiazem and verapamil)
  - Diltiazem is somewhere in the middle between nifedipine and verapamil
- **Both DHP and non-DHP:**
  - Reduce myocardial oxygen requirements
  - They increase blood supply to myocardium (because they cause vasodilation in coronary arteries)
  - Cause dilatation of peripheral arteries (reducing the afterload)
- **Non-DHP** (diltiazem and verapamil)
  - Reduce the myocardial oxygen requirement
    - Because they reduce the heart work and cardiac output by influencing the SA and AV node conduction
  - Their benefits are used for the management of angina pectoris
    - Stable, unstable and vasospastic angina pectoris

- Dihydropyridines are divided into 3 generations (1st, 2nd and 3rd generations)
  - 2nd and 3rd generations have extended half-life
  - In 3rd generation there are long-acting calcium channel blockers
    - They are very good for the management of hypertension

Chemical structure	1. Generation	2. Generation	3. Generation
1. Dihydropyridines:	**Nifedipine Only SR**	**Felodipine**	**Amlodipine**
	Nicardipine	**Isradipine**	**Lacidipine**
		Nitrendipine	**Barnidipine**
		Nisoldipine	**Lercanidipine**
		Nimodipine	
2. Non-dihydropyridines:			
Benzothiazepines	**Diltiazem**		
Phenylalkylamines	**verapamil**		

Vasodilatory + direct myocardial effect **Increase half-life** **Lipophilic – therapy of SAH**

- Don't forget that **nifedipine** is only used in slow-release (SR) forms
  - Because nifedipine causes very strong vasodilation and it also has rapid onset of action
    - And rapid reduction in blood pressure can lead to reflex sympathetic nervous system activation and a very strong tachycardia
    - So, for this reason, it is only given in the form of slow-release tablets
  - But the advantage of nifedipine is the low price
- Another indication for calcium channel blockers is hypertension
  - 2nd and 3rd generation CCB's are used for this indication because of their prolonged effect
- The 3rd generation dihydropyridines (amlodipine, Lacidipine, barnidipine, lercanidipine) have prolonged half-life
  - They are administered as 1 per day
  - They are used in the treatment of hypertension
- Don't forget that non-dihydropyridines, diltiazem and verapamil have vasodilatory and direct myocardial effect

11. Side effects of antihypertensive drugs (58)

Side effects of Diuretics:

→ **Loop diuretics (furosemide + torasemide)**

- They inhibit co-transport of Na, K and Cl in loop of Henle = these ions will be lost in urine
  - → Water follows → ↓ plasma volume → ↓ preload → ↓ blood pressure
- **Compensatory mechanisms**:
  - Hyponatremia → exchange of Na+ with proton or potassium = **metabolic alkalosis/hypokalemia**
  - Potassium is reabsorbed back into blood → ↑positive charge inside tubule → positively charged calcium (Ca^{2+}) + magnesium (Mg^{2+}) leaks out = **Hypocalcemia** and **hypomagnesemia**
- When the drug is eliminated, it is exchanged with uric acid and glucose → **hyperuricemia + hyperglycemia**
  - = ***Negative metabolic profile***
- **Ototoxicity (dose dependent, reversible, aminoglycoside ATB)**
  - Due to increased penetration of loop diuretics into the fluid of inner ear
  - A very typical side effect of loop diuretics
- **Dehydration**

→ **Distal tubule diuretics (thiazides + sulfonamides)**

- **Sodium and chloride co-transport** from urine back to blood is **inhibited** → water follows
  - = decreased preload, ↓ cardiac output and ↓ blood pressure
- **Compensatory mechanisms**:
  - Inhibition of Na/Cl cotransporter leads to ↓ Na inside tubular cells → compensation: Na into cell from blood and more calcium into the blood in exchange through the Na/Ca antiporter → hyponatremia + **hypercalcemia** (side effects)
  - Hyponatremia → exchange of Na and proton or potassium = **metabolic alkalosis/hypokalemia**
- **Ion disbalance**
  - **Hyponatremia, Hypokalemia, Hypercalcemia** (in contrast to loops!)
- **Hyperuricemia, Hyperglycemia, Hyperlipidemia, Allergic reaction**
- When the drug is eliminated, it is exchanged with uric acid and glucose → **hyperuricemia + hyperglycemia**
  - = ***Negative metabolic profile***

→ **Potassium sparing diuretics**

- **Hyperkalemia**
- **Metabolic acidosis**

Side effects of ACE-inhibitors and antagonists of angiotensin receptor type 1

→ **ACE inhibitors**

- Due to bradykinin accumulation: dry cough + angioedema
- Hypotension after first dose + hypokalemia

→ **Antagonists of angiotensin receptor type 1 (sartans)**

- Without effects on bradykinin → no dry cough, no angioedema
- Hypotension + hyperkalemia

Metabolic effects of antihypertensives

- **Metabolic negative effects:**
  - **β-blockers, diuretics**
    - **Thiazides** can be **combined with all classes** of basic antihypertensives, **except for beta blockers**
    - The combination between beta blockers and thiazides is less suitable due to synergic negative metabolic impact
- **Metabolic neutral:**
  - **Calcium channel blockers**
- **Metabolic positive effects:**
  - **ACE-I and ARB, I_2 receptor agonists**

12. Treatment of angina pectoris (21)

Angina pectoris is the medical term for **chest pain** due to **coronary heart disease**.
It occurs when the heart muscle doesn't get as much blood as it needs.
This usually happens because one or more of the heart's arteries is narrowed or blocked, also called **ischemia**

Clinical signs of angina pectoris

- The typical symptom of angina pectoris is **adstingent pain behind the breastbone** (stenocardia)
  - The discomfort caused by myocardial ischemia is usually located in the chest, near the sternum
  - The duration of the discomfort is brief, can last for several minutes or less
- An important characteristic is the relationship to exercise
  - Symptoms classically appear to become more severe with increased level of excretion

Angina pectoris

- **Stable angina** (or typical, or exertional, or classical)
  - Angina induced by effort and relieved by rest → manifested during exercise
  - Atherosclerotic plaque hasn't ruptured
- **Unstable angina**
  - Occurs during minimal effort or at rest
  - Atherosclerotic plaque hasn't ruptured
- **Prinzmetal's angina** (or vasospastic, or variant angina)
  - This occurs without provocation, usually at rest as a result of coronary artery spasm
- **Microvascular** – spams in the walls of very small coronary arterial blood vessels

Treatment

- **1. Nonpharmacological (lifestyle changes)**
  - Smoking cessation, healthy diet, physical activity, maintain healthy weight
- **2. Pharmacological**
- **3. Surgical –** PTCA (percutaneous transluminal coronary angioplasty), coronary by-pass

Pharmacotherapy of angina pectoris

- In angina pectoris there is an *imbalance of oxygen requirement and oxygen supply to the heart*
- Goal of treatment: to **decrease the oxygen requirement of heart** decrease heart work) and to **increase the oxygen supply**
- → We combine drugs with **direct cardiac effect** with **vasodilatory substances**
  - Drugs with **direct cardiac effects** *reduce the cardiac output*, → ↓ cardiac work
    - → ↓ ***reduce the oxygen requirements of the heart***
    - Examples: Beta blockers, ivabradine, calcium channel blockers (non-dihydropyridines)
  - Drugs with **vasodilatory properties** → *Reducing peripheral* and *coronary vascular resistance*
    - → ↑ ***blood flow*** (↑ oxygen supply to heart)
    - Examples: Nitrates, calcium channel blockers (dihydropyridines), vasodilatory beta blockers (nebivolol, carvedilol)
- Initial drug therapy, usually, consists of one anginal drug from the first-line therapy + drugs for secondary prevention of cardiovascular diseases
  - **Beta blockers/calcium channel blockers** are recommended as first-choice (with secondary prevention)
- More serious states are treated with combination of drugs from first-line therapy + some drugs from the second-line therapy
- **Nitrates are recommended as first-line therapy for acute attack**
  - Otherwise, they only administered if calcium channel blockers or beta blockers are contraindicated or not working
- **Nitrates for long-term are second-line drugs**

First line therapy
- **Calcium channel blockers**
- **Beta blockers**
- **Nitrates (for acute attack)**

Second line therapy
- **Bradines (ivabradine)**
- **Nicorandil, ranolazine, trimetazidine**
- **Nitrates (for long-term treatment)**

13. Nitroglycerine (13)

Intro = topic 11

Nitrates:

- Nitrates are the oldest group of vasodilatory drugs, nitroglycerin is the prototype of this group
- These drugs are used to relieve both stable and vasospastic angina
- Generally divided into 2 generations
  - → 1st generation (**nitroglycerine** + ISDN), 2nd generation (ISMN + Molsidomine)

Mechanism of action:

- Nitrates form **nitric oxide** in the endothelium
  - Nitric oxide diffuses from the endothelium into smooth muscles and enters the cells
  - Nitric oxide activates the ***Guanylyl cyclase***, which increases the formation of **cyclic GMP** (cGMP)
- In smooth muscles, cGMP stimulates ***protein kinase G*** activity which activates ***myosin-light chain phosphatase***
  - This causes dephosphorylation of myosin-light chain and causes the **relaxation of the smooth muscle**
- In short: release of nitric oxide → cGMP formation → dephosphorylation of myosin-light chain kinase → inhibition of contraction → relaxation

Effects of nitrates

- Nitrates generally cause dilatation of peripheral and coronary arteries but ***mostly in peripheral veins***
  - (Due to venodilation, orthostatic hypotension is the most common side effect of nitrates)
  - **↓ Venous return to the heart** (venodilation → ↓ preload) = main effect!!
    - = **↓ heart oxygen requirement**
- Moderate arteriolar dilation → very moderately ↓ afterload (by very low degree)
- Relaxation of smooth muscle of the coronary arteries, relieve the vasospasm

Complications in therapy

a. ↓ Bioavailability

- We prefer **sublingual**, **buccal** and **transdermal patches** in therapy due to low bioavailability of nitrates
  - After peroral administration nitrates are hydrolyzed by nitrate reductase
    - → 70% of the drug is destroyed after p.o. administration
- Therefore, administration of ***transdermal patches*** *for* ***long-term therapy*** is preferred
- And ***sublingual*** *and* ***buccal*** *forms are preferred for* ***acute treatment***

b. Tolerance (critical step)

- After administration of nitrates, first **nitrate anions** are created, which then have to be converted to nitric oxide by the enzyme *nitrate reductase* → this enzyme contains ***sulfhydryl groups***
  - Depletion of sulfhydryl groups (inactivity of this enzyme) in the body after nitrate administration causes loss of effectiveness of nitrates (tolerance)
- Nitrate tolerance is a major problem with their long-term use
  - Solution to this problem is to discontinue nitrate administration minimally for 8 hours
    - = (**nitrate-free period**) → Avoid evening dose or remove transdermal patch from skin for 8 hours

Nitrate indications

- **Angina pectoris**
  - **Short-acting nitrates** are the **drug of choice to relieve** **acute attack** (sublingual tbl. or buccal spray)
  - **Long-acting nitrates** are used for **angina prophylaxis** before physical activity (transdermal patch)
- **Cyanide poisoning**
- **Myocardial infarction** (reducing size of infarct)
- **Hypertensive crisis**

Nitrates side effects/contraindications

- Most common side effect = **orthostatic hypotension** → Due to **venodilation** (increased venous capacity)
  - Typical symptoms of orthostatic hypotension: Headache, flushing, dizziness…
  - Orthostatic hypotension → reflex tachycardia → worsening of perfusion
- **Methemoglobinemia** (Less typical and less frequent)
  - **Only high doses**
  - **Nitrates react with hemoglobin and cause tissue hypoxia**
  - **Treatment – methylene blue (i.v.)**

Nitrates – important interactions

- **Combination with PDE 5 inhibitors (sildenafil, tadalafil, vardenafil)** → erectile dysfunction medication
  - **Severe hypotension**
- **Nitrates are contraindicated if taken PDE 5 inhibitor within the previous 24 hours**

- Erectile dysfunction is a frequently encountered problem whose risk factors are parallel to those of coronary artery disease
  - Those many men desiring therapy for erectile dysfunction may also already be receiving anti-anginal therapy
  - The combination of *sildenafil* and other phosphodiesterase 5 inhibitors (*tadalafil* and *vardenafil*) with organic nitrates (vasodilators) can cause **extreme severe hypotension**
  - Due to this, nitrates are contraindicated for patients who have taken phosphodiesterase 5 inhibitors within the previous 24 hours

Cyanide poisoning

- Nitrates can be used for a very specific indication – the treatment of cyanide poisoning
- Cyanide poisoning must be seriously considered in victims of smoke inhalation from enclosed space fires and cyanide is also used in terrorism
- The treatment of cyanide poisoning is based on administration of antidote
  - Hydroxocobalamin is currently the drug of choice
- But nitrate administration is very a cheap, quick and elegant way how to treat cyanide poisoning
  - It is a double step treatment:
    - 1. The first step is administration of sodium nitrate or amylnitrite,
      - From this dose develops methemoglobinemia, approx. 30-40%
    - 2. Immediately after methemoglobinemia appears, the second step is intravenous application of sodium thiosulphate (S2O3)
- The treatment is based on the gradual chemical reactions in the body
- Nitrate anions, which are formed in the body after nitrate administration have higher affinity for hemoglobin – producing methemoglobin (and methemoglobinemia)
- Methemoglobin binds to cyanide anions and produce the **cyano-methemoglobin**
  - So, cyano-methemoglobin is formed in the body
- The next step is intravenous administration of thiosulphate (S2O3)
  - Which reacts with cyano-methemoglobin forming **thiocyanide anion** (SCN^-) which is not dangerous in the body and is excreted by the kidneys
- So, a very quick and very cheap way of treating cyanide poisoning is administration of nitrates

Nitrates and treatment of cyanide poisoning

- **1. Step – Nitrates**
  - **Amylnitrite (1 amp. 0,2 ml 30-60 s)**
  - **Sodium nitrite (300 mg i.v. 15-20 min)**
  - **!!! Methemoglobinemia 35-40%**
- **2. Step – administration of S_2O_3**

14. Peripheral vasodilators (61)

Into - General:

- Peripheral vasodilators are used in ***peripheral arterial diseases*** + ***intermittent claudication***
- Aim is to dilate/open arteries in order to improve circulation

Intro – Peripheral Arterial disease

- *Narrowing or occlusion of peripheral arteries causing ↓ blood flow*
- Etiology:
  1. **Medium + small vessel:**
     - DM, Chronic recurrent trauma, multiple small emboli, collagen vascular disease, drug reaction, vasospasm
  2. **Large arteries:**
     - Atherosclerosis, thromboembolism, trauma, arteritis
- Clinical features:
  - Intermittent claudication, absent/diminished pulses, tissue changes (e.g., hair loss), rest pain, Ischemia

Peripheral vasodilation:

- Peripheral vasodilators are mixture of drugs with different mechanism of action (relax vessels in different way)

Drugs:

- Alpha receptors have dominant mechanism of control in vascular smooth mm.

1. **Nonselective α blocker** (***Tolazoline***)
   - α1 action → direct ⊖ of vasocontraction in vessels (↑ cAMP)
   - α2 action → ⊖ α2 receptors in presynaptic neurons → ↓ NE release → centrally mediated vasodilation
2. **Calcium channel blocker:** (***cinnarizine + flunarizine***)
   - ***Dihydropyridines*** have higher vasodilatory effect than non-DHP
   - Less Calcium in the cell → less vascular smooth mm. contraction
3. **Analogs of prostaglandins:** (***alprostadil***)
   - They work directly on vessels smooth mm. (↓ cAMP)
4. **PDE 3 inhibitors:** (***Cilostazol***)
   - ⊖ cAMP degradation → ↑ cAMP → vasodilation
     - We ↑ cAMP in vessels → ↓ available adenosine → ↓ ATP formation in vessels → vasodilation
     - = Indirect vasodilation
   - Cilostazol also inhibits thrombocyte activation and aggregation
     - In platelets → ↑ cAMP → ↓ aggregation of platelets
     - So, it has very good anti-thrombotic effect
   - And it is able to control lipoprotein lipase activity
     - Reduces triglyceride synthesis and increases the concentration of high-density lipoproteins (HDL)
5. **Drugs that are donors of NO**
   - ↑ cGMP → Vasodilation

- Drugs with ***triple effect*** is said to be good against PAD
  - Then we use drug with 3 different effects → improve RBC deformability, vasodilation, antithrombotic
  - Drug:
    a) *Pentoxiphylline* → PDE inhibitor
    b) *Iloprost* → Prostaglandin analogue (additional anti-inflammatory effect)
    c) *Naftidrofuryl* → 5-HT_2 antagonist

Side effects:

→ In general, for peripheral vasodilators:

- Peripheral vasodilators, due to very strong vasodilation cause:

1 Sweating, redness of face, flushing
2 Headache
3 Hypotension, Edema, reflex tachycardia
4 Steal phenomenon
   - Steal phenomenon is the phenomenon where there is alteration of circulation pattern leads to reduction in the blood flow
   - It is caused when there is narrowing, atherosclerotic obstruction and a vasodilator is used
     - This vasodilation steals the blood away from the ischemic part of the vessel to the healthy part – improving the ischemia
       - The ischemic region of the vessels has impaired regulation and is unable to respond to the effect of vasodilators
     - This phenomenon is very rare

15. Treatment of chronic heart failure (29)

Intro:

- Heart failure = inability of the heart to act as a pump to maintain adequate tissue perfusion
- Newer definitions also include the molecular and ***neurohumoral role*** in heart failure
  - → The addition of RAAS and activation of sympathetic nervous system
- **Causes:**
  - Coronary artery disease, hypertension, myocardial ischemia, arrhythmias, chronic alcohol abuse….
- **Typical symptoms:**
  - Breathlessness, orthopnea, paroxysmal dyspnea, nocturnal cough, peripheral edema, ankle swelling, tachycardia, ascites, reduced exercise tolerance, confusions…

Classification:

Acute/chronic:

- **Acute heart failure:** (or acute decompensation of chronic heart failure)
  - Treatment is to **increase contractility** + **support and maintain organ perfusion**
  - Drug of choice: ***Positive ionotropic substances***
- **Chronic heart failure**:
  - *Reduced cardiac output* → causes *chronic overstimulation of sympathetic nervous system and RAAS*
  - Thus, in chronic heart failure, in addition to increase the contractility, the aim of the treatment is to *inhibit sympaticus and RAAS*
  - Drug of choice: ***ACE inhibitors***

Systolic/diastolic (according to ejection fraction – *EF = amount of blood ejected from heart in each contraction*)

- **1. Systolic heart failure:** (ejection fraction lower than 40%)
  - **Reduced ejection fraction**
  - ↓ mechanical pumping action = reduced contractility → reduced cardiac output → overstimulation of neurohumoral system (RAAS + sympaticus)
  - Can be caused by changes in myocytes or changes in geometry of ventricles
- **2. Diastolic heart failure:** (ejection fraction higher than 50%)
  - **Preserved ejection fraction**
  - Also leads to reduced cardiac output → overstimulation of neurohumoral system *(RAAS + sympaticus)*
  - Caused by stiffening of ventricles → loss of the ability to relax *(decreased elasticity – more frequent in elderly)*

Pharmacotherapy of chronic heart failure with reduced ejection fraction (systolic)

1. Reduction of neurohormonal changes:

- Drug of choice for systolic heart failure = **ACE inhibitors**
- Also, **ARBs (sartans)**, **beta blockers**, **mineralocorticoid receptor blockers (MRA)**, **ARNI**

2. Reduction of symptoms:

- **Diuretics**
- **Ivabradine**

3. Increased inotropy

- **Cardioglycosides**
- **Beta1 agonists**, **PDE3 inhibitors**, **calcium sensitizers**

- **Contraindications**
  - **Renin inhibitor (aliskiren)**
  - ***Calcium channel blockers*** (cause worsening of edema)

- **First line therapy:**
  - **ACE-I**
  - **Beta blockers**
  - **MRA**, **diuretics**
- **Second line therapy:**
  - **ARB**
  - **ARNI**
  - **Ivabradine**
  - **Aquaretics (Increase ADH with hyponatremia)**
  - **Cardioglycosides**

Steps in therapy:

- 1. Therapy is started with **ACE inhibitors** + **beta blockers**
- 2. If symptoms persist → add **mineralocorticoid antagonist**
- 3. If symptoms persist → **ARNI** can replace ACE-I (or ARBs) and **ivabradine** can be added if heart rate is over 70 bpm
- → **Diuretics** are used to relieve symptoms and signs of congestion

Pharmacotherapy of chronic heart failure with preserved ejection fraction (diastolic)

- Diastolic heart failure is the problem with relaxation of the myocardium (stiffening of chambers)
- The therapy is relatively the same, only we have to exclude the cardioglycosides and other drugs which stimulate the contractility
  - They are counterproductive in the case of diastolic heart failure
- **First line therapy:**
  - **Beta blockers**, **ACE-I**, **angiotensin receptor blockers**, and **calcium channel blockers** (only **verapamil**)

Classification according to way of administration
- **Peroral:**
  - **Cardioglycosides**
- **Parenteral:**
  - Beta adrenergic agonists (dopamine, dobutamine, NE)
  - Phosphodiesterase (PDE) 3 inhibitors
  - Calcium sensitizer

16. Positive inotropic drugs (9)

Intro:
- Heart failure = inability of the heart to act as a pump to maintain adequate tissue perfusion
- Newer definitions also include the molecular and neurohumoral role in heart failure
  - → The addition of RAAS and activation of sympathetic nervous system

Classification:
Acute/chronic:
- **Acute heart failure:** (or acute compensation of chronic heart failure)
  - Treatment is to **increase contractility** + **support and maintain organ perfusion**
  - Drug of choice: ***Positive ionotropic substances***
- **Chronic heart failure**:
  - *Reduced cardiac output* → causes *chronic overstimulation of sympathetic nervous system and RAAS*
  - Thus, in chronic heart failure, in addition to increase the contractility, the aim of the treatment is to *inhibit sympaticus and RAAS*
  - Drug of choice: ***ACE inhibitors***

Systolic/diastolic (according to ejection fraction – *EF = amount of blood ejected from heart in each contraction*)
- **1. Systolic heart failure:** (ejection fraction lower than 40%)
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  - ↓ mechanical pumping action = reduced contractility → reduced cardiac output → overstimulation of neurohumoral system (RAAS + sympaticus)
  - Can be caused by changes in myocytes or changes in geometry of ventricles
- **2. Diastolic heart failure:** (ejection fraction higher than 50%)
  - **Preserved ejection fraction**
  - Also leads to reduced cardiac output → overstimulation of neurohumoral system *(RAAS + sympaticus)*
  - Caused by stiffening of ventricles → loss of the ability to relax *(decreased elasticity – more frequent in elderly)*

Intro:
- Positive inotropic agents **increase the contractility → ↑ cardiac output** and **↑ the perfusion of organs**
- They are used to treat patients with **acute decompensated systolic heart failure**
  - (Also used as 2nd line drugs in treatment of chronic systolic heart failure)

Classification according to way of administration
- **Peroral:**
  - *Cardioglycosides*
- **Parenteral:**
  - *Beta adrenergic agonists (dopamine, dobutamine, NE)*
  - *Phosphodiesterase (PDE) 3 inhibitors*
  - *Calcium sensitizer*

Mechanism of action of how to stimulate contraction:
- **A. Cardioglycosides:** (peroral)
  - **Inhibit the sodium-potassium pumps = ↑ Sodium inside the cell → rise in sodium inhibits the function of Na^+/Ca^{2+} exchanger → rise in intracellular calcium = *increased contraction***
- **A. Beta1 agonist:** (parenteral) – ***dopamine***, ***dobutamine***, ***norepinephrine***
  - **Stimulate the formation of cAMP → stimulates the activity of protein kinase A → ↑ influx of Calcium into cardiomyocytes = ↑ contractility**!
  - ***Stimulates the release of Ca from sarcoplasmic reticulum*** (by stimulation of Ryanodine receptor)
  - ↓ reabsorption of Calcium in sarcoplasmic reticulum
- **B. Phosphodiesterase 3 inhibitors:** (parenteral)
  - **Inhibits cAMP degradation → ↑ cAMP → ↑ influx of Calcium into cardiomyocytes**
- **C. Calcium sensitizer – *Levosimendan*** (parenteral)
  - **Binds to troponin C → prolongs binding of Calcium to Troponin C → prolongs systolic actin-myosin interactions**
  - Only positive ionotropic drug that does not ↑ intracellular Calcium

Classification according to way of administration

- **Peroral:**
  - Cardioglycosides
- **Parenteral:**
  - Beta adrenergic agonists (dopamine, dobutamine, NE)
  - Phosphodiesterase (PDE) 3 inhibitors
  - Calcium sensitizer

17. Digoxin, digitoxin (42)

Intro:

- Positive inotropic agents **increase the contractility** → **↑ cardiac output** and **↑ the perfusion of organs**
- They are used to treat patients with **acute decompensated systolic (reduced ejection fraction) heart failure** (also used as 2nd line drugs in treatment of chronic systolic heart failure)

Cardioglycosides – also called *cardiotonics*

- These are natural products derived from plants (digitalis purpura and digitalis lanata
- Prototype of cardioglycosides = digoxin

Mechanism of action

1. Positive inotropic effects (contraction)

- Cardioglycosides ***inhibit the sodium-potassium pumps*** = ***↑ Sodium inside the cell → rise in sodium inhibits the function of Na^+/Ca^{2+} exchanger → rise in intracellular calcium → increased contraction***
  - Rise in intracellular sodium levels inhibits the function of sodium-calcium exchanger (NCX), which is responsible for *pumping calcium ions out* and *sodium in*
  - Results of inhibiting NCW will be ***increased levels in intracellular calcium*** → increasing the force of contraction **(=↑inotropy)**

2. Negative dromotropic effects (conduction) + **negative chronotropic effects** (heart rate)

- Cardioglycosides increases the contractility (inotropy) without influencing other functions of the myocardium, without influencing conductivity and frequency of contraction
  - So, **negative chronotropic** (heart rate) and **dromotropic** (conductivity) effects

3. Very mild diuretic effects (clinically non-significant)

Indications for cardioglycosides

→ Chronic systolic (reduced ejection fraction) heart failure

- Digoxin can be used when patient is ***in sinus rhythm*** with ***symptomatic reduced ejection fraction***
  - → Digoxin reduces the symptoms and hospitalization → **without improving survival**
- It is indicated in severe forms of heart failure, as a last step of the therapy in combination with other treatment to improve symptoms of HF
- Can NOT be used in diastolic heart failure or acute myocardial infarction related heart failure

Complications of cardioglycosides

- Cardioglycosides have a narrow therapeutic index → plasma concentration has to be monitored!
- Chronic renal failure decreases the volume of distribution of digoxin and therefore, requires a decrease in the maintenance dose of the drug

Interactions

- Avoid the combination of cardioglycosides with diuretics → imbalance in ions → toxicity

Side effects

- **1. GIT** (common) → anorexia, abdominal pain, vomiting, diarrhea
- **2. CNS disturbances** (vision disturbances, alteration of color perception…)
- **3. Cardiac →** sinus bradycardia, arrhythmias, AV blockade, fibrillation
- **4. Ion abnormalities**
  - Chronic toxicity → hypokalemia + hypomagnesemia
  - Acute toxicity → hyperkalemia

Drugs

- ***Digoxin, Digitoxin***
- ***Digoxin*** is preferred → has quicker onset of action, lower therapeutic plasma concentration, lower protein binding (less capacity to produce interaction)
  - Bad thing about *Digoxin* → narrower therapeutic index
    - Meaning dose higher than 2ng/L can be toxic

18. Symptoms and therapy of cardioglycoside poisoning (28)

Intro = Topic 17

Symptoms of intoxication:

- **1. GIT** (common) → anorexia, abdominal pain, vomiting, diarrhea
- **2. CNS disturbances** (vision disturbances, alteration of color perception…)
- **3. Cardiac** → sinus bradycardia, arrhythmias, AV blockade, fibrillation
- **4. Ion abnormalities**
  - Chronic toxicity → hypokalemia + hypomagnesemia
  - Acute toxicity → hyperkalemia
- Laboratory abnormalities are very important characteristics of intoxication
  - However, many controlled studies have shown that hyperkalemia is typical for acute phase of poisoning, which is more common (and a prediction of poor prognosis)
    - If hyperkalemia occurs during acute poisoning with cardioglycosides, antidote (digoxin specific antibodies = digibind) has to be administered immediately
  - Hypokalemia is more typical for chronic toxicity
  - And hypomagnesemia for both (acute and chronic)

Therapy of intoxication with cardioglycosides

- **Stop administration**
- **Laboratory investigation**
  - **Monitor plasma drug concentration**
  - **Monitor electrolyte concentration (especially potassium)**
- **Decontamination and elimination**
  - Up to 1 hour after administration → **Active charcoal** **(1g/kg)** binds to the surface of cardioglycosides and prevents the absorption trough GIT
- **Therapy:**
  - **Bradycardia – managed by atropine administration**
  - **Treatment of hyperkalemia – managed by insulin administration covered with glucose, inhalation with salbutamol or some diuretic therapy**
  - **Hypomagnesemia is managed with magnesium supplements**

- **Administration of Specific antidote**
  - **Digibind IgG antidigoxin**
  - **Selective antidote**
  - **Pork Fab fragments - digoxin antibodies**
  - **Onset of action – 1 hour**
  - **40 mg digibind binds 0,6 mg of digoxin**

- Severe complications of digoxin poisoning have to be treated with administration of specific antidote
  - = Digibind IgG antidigoxin antibodies (DifiFab)
  - They are fab fragments of specific digoxin antibodies
  - They are prepared with immunization of digoxin albumin complexes which produce specific antibodies
- Onset of action is 1 hours
- The rule is: 40 mg Digibind (the antibodies) binds approx. 0,6 mg of digoxin

Classification according to way of administration

- **Peroral:**
  - Cardioglycosides
- **Parenteral:**
  - **Beta1-adrenergic agonists (dopamine, dobutamine, NE)**
  - **Phosphodiesterase (PDE) 3 inhibitors**
  - **Calcium sensitizer (Levosimendan)**

19. Positive inotropic drugs: non-glycosides (12)

Intro:

- Positive inotropic agents **increase the contractility** → **↑ cardiac output** and **↑ the perfusion of organs**
- They are used to treat patients with **acute decompensated systolic (reduced ejection fraction) heart failure** (also used as 2nd line drugs in treatment of chronic systolic heart failure)

Parenteral positive inotropic drugs (non-glycosides)

- Parenteral forms are recommended for
  - **Acute heart failure**
  - Or **severe acute decompensation of chronic heart failure**

A. Beta1 adrenergic agonists

- **Mechanism of action**
  - Stimulate the formation of **cAMP** → stimulates the activity of protein kinase A → **↑ influx of calcium into cardiomyocytes**
  - Stimulate the release of calcium from sarcoplasmic reticulum (through ***ryanodine receptor***)
  - Decreased reabsorption of calcium in sarcoplasmic reticulum
- **Drugs:**
  - **1. Dopamine**
    - Inotropic and chronotropic effect (intermediate dose)
    - In high doses → alpha receptor mediated vasoconstriction → **increased afterload** (→ a bad thing)
  - **2. Dobutamine**
    - β1 and β2 agonistic properties which help improve myocardial contractility
    - Used in patient with **cardiogenic shock** due to decompensated heart failure → dobutamine decreases left ventricular end-diastolic pressure → raises blood pressure by increasing the cardiac output
  - **3. Norepinephrine**
    - Used in case patients has heart failure which is causing **hypotension**
    - Increases cardiac chronotropic and inotropic response along with peripheral vasoconstriction

B. Phosphodiesterase (PDE) 3 inhibitors

- **Mechanism of action**
  - Inhibits cAMP degradation → ↑ cAMP → influx of calcium into cardiomyocytes = increased cardiac contractility
- **Indications:**
  - Only given intravenously for short-term management of acute heart failure
- **Side effects:**
  - PDE3 are dominantly localized in myocardium and vessels → due to their localization in vessels, dominant side effects are → **Vasodilation**, **hypotension**, **reflex tachycardia**
- **Drugs: Milrinone, enoximone**

C. Calcium sensitizer – Levosimendan

- Levosimendan ***increases the sensitivity of cardiomyocytes to calcium***
- **Mechanism of action**
  - Binds to troponin C → prolongs binding of calcium to troponin C → prolongs systolic actin-myosin interactions = increases contraction of cardiomyocytes
  - No increase in intracellular calcium (in contrast to previous agents)
  - So, increased contractility without worsening calcium metabolism and increased O2 demands
- **Indication**: Intravenous treatment for acute decompensation of chronic heart failure
- **Side effects**: Hypotension and consequences of that → headache and reflex tachycardia

20. Drugs for the treatment of myocardial infarction (32)

- Myocardial infarction occurs when blood flow decreases or stops to a part of the heart, causing damage to the heart muscle
- Most commonly due to occlusion (blockage) of a coronary artery following the rupture of a vulnerable atherosclerotic plaque, which is an unstable collection of cholesterol and fatty acids and WBCs in the wall of an artery.
- It results in ischemia (restriction in blood supply) and ensuring oxygen shortage, if left untreated for a sufficient period of time, it can cause damage or death (infarction) of heart muscle tissue.

Symptoms

- Chest pain (angina pectoris) radiating to jaw, left arm or left side of neck
- Dyspnea
- Nausea
- Vomiting
- Palpitations
- Sweating
- Anxiety
- Silent: without symptoms (DM-patients)

Myocardial infarction – Treatment:

Goal of therapy

- To ***increase the oxygen supply to the heart***, reperfusion
- ***Decrease ischemic pain***
- Treatment of life-threatening conditions such as hypotension, lung edemas and arrhythmias.

Drugs used to treat

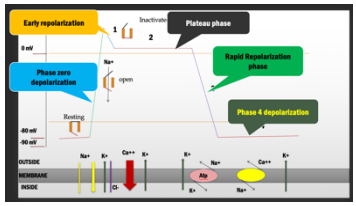
- M: Morphine → Pain, ↓ anxiety, ↑ vasodilation
- O: Oxygen → ↓ dyspnea
- N: Nitroglycerine → angina pectoris (↓ chest pain) by ↑ vasodilation
- A: Aspirin → ↓ platelet aggregation
- T: Thrombolytics → dissolve thrombus
- A: Anticoagulants
- S: Stool softeners
- S: Sedatives (diazepam)
- **+ Reduction of infarct area** → beta blockers, ACE-I

Drugs for prevention of MI

→ Indication: in patients after MI, or who have had it before, patients with MI or IHD in family, patients with angina pectoris

- **Antiplatelet drugs**: Aspirin, Clopidogrel – to reduce rupture of plaque and recurrent MI
- **Beta blockers**: Metoprolol or Carvedilol – beneficial in high-risk patients such as those with left ventricular dysfunction. They also improve cardiac ischemia in NSTEMI
- **ACE-I**: 24-48 hrs. as post-MI therapy in hemodynamically stable patients. Especially if history of MI, DM, HT
- **Aldosterone antagonist**: Eplerenone - reduce risk of cardiovascular death post MI patients with heart failure

Other types of prevention of recurrent MI
Smoking cessation, exercise, diet, decrease alcohol intake



Intro into antiarrhythmics

Action potential in cardiomyocytes (non-automatic) vs. pacemaker cells (automatic)

AP of cardiomyocytes (Sodium dependent)

- Action potential of **cardiomyocytes** has 5 phases:

Phase 4 (= resting phase)

- The myocytes membrane slowly depolarizes, caused by the leakage of calcium ions through gap junctions (= openings through 2 neighboring cells) → this makes the membrane depolarize to its threshold potential
- This marks the start of phase 0

Phase 0 (= depolarization phase)

- Voltage-gated sodium channels open up when they reach threshold potential
- They allow sodium to rush into the cell → this rapid influx of sodium causes the cardiomyocyte's membrane potential to become more positive
- After the membrane has depolarized, we enter phase 1

Phase 1 (= initial repolarization)

- At this point, sodium channels close, and voltage-gated potassium channels open up, allowing positive changed potassium ions to leave the cell (↓K^+ inside the cell = ↓ membrane potential)
- This creates a small fall in the membrane potential

Phase 2 (= plateau phase)

- When voltage-gated calcium channels open up → ↑ calcium into the cell
- This counterbalances the ↓ K^+ → so membrane potential remains stable

Phase 3 (= repolarization phase)

- Calcium channel close, but potassium channels remain open (↓ K^+ = ↓ membrane potential)
- At the same time, ion pumps start to pump calcium ions back out of the cell = causes the heart to relax
- And eventually, the myocyte returns to the resting membrane potential → phase 4 again

AP of pacemaker cells (Calcium dependent)

- Action potential in **pacemaker cells** has 3 phases:

Phase 4 (= pacemaker potential)

- Starts with the opening of pacemaker cannels → the current through these channels is called pacemaker current or "funny current (If)"
- The funny current mainly consists of sodium ions → these sodium ions cause the membrane potential to begin to spontaneously depolarize
- As the membrane potential depolarizes – voltage-dependent T-type calcium channels open up
  - Thereby, further depolarizing the pacemaker cell
- As calcium enters the cell, voltage-dependent L-type calcium channels open up, causing even more calcium to rush into the cell, ultimately depolarizing the membrane to its threshold potential
- This marks the start of phase 0

Phase 0 (= depolarization phase)

- Phase 0 is caused by an influx of calcium through L-type **calcium channels** which started to open during phase 4
- This influx of calcium isn't so rapid – so the slope of phase 0 is gradual
- Also, during phase 0, the pacemaker channels and T-type calcium channels close

Phase 3 (= repolarization phase)

- During phase 3, L-type calcium channels close and potassium channels open up
- This results in a net outward positive current

At the end of repolarization, pacemaker channels open up again, and we start over with phase 4

- During phase 4 there is also an outward movement of potassium ions, as the potassium channels responsible for repolarization phase continue to close

Phase 4 (pacemaker potential) → funny channels (Na influx) → T-type calcium channels open → Ca influx
Phase 0 (depolarization phase) → L-type calcium channels open → Ca influx
Phase 3 (repolarization phase) → L-type calcium channel close, potassium efflux

SA node is the pacemaker because it has the fastest phase 4

Classification of arrhytmia

- **According to location:**
  - **Supraventricular**
    - → sinus (SA) arrhytmia, atrial (AV) arrhytmia, nodal arrhytmia
  - **Ventricular arrhytmia**
    - → Originates below the AV node
- **According to heart rate:**
  - **Bradyarrhythmia** → Arrhytmia with < 60 bpm
    - (e.g., AV block)
  - **Tachyarrhythmia** → Arrhytmia with > 1000 bpm
    - (e.g., atrial flutter)

21. Antiarrhythmics class I (46)

Cardiac arrhythmias – general

- Normal heart rhythm = HR: 60-100 bpm – Originates from SA node
  - = ***Cardiac impulses propagate through normal conduction pathway at normal velocity***
    - SA → AV → bundle of His → purkinje fibers
- **Arrhytmia** = any deviation from the normal heart rhythm

Mechanism of Cardiac Arrhythmia:

1 **Abnormal Impulse Generation:**
- ➢ There can be ↑/↓ automaticity of pacemaker or ectopic pacemaker
- ➢ Also, can be triggered activity after-depolarization
  - **Early after-depolarization** → Phase 3 repolarization is interrupted (due to ⊖ of delayed K current)
  - **Late after-depolarization** → Phase 4 is interrupted (generally due to Ca overload → ↑ Na activity)

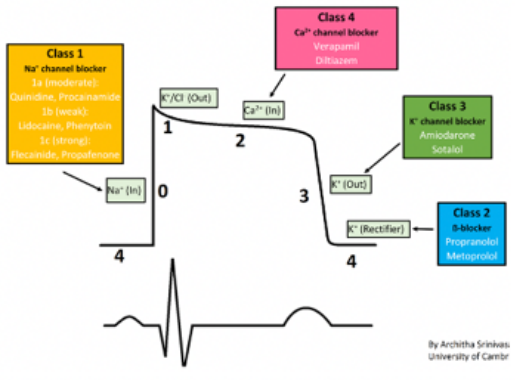
2 **Abnormal Impulse Conduction:**
- ➢ Conduction block (e.g., AV block), re-entry phenomenon, accessory tract pathway

Antiarrhythmics – intro

- Antiarrhythmics act in order to normalize the sinus rhythm
- They can act on different targets:
- **1. Ion channels** (= The main targets of antiarrhythmics)
  - *Normal non-automatic cardiomyocytes = Na^+ driven tissue*
    - → **Sodium channel blockers** (class 1)
  - *Pacemaker cells* (SA, AV, bundle of his, purkinje) = *Ca^{2+} driven tissue*
    - → **Calcium channel blockers** (class 4) + **beta blockers** (class2)
- **2. Regulation of autonomic nervous system**
  - **Parasympathetic (vagus nerve stimulation):**
    - **Acetylcholine** binds to **M2 receptor → opening of K^+ channels → K^+ out → hyperpolarization**
  - **Sympathetic:**
    - **Activation of β1 receptors → opening of Ca^{2+} → ↓ intracellular Ca^{2+}**
- **3. Other inotropic receptors**
  - E.g., purinergic receptors

Classification of antiarrhythmic drugs: (from 1970)

- **Class I: Blockers of Na^+ channels**
  - **Ia (Quinidine, Procainamide, Disopyramide)**
  - **Ib (Lidocaine)**
  - **Ic (Propafenone, Flecainide)**
- **Class II: β-blockers**
  - **(Propranolol, Esmolol, Pindolol, Metoprolol)**
- **Class III: Blockers of K^+ channels**
  - **(Amiodarone, Dronedarone, Dofetilide, Sotalol)**
- **Class IV: Ca^{+2} channel blockers**
  - **(Verapamil, Diltiazem)**
- **Class V: Other drugs**
  - **(Digoxin, Adenosine, Mg^{2+})**



Phase 0 → Rapid depolarization, Na^+ influx
Phase 1 → Short repolarization, beginning of K^+ outflow + Ca^{2+} influx
Phase 2 → Plateau phase, balance of K^+ + Ca transport
Phase 3 → Rapid repolarization, Ca^{2+} close + K^+ outflow
Phase 4 → Resting phase, normal Na/K transport

Class 1 antiarrhythmics → *Sodium channel blockers*

General mechanism of action of sodium channel blockers

- Reduce or block sodium channel activity → prolong (1a + 1c) or shorten (b) action potential duration or QRS prolongation
- Mechanism of action is **state-dependent** → the faster the heart rate = the greater the effect
- Generally, there will be a **decrease in the slope of phase 0** (does not apply to class 1b)

Sodium channel blockers are then further divided into subcategories 1a, 1b and 1c

Class 1 effects:

1 **Parasympatholytic effect** (Ia, Ic)
   - ➢ Direct Inhibitory effect on M2 receptor → ↑ sinus frequency, ↑ AV conduction velocity?,
     - ▪ So just ↑ HR

2 **Indirect Negative Inotropic effect** (Ia, Ic)
   - ➢ Less intracellular Na → Na/Ca transport will occur → less intracellular Ca
     - ▪ Less intracellular Ca for next contraction

3 **Proarrhythmogenic effect** (Ia)
   - ➢ Prolonged AP duration, prolonged effective refractory period, shorter repolarization

Effective Refractory period (ERP) = Period where new AP cannot be initiated

Antiarrhythmics – Class 1		
Ia	**Ib**	**Ic**
Effects: • Moderate **Na channel blocker** in the middle of Phase 0 + **weak K channel blocker** (Phase 3) • **Prolongs AP duration** - Prolonged depolarization + repolarization → prolonged QT interval + QRS complex - It will cause prolonged ERP → ↓ HR <u>They work on atrial, ventricular myocytes + purkinje fibers</u> **Indication:** • Supraventricular and ventricular arrythmias **Drugs:** 1. *Quinidine* - Was prototype of 1a → not used anymore 2. ***Prajmaline, Disopyramide, Procainamide*** - Has advantages in both pharmacokinetics + side effect profile **Side effects:** • QT prolongation → Torsade de pointes • Lupus erythematosus • Headache	**Effects:** • Weak Na blocker (**limited** effect on **phase 0**) + minimal K channel blocker (**little** effect on **phase 3**) • **Shorten AP duration** - No or slight prolonged ERP - No or slightly shorter QT interval <u>They work on Purkinje fiber, ventricular myocytes,</u> • **NOT atrial myocytes** - Strongest effect on **Ischemic** or depolarized purkinje cells and ventricular myocardium - *Osmosis*, more likely to bind to depolarized cells or ischemic myocardial cells **Indication:** • Ventricular arrythmias (mainly ischemic arrythmias) • Digitalis (*digoxin*) induced arrythmia **Drugs:** **1. *Lidocaine + Mexiletine*** - *Mexiletine* has no first pass mtb. (*lidocaine* has high) **Side effects:** • CNS depression (dizziness, nausea, seizures)	**Effects:** • Strong Na channel blocker → prolonged depolarization - No effect on repolarization • **No change in AP duration** - Strong prolongation in QTS complex - Prolonged ERP (only in atrias, not purkinje or ventricles) <u>They work on atrial, ventricular myocytes + purkinje fibers</u> **Indication:** • Supraventricular + ventricular arrythmias - Only used as reserved drug for ventricular arrythmias **Drugs:** **1. *Propafenone + Flecainide*** - Structurally similar to Beta blocker **Side effects:** • Because they are structurally similar to BB → Cause side effects of BB

OSMOSIS

Classification of arrhytmia

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22. Antiarrhythmics – class II and IV (35)

Cardiac arrhythmias – general

- Normal heart rhythm = HR: 60-100 bpm – Originates from SA node
  - = ***Cardiac impulses propagate through normal conduction pathway at normal velocity***
    - SA → AV → bundle of His → purkinje fibers
- **Arrhytmia** = any deviation from the normal heart rhythm

Mechanism of Cardiac Arrhythmia:

3 **Abnormal Impulse Generation:**

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- Also, can be triggered activity after-depolarization
  - **Early after-depolarization** → Phase 3 repolarization is interrupted (due to ⊖ of delayed K current)
  - **Late after-depolarization** → Phase 4 is interrupted (generally due to Ca overload → ↑ Na activity)

4 **Abnormal Impulse Conduction:**

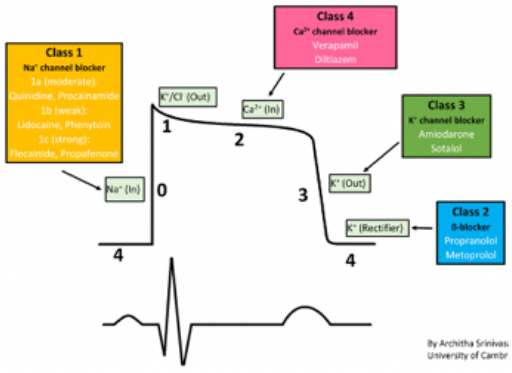
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  - **(Verapamil, Diltiazem)**
- **Class V: Other drugs**
  - **(Digoxin, Adenosine, Mg^{2+})**



Phase 4 (pacemaker potential) → funny channels (Na influx) → T-type calcium channels open → Ca influx
Phase 0 (depolarization phase) → L-type calcium channels open → Ca influx
Phase 3 (repolarization phase) → L-type calcium channel close, potassium efflux

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Phase 2 → Plateau phase, balance of K^+ + Ca transport
Phase 3 → Rapid repolarization, Ca^{2+} close + K^+ outflow
Phase 4 → Resting phase, normal Na/K transport

Class 2 (BBs) and Class 4 (CCBs) = first line therapy of arrhytmia

Class 2 antiarrhythmics – Beta blockers

Mechanism of action:

- The autonomic nervous system affects cardiovascular function via beta1 and beta2 adrenergic receptors
  - **Beta1 receptors is the predominant subtype in the heart**
    - (While beta2 receptors are primarily found in smooth muscle cells – e.g., inside blood vessels)
- Beta1 receptors are found on both pacemaker cells and cardiomyocytes
  - Once beta1 receptors are stimulated (by epinephrine or norepinephrine) → beta1 receptors activate adenylyl cyclase → ↑cAMP → opening of calcium channels → **influx of Ca**
    - In pacemaker cells – this influx happens at the end of phase 4
    - In cardiomyocytes – this influx happens during phase 2 (plateau phase)
- Beta blockers bind beta1 receptors in both pacemaker cells and cardiomyocytes
  - Thereby preventing catecholamines from binding them
- **In pacemaker cells**:
  - Beta blockers are antagonists of catecholamines on the beta receptors
  - Thereby, ↓ influx of Ca^{2+} through L-type calcium channels
    - = ↓ Ca that enters the cells at the end of phase 4
    - = Slower pacemaker potential
    - = Less steep slope during phase 4
  - → Beta blockers decrease the rate at which the SA node fires, therefore **↓ heart rate**
  - Also, they ↓ conduction velocity of the AV node (= longer PR interval)
  - The decrease in calcium ion channels → increased effects of potassium channels = increased outflow of K+ → this is responsible for the prolonged refractory period
- **In cardiomyocytes:**
  - Beta blockers prevent the opening of L-type calcium channels
  - ↓ intracellular calcium available for the muscle fibers → weaking the force of contraction
    - **= ↓ contractility** (decreased inotropy)
- By reducing the heart rate and contractility, beta blockers **reduce** the **oxygen demand of the heart**

Indications

- **Supraventricular tachycardias** (such as atrial fibrillation and atrial flutter)
- They are also used as a **prophylaxis for patients who experienced a recent myocardial infarction**

Side effects

- Cardiac
  - SA node depression → can result in sinus bradycardia, heart block and heart failure
- Extracardiac
  - Fatigue, sedition, sleep disturbances, sexual dysfunction, dyspnea and bronchospasm
  - Hypoglycemia

- Beta blockers can be divided according to their selectivity:
  - **Selective beta1 blockers:**
    - ***Esmolol*** (reserved only for acute use)
    - ***Metoprolol*** (most optimal for patients with poly-morbidity)
  - **Non-selective:**
    - ***Propranolol*** (the most lipophilic beta blocker → can cross BBB)
    - ***Pindolol***

Class 4 antiarrhythmics – calcium channel blockers

Calcium channel blockers are divided into 2 main groups:

- Dihydropyridines
  - Highly selective for calcium channels on vascular smooth muscle tissue
  - They are primarily used to treat hypertension
- **Non-dihydropyridines**
  - These are the class 4 antiarrhythmics
  - **Verapamil + diltiazem**

Mechanism of action of non-dihydropyridines

- Calcium channel blockers bind and inhibit L-type calcium channels
- They target both pacemaker cells and cardiomyocytes in the heart
- In pacemaker cells, they decrease the amount of calcium entering the cell during phase 4 and 0
  - Causing slower pacemaker potential and slower depolarization
  - By prolonging phase 4 and 0, they also prolong the effective refractory period (ERP)
    - This is the period of time, which the cell is un-excitable to new stimuli
  - This way, non-dihydropyridines reduce firing of the SA node → ↓ **heart rate**
  - But they also decrease conduction velocity through AV node = longer PR interval
- In cardiomyocytes, non-dihydropyridines decrease the amount of calcium entering the cell
  - This way, they caused ↓ Ca available inside the cells → ↓ **contractility**

Verapamil

- Highly selective for cardiac calcium channels, thus, it is primarily used to treat anginal pectoris and nodal arrhythmias (such as ***supraventricular tachycardia***)
  - Supraventricular tachycardia is type of arrhytmia caused by an impulse that originates above the heart's ventricles (paroxysmal supraventricular tachycardia, atrial fibrillation, atrial flutter)

Diltiazem

- In contrast, diltiazem blocks both cardiac and vascular calcium channels
- So, it can be used to treat hypertension in addition to supraventricular tachycardia
- Even though it is less cardio-selective than verapamil, diltiazem is still more cardio-selective than the dihydropyridines
- Suitable for patients with ischemic heart disease

Side effects

- Common side effects include:
  - Constipation, flushing and hyperprolactinemia
- The most dangerous side effects are heart block and SA node depression
  - These can lead to heart failure

Interactions

- Do not combine CCBs with BBs because beta blockers also depress conduction velocity through the AV node
  - This can result in AV block

Phase 0 → Rapid depolarization, Na^+ influx
Phase 1 → Short repolarization, beginning of K^+ outflow + Ca^{2+} influx
Phase 2 → Plateau phase, balance of K^+ + Ca transport
Phase 3 → Rapid repolarization, Ca^{2+} close + K^+ outflow
Phase 4 → Resting phase, normal Na/K transport

23. Antiarrhythmics – class III. (11)

Mechanism of action

- Class 3 antiarrhythmics bind and inhibit potassium channels which are responsible for repolarization during phase 3 of AP of cardiomyocytes
  - These potassium channels are also called ***delayed rectifier potassium channels*** (**iKr**)
- When potassium channels are blocked, there is less potassium leaking the cell → leads to slower rate of repolarization
  - This results in **prolonged duration of action potential** and **effective refractory period**
    - EFR = the period of time which the cell is un-excitable by a new stimulus
  - Longer repolarization → ↓ heart rate
- On ECG, this is manifested by longer QT interval
  - = risk of Torsades de pointes!! (= the twisting of points → because QRS complexes seem to twist around the isoelectric line)

Agents:

Amiodarone

- = mostly used agent of potassium channel blockers
- Despite being classified as **potassium channel blocker**, amiodarone also:
  - **Blocks inactivated Na+ channels** like class 1b antiarrhythmics
  - **Blocks β receptors** like class 2
  - And also blocks **L-type calcium channels** like class 4
- Its main mechanism of action makes it very useful in treatment of most types of arrhythmias
  - Including atrial fibrillation, atrial flutter and life-threatening ventricular tachycardia
- Amiodarone contains a high level of **iodine** in its structure, which makes it lipophilic and easy to deposit throughout the body
  - This limits the use if amiodarone due to its **toxicity** and **long half-life** (20-100 days)
- Long-term used of amiodarone can case **thyroid dysfunction** (hypo- or hyperthyroidism), **pulmonary fibrosis**, **liver dysfunction**, **constipation**, **corneal deposits**, **blue-grey skin discoloration**
  - Also, cardiovascular side effects → **bradycardia**, **heart block** and **heart failure**
- Due to these numerous side effects, individuals on long-term amiodarone therapy should regularly check *thyroid-*, *pulmonary-* and *liver function* tests

Dronedarone

- Has same mechanism of action as amiodarone
- But in contrast to amiodarone, dronedarone has significantly shorter half-life (about 24 hours)
  - This is because it doesn't have iodine in its structure
- Thus, it is only used to treat atrial fibrillation and flutter
- On the other hand, the lack of iodine makes it less toxic
- Therefore, the most common side effects are GIT disturbances (diarrhea, nausea, abdominal pain and vomiting

Sotalol

- Besides being a K+ channel blocker, sotalol is also a non-selective beta blocker = it can slow down heartbeat and decrease myocardial contractility
- It can be used to treat life-threating ventricular arrhythmias and atrial fibrillation + flutter
- Side effects: sotalol can cause a long QT interval and torsade de pointes
  - It can also lead to bradycardia, hypotension and lightheadedness

Ibutilide + Dofetilide

- Both of these medications work as selective potassium channel blockers
- But they differ in their route of administration and their indications
- Ibutilide is administered intravenously and is used to treat acute atrial fibrillation
- Dofetilide is taken perorally and is used for prophylaxis and long-term treatment of atrial fibrillation
- Since they prolong the QT interval, their main side effect is torsade de pointes

24. Drugs influencing hemostasis (22)

3 Phases of hemostasis

1. Primary hemostasis

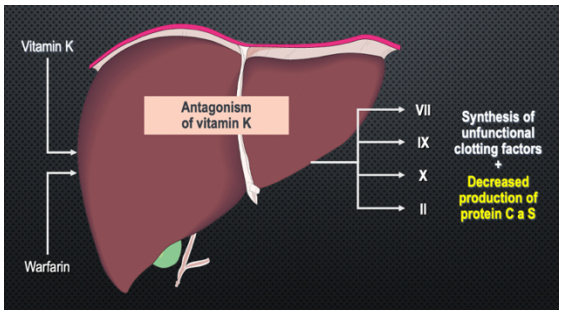
- *Vasoconstriction* (immediate) → *Platelet adhesion* (within seconds) → *Platelet aggregation* (within minutes)
- Here we use **antiplatelet agents**:
  - **COX inhibitors** (*aspirin*), **PSY12 receptor blockers**, **GP IIb/IIIa inhibitors**, **phosphodiesterase inhibitors**

2. Secondary hemostasis

- *Activation of coagulation factors* (within seconds) → *Formation of fibrin* (within minutes)
- Here we use **anti-thrombotics**: (mainly ***preventive purposes***)
  - **Oral agents:** Warfarin (anti-vitamin K) → extrinsic pathway (INR)
  - **Parenteral agents:** Heparin (UFH, LMWH, pentasaccharides) → intrinsic pathway (aPTT)
  - They inhibit the coagulation cascade by different mechanisms
    - They are the most rational approach in the prevention or treatment of deep venous thrombosis (which is associated with excessive formation of stabilized fibrin)

3. Fibrinolysis

- *Activation of fibrinolysis* (within minutes) → *Lysis of the plug* (within hours)
- Here we use fibrinolytics → Only used for ***therapeutic purposes***
- Fibrinolytics basically mimic the natural anticoagulant process
  - They lead to the activation of the inactive plasminogen to the active protease plasmin
  - Fibrinolytics serve for the dissolution of already developed thrombi, regardless of where in the circulation they have formed



25. Coumarine anticoagulants (39)

Coumarin derivatives or **anti-vitamins K intro:**

General mechanism of action

- Anticoagulant effect by ***blocking the ability of vitamin K to carboxylate the vitamin K dependent clotting factors***
  - Inhibition of ***vitamin K reductase*** → ***block the ability of vitamin K to activate of clotting factors*** + Protein S and C
- The particular vitamin K dependent clotting factors are:
  - ***Thrombin*** (factor 2), and ***factors 7, 9 and 10*** (= pro-thrombin complex)
  - The pro-thrombin pathway → *Extrinsic pathway*
- However, formation of **anticoagulant proteins**, especially **protein C**, is also dependent on vitamin K metabolism
  - This involvement in the mechanism of action represents the **source of problems**
  - This effect is the reason for their **slow onset of effect**, and **slow termination of effect**

- The prothrombin complex (**factors 2, 7, 9 and 10**) is a group of factors mostly involved in the in vivo pathway (***extrinsic***) → This pathway can be tested by the **INR test**

Coumarin derivatives:

- **Acenocoumarol** (half-life = 8 hours)
- **Warfarin** (half-life = 47 hours)
- **Phenoprocoumon** (half-life = 160 hours)

A common property of all coumarin derivates is **long**, or **extremely long biological half-life**

Warfarin (→ the most commonly used coumarin derivative)

Pharmacokinetics of warfarin

- Warfarin is a small molecule → very easily absorbed through the gastric mucosa
- Very strongly bound to plasma proteins, and it has complete liver metabolism based on cytochrome P
  - This is the reason for **huge amounts of pharmacokinetic interactions**
  - Interactions with other drugs (due to cytochrome metabolism) + foods containing vitamin K!
    - Food containing vitamin K = sauerkraut, cabbage, spinach…)
- **Safe** during → lactation + later phases of pregnancy (***only not during 1st trimester***)

Mechanism of therapy

- Warfarin has **late anticoagulation effect**
  - It takes up to 60 hours for warfarin to produce anticoagulant effects (due to stored clotting factors)
    - The onset of effect of warfarin does not appear until these stores have been depleted
- Warfarin has **early pro-coagulation effect**
  - Because the stores of protein C + S are limited, only for maximally **6 hours**

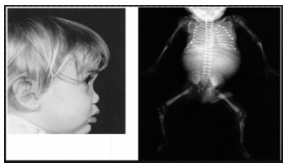
Start of warfarin treatment:

- 1. *Warfarin* + **immediately acting anticoagulation** → because of ***late anticoagulation effect***
  - Usually, ***heparin*** is used and should be given **first 2 days** (then heparin **is** discontinued)
- 2. On the 3rd day of treatment → Measure INT levels
  - Physiological levels = 0,8-1,2 but we should see **prolongation of INR** → therapeutic range = **2-3**
    - (**2,5-3,5** for patients with artificial valve)
- 3. Then INR levels should be **monitored every 1-4 weeks** (every 12 weeks for stabile patients)

Side effects

- Generally, side effects are rare

- **Bleeding** (the only common side effect – still rare 3%)
- **Warfarin induced skin necrosis**
  - Caused by paradoxical local thrombosis in the small diameter veins
- **"Purple toes syndrome"**
- **Osteoporosis** (because vitamin K is involved in the process of bone mineralization)



Teratogenic effects of warfarin

- **Warfarin embryopathy** (**Di Sala syndrome**)
  - Occurs in children born to mothers exposed to warfarin during the **1st trimester** (5-30%)
  - **Classic features of warfarin embryopathy**
    - **Nasal hypoplasia** (Development of fetal cartilage = vitamin K dependent process)
    - **Chondrodysplasia Puncatata (Epiphyseal and vertebral bone stippling)**
- After 1st trimester of pregnancy, the administration of warfarin is regarded as relatively safe

Overdose by warfarin

- **INR 3,0-6,0**
  - **Reduce or withdraw the subsequent dose of warfarin up to INR < 5,0**
- **INR 6,0-10,0**
  - **Withdraw the subsequent dose of warfarin up to INR < 5,0**
  - **Vitamin K in dose 2,5-5 mg i.v. only in presence of bleeding**
- **INR 10,0-20,0**
  - **Withdraw the subsequent dose of warfarin**
  - **Vitamin K in dose 5-10 mg i.v.**
- **INR over 20,0 and intensive bleeding**
  - **Fresh frozen plasma or prothrombin complex concentrate**
  - **Vitamin K in dose 10 mg i.v.**
  - **Recombinant Factor VII (NovoSeven)**

- Antidote of warfarin = Vitamin K!!!

Heparin and heparin derivatives are the mostly used group of ***parenteral*** anticoagulants

26. Heparin and derivatives (47)

Heparin and derivatives of heparin – intro

- Heparin = a ***heterogenous mixture of mucopolysaccharides*** (containing **glycosaminoglycan** + **pentasaccharide**)
- They are physiologically synthesized and released from mast cells, pneumocytes and liver cells

They heparin derivatives are:

- **Unfractionated heparin** (UFH)
  - Very large molecule
  - Has longer glycosaminoglycan chain
    - → Can bind to antithrombin 3, factor 10 and thrombin (f. II) + other factors of intrinsic pathway
    - = Heparin poses similar effects as antithrombin 3 itself
- **Low molecular weight heparins**
  - Fragments of unfractionated heparin
  - Has shorter glycosaminoglycan chain → can only bind to antithrombin 3 and f. 10
    - (Some can partially bind to f. II)
- **Pentasaccharides**
  - Have no protein structure (no glycosaminoglycan chain) – they consist of 5 monosaccharide units
  - They only represent the **active site of heparin** for **bond of antithrombin 3**

Mechanism of action of heparin and its derivatives

- **Antithrombin 3 inhibits activity of clotting factors:**
- The mechanism of action of heparins is mediated through **antithrombin 3**
  - Bind to AT3 → inhibit the activity of clotting factors **IIa, Xa, IXa, XIa, XIIa (2, 9, 10, 11, 12)**
- Inhibition of AT3 → inhibition of f. 10 → ↓ prothrombin activation → ↓ thrombin → ↓ fibrin

Indications

- Mainly used for **prevention + treatment of venous thromboembolism**

Unfractionated heparin

- The mechanism action of unfractionated heparin involves the **complete intrinsic and common pathway**
  - Therefore, **aPTT test** is the standard test which is used for monitoring of heparin effect
    - **Adults**: activated partial thromboplastin time (aPTT)
    - **Children**: Anti-Xa activity

Pharmacokinetics of heparin

- Because heparin is a large molecule → it is poorly distributed through biological membranes
  - Therefore, must be administered only parenterally (i.v. for prompt effect or s.c. for delayed effect)
- Heparin **does not cross placenta** and **does not appear in breast milk**
  - = Safe during pregnancy and breast-feeding period

Side effects of heparin

- **Bleeding** (= the most common side effect)
  - = Protamine sulfate is used as an antidote → effective both for UFH and LMWH, but completely ineffective against pentasaccharides
  - **Protamine sulfate 1 mg i.v. to each 100 IU administered heparin**
- **Thrombocytopenia: HIT 2 (cross reactivity with LMWH)**
  - A very important and common complication after heparin administration
  - Thrombocytopenia is associated with high risk of life-threatening thrombosis in both arterial and venous part of the circulation and high risk of the consequences, including death
- **Osteoporosis (when duration of treatment is longer than 6 month)**
  - Because heparins are direct stimulators of osteoclasts

- **Contraindications:**
  - **Allergy, thrombocytopenia**
  - **Active bleeding or high risk of bleeding (hypertension, ulcers and tumors…)**
  - **Severe renal or liver failure**

Low molecular weight heparins

- From all available low molecular weight heparins, the mostly used in clinical practice are especially **Dalteparine**, **Enoxaparine**, **Nadroparine** and **Bemiparine**
- Their effect mostly involves activated factor 10
  - (Also, partly (*not fully*) inhibit the activity of thrombin (*factor 2*) – depends on their size)
- Low molecular weight heparins have several advantages in comparison with unfractionated heparin
  - This is especially longer biological half-life (can be administered 1x daily)
  - The selective mechanism of action of LMWH means **no necessity of excessive laboratory monitoring**
- The standard evaluation of response of LMWH is provided by the factor 10 activity assay **(anti-Xa assay)**
- Low molecular weight heparins are regarded as a very safe drug
  - They have extremely low risk of overdosing when dose is calculated according to weight of patient

Semisynthetic pentasaccharides

→ **Fondaparinux**

- Semisynthetic, active moiety of heparin → They have **no protein structure** (non-proteins)
  - So, they have **no cross-reactivity with low molecular weight heparins or unfractionated heparins**
- They exhibit a **very selective activity against the activated factor 10**
  - AT specificity does not allow binding to other plasma proteins – Targets only FXa
- Their pharmacokinetic properties are better than those of classic heparins
  - Their biological half-time is very long, longer than 12 hours = They are administered only in 1x daily
- **Do not cause heparin-induced thrombocytopenia** (HIT)

Clinical use:

- Deep venous thrombosis prevention **during surgical procedures → superior to LMWH**
  - They can be used preventive tool against deep venous thrombosis, or during surgical procedures
- **Approved for treatment of VTE (7,8-10 mg QD)**
- HIT type 2
  - Pentasaccharides can be used as alternative for patients who experience heparin-induced thrombocytopenia type 2 by unfractionated heparin or low molecular weight heparin
  - They do not cause (HIT) and because they don't have protein structure – there is no cross-reactivity with UFH or LMWH

Disadvantage of pentasaccharides:

- **Inefficiency of protamine sulphate** as an antidote

Heparin induced thrombocytopenia type II (auka)

- Heparin induced thrombocytopenia type 2 is an immunologically conditioned complication characterized by the creation of activatory antibody of the class IgG
- They are produced against the antigen which is heparin-bounded on platelet factor 4
  - And the bond of these antibodies leads to 2 results:
    - The bond of antibody is a signal for the immune system for very prompt thrombocyte elimination
      - So, one result is progressive thrombocytopenia
    - And because they are activatory, they also lead to excessive aggregation of thrombocytes
      - So, the second result is severe type of thrombosis
- **Treatment:**
  1. **The prompt cessation of heparin**
  2. **Alternative (non-heparin) anticoagulation pentasaccharide → fondaparinux**
  3. **Platelet count – on day 1 and every 2-4 days in all patients receiving prolonged heparin**

Intro – Hemostatic system

1. **Primary hemostasis:**
   - Vasoconstriction, Platelet adhesion, **Platelet aggregation**
2. **Secondary hemostasis:**
   - Activation of coagulation, formation of fibrin
3. **Fibrinolysis**

27. Antiaggregants (51)

Intro – Mechanism of action of Platelet aggregation:

- Damage to endothelium will cause secretion of **von Willebrand factor** which binds collagen at damaged site → platelet will bind to vWF on **GP-Ib receptor** → this will cause platelets to become activated → activated platelet will change shape + express **GP-IIb/IIIa receptors** + secrete granules **(ADP, TXA_2, 5-HT)** + secrete more **vWF** → these granules will cause further activation + aggregation of other platelets → circulating fibrinogen will bind **GP-IIb/IIIa** which will allow platelets to link to each other.

Intro – Antiplatelets/Antiaggregants

Antiplatelets – Classification:

1. **COX inhibitors**
2. **P2Y12 Receptor blockers**
3. **GP IIb/IIIa inhibitors**
4. **Phosphodiesterase inhibitors**

- *Drugs that inhibit enzymes or receptors required for platelet activation + aggregation*

1. COX inhibitors - General

COX – General:

- Has 2 isoforms:
  1. **COX-1** → Important for normal physiological function in our body, its expressed after physiological stimuli
     - COX enzyme function is converting arachidonic acid → **Prostaglandin**
  2. COX-2 → its expressed after inflammatory stimuli
- Prostaglandin forms different mediators:
  - **TXA_2** → activator of platelets
  - **Prostacyclin** → important for normal function of endothelial cells + anti-thrombotic properties

Aspirin

Mechanism of action:

- Irreversible ⊖ of COX → ⊖ TXA_2 synthesis → ⊖ platelet activation + aggregation
  - Because its irreversible → that platelet will never function
- **Effects** → Antiplatelet (low dose), analgesic + antipyretic (intermediate dose),anti-inflammatory (high dose)

Indication:

1. **Secondary prevention of coronary heart disease** (after MI or bypass)
   - Lifelong *aspirin* administration → ↓ risk of recurrent CVS events in patients who had MI, ischemic stroke or TIA
2. **Primary prevention for patients w. ↑ risk of thrombosis**
3. **Acute MI, Acute Ischemic stroke, Unstable AP**

Primary prevention → prevention of disease
Secondary prevention → try to prevent disease from getting worse

Side effects:

1. ↑ risk of bleeding
2. GIT → ↑ risk of ulcers, bleeding, perforation (*Aspirin* is an NSAID → ↓ PG)
3. Allergic rection → Swelling, bronchospasm
4. Tinnitus (in high doses)

2. P_2Y_{12} Receptor Inhibitors – ADP receptor inhibitor

- *P_2Y_{12} receptors are located on platelets and bind to ADP, G_i coupled receptor*

Mechanism of action:

- Normally → ADP binds P_2Y_{12} receptor → ⊕ adenylyl cyclase → ↓ cAMP Changes GP-IIb receptor to active form → platelet aggregation
  - So we ⊖ P_2Y_{12} receptor → ↑ cAMP → ⊖ platelet aggregation

Indication:

- **Dual antiplatelet therapy** (w. *Aspirin*)
  - Acute Coronary syndrome **(STEMI/NSTEMI)**
- **Secondary prevention of cardiac events**
- Generally alternative if *aspirin* is not tolerated

Side effect:

- Allergic reactions, **Bleeding**, GIT disturbances

Drugs:

1 ***Clopidogrel + Ticlopidine*** + ***Prasugrel***
  - All → Irreversible ⊖ P_2Y_{12} receptor, Prodrugs
  - *Clopidogrel* → activation depends on CYP450 enzymes (low conversion to active form)
  - *Ticlopidine* → slow onset of action + high risk of side effect = not used
  - *Prasugrel* → Faster onset of action

2 ***Ticagrelor***
  - Reversible ⊖ P_2Y_{12} receptor, Fast onset of action

3. GP-IIb/IIIa inhibitors – Fibrinogen receptor inhibitor

Mechanism of action:

- ⊖ Binding of fibrinogen to GP-IIb/IIIa on platelets → ⊖ platelet aggregation

Indication:

- Prevention of thrombosis in patients w. risk of acute coronary syndrome planned for PCI

Side effects:

- Bleeding, acute thrombocytopenia

Drugs:

1 ***Abciximab***
  - Antibody against GP-IIb/IIIa receptors, irreversible,

2 ***Eptifibatide, Triofiban***
  - Reversible, shorter T ½

4. Phosphodiesterase Inhibitors – PDE-I

- Enzyme that destroys cAMP and cGMP

Mechanism of action:

1 ↑ cAMP → ↓ platelet aggregation

2 ↓ Adenosine reuptake → ↑ extracellular adenosine → vasodilation

Indication + Drugs:

- *Cilostazol* (PDE3-I)→**Intermittent claudication**
- *Dipyridamole* (nonselective PDE-I)→ Stroke prevention (in combination with *aspirin*)

Side effects:

- Arrythmia, hypotension, GIT disturbances

28. Thrombolytics (45)

Intro – Fibrinolysis:

- *Degradation of fibrin network of clot by enzyme plasmin*
- Tissue injury leads to release + activation of plasminogen activators → which converts plasminogen to plasmin
  - Plasmin breaks down fibrin and fibrinogen → release of fibrin degradation products (e.g. D-dimer)

Fibrinolytics/Thrombolytics:

- They ⊕ degradation of thrombi by activating plasminogen → plasmin
- To get the best effectiveness, early administration is required
  - Generally recommended to use drug 6 h from onset of symptoms

Main indication:

1 Arterial → acute MI, acute thrombotic stroke, acute peripheral thrombosis
2 Venous → DVT, pulmonary emboli
3 Both → thrombotized A-V shunts

Side effects:

1 **Bleeding**
  - Treated with antifibrinolytics (*aprotinin*), fresh frozen plasma
2 Allergic reaction
3 Formation of antibodies

Non-Selective Fibrinolytics – 1st generation:

- Cause degradation of both fibrin + fibrinogen
- Break down both Pathological and Defensive thrombi
- Short T ½
- Risk of: **Generalized lytic state** → high risk of severe bleeding

Drugs:

1 ***Streptokinase*** → Oldest fibrinolytic, produced by group A streptococci
  - Converts Plasminogen to plasmin, can produce antibodies (SE)
2 ***Urokinase*** → Natural protein, physiologically synthesized by endothelial cells of vessels and kidney
  - Directly activate plasminogen

Selective Fibrinolytics	
2nd Generation - *Alteplase*	**3rd Generation – *Reteplase***
= Tissue plasminogen activators (tPA) ❖ Golden standard for fibrinolytic treatment ❖ Highly selectivity to plasminogen bound on fibrin (less systemic effect) ❖ Its serine protease produced by endothelial cells of vessels (under physiological conditions) ❖ Highest effectiveness than other fibrinolytics ❖ They have Longer T ½ than 1st generation	= **Recombinant plasminogen activator (rPA)** ❖ 3rd Generation are group of new drugs with improved pharmacokinetics due to new method of synthesis ❖ Selective for plasminogen bound on fibrin (less systemic effect) ❖ Enter into thrombi → ⊕ recanalization ❖ Longer T ½ than 2nd Generation, but still used less because of frequent incidences of severe bleeding

Newer selective Fibrinolytics:

- *Desmoteplase, Staphylokinase, Amediplase*

29. Hypolipidemics (8)

Intro – Dyslipoproteinemia

Dyslipoproteinemia = **disorder of plasma lipid metabolism** (risk factors of CVS diseases)

We can recognize 3 types of dyslipoproteinemias:

- **Hypercholesterolemia** → ↑ LDL + ↑ Cholesterol
- **Hypertriacylglycerolemia** → ↑ Chylomicrons or ↑ VLDL + ↑ TAGs
- **Combined hyperlipoproteinemia** → ↑ Cholesterol + ↑ TAGs

Therapy of dyslipoproteinemias

1. **Non-pharmacological therapy**
- **Diet, enough of the physical activity, body weight, smoking, alcohol!**
2. **Pharmacological therapy → Hypolipidemics**
- Drugs that ↓ level of lipids and lipoproteins
- We can divide them into:
  - **1. Plasma cholesterol-lowering drugs**
  - **2. TAG-lowering drugs**

1. Plasma cholesterol-lowering drugs
- **a. statins**
- **b. Drugs which block LDL receptors (PCSK9)**
- **c. Niacin (nicotinic acid)**
- **d. Bile acid sequestrants (resins)**
- **e. Drugs that increase cholesterol clearance**
- **f. Selective inhibitors of cholesterol absorption**

1. Plasma cholesterol-lowering drugs:

→ **First line treatment for hypercholesterolemia = combination of statins + Ezetimibe**

a. Statins (→ Statins are the one the most prescribed drugs in the world)

- **Fluvastatin**, **Simvastatin**, **Rosuvastatin** and **Atorvastatin** are the most commonly used

Mechanism of action:

- Statins are competitive inhibitors of ***HMG-CoA reductase*** → thus, inhibit the ***synthesis of cholesterol***
  - By inhibiting cholesterol synthesis → **↑ Number of LDL receptors = ↓ LDL**
- Also, **↑ HDL**
- **Pleotropic effects of statins** (= **additive effects**)
  - **Antiproliferative effects**, **anti-aggregation**, **stabilize atherosclerotic plaques**, **antioxidant effects**…
    - These pleotropic effects = good for prevention of CVS diseases

Indications of statins:

- **1. Hypercholesterolemia (IIa)**
- **2. Combined hyperlipoproteinemia** (both ↑ cholesterol + ↑ TAGs)
  - Combine statins with fibrates (beware of rhabdomyolysis!)

Side effects of statins

- Statins are considered as very safe drugs
- **1. GIT symptoms**
- **2. ↑ Hepatic enzymes (ALT, AST) → hepatotoxicity is questionable** (only temporary increase in hepatic enzymes)
- **3. ↑ Activity of creatin kinase (10x) → myalgia, myopathy, rhabdomyolysis**
  - (myalgia + myopathy more typical)
  - Rhabdomyolysis = breakdown of skeletal muscles → **nephrotoxicity**
- **Contraindications:**
  - **Pregnancy, lactation, children, liver and kidney disease**
- **! interactions at cytochrome level**

B. Other plasma cholesterol lowering agents:			
Drugs blocking LDL receptor (*PCSK9*)	**Niacin (*vit. B3*)**	**Bile acid sequestrants - Resins**	**Selective inhibitors of cholesterol absorption**
Mechanism of action • Antibodies against LDL receptor → ↑ LDL clearance (↓ LDL) **Drugs:** • *Evolocumab, Alirocumab*	**Mechanism of action:** • ↓ synthesis of TAG → ↓ VLDL secretion → ↓ LDL → ↓ CH • ↑ HDL **Indication:** • Hypercholesterolemia, Hypertriacylglycerolemia, combined hyperlipoproteinemia So, both CH lowering + TAG lowering	**Mechanism of action:** • Bind bile acid in GIT → ↓ uptake of CH + bile acid → compensatory ↑ conversion of CH to bile acid in liver → ↓ CH in liver → ↑ LDL receptors → ↑ LDL clearance (↓ LDL) • ↓ LDL, ↑ TAGs, ↑ HDL **Indication:** • Hypercholesterolemia • Not used in Europe anymore	**Mechanism of action:** • ⊖ transport protein required for CH absorption → ↓ CH in liver → ↑ LDL receptors → ↑ LDL clearance (↓ LDL) **Indication:** • Combined therapy - Not effective alone **Drug:** • ***Ezetimibe***

2. Triacylglycerol-lowering drugs

a. Fibrates (fibric acid derivatives)

Mechanism of action

- **1.** They activate **nuclear factor PPARα → ↑ lipoprotein lipase activity → ↑ degradation of LDL + TAGs**
  - ↓↓↓ TAG, ↑ HDL, ↓ LDL
- **2.** ↑ Catabolism of VLDL, ↓synthesis of VLDL, also stimulate β oxidation of fatty acids
- Non-lipid effects: (**Pleotropic effects**)
  - ↓ fibrinogen, ↓ platelet aggregation, ↓ viscosity of blood, ↓ uric acid level, ↑ insulin effect

Indications of fibrates

- **Hypertriglyceridemia**, **combined dyslipidemia** and in **patients with low concentration of HDL**
- Fibrates decrease triacylglycerols, increase HDL – But they have poor effect on LDL particles

Drug

- Fenofibrate is the most important fibrate (the only one available on market)

Side effects of fibrates

- The side effects are very similar to the side effects for statins
- **GIT → pyrosis, nausea, vomiting**
- **Cholelithiasis** (fibrates = ↓ bile acid synthesis → disbalance of CH/bile acid ratio
- **↑ creatine kinase activity → myalgia, myositis, rhabdomyolysis**
  - → **Kidneys! statins!**
  - It is important to remember that we must be very careful when combining statins with fibrates, why?
    - Because we increase the incidence of side effects – increased risk of rhabdomyolysis
  - In severe cases we can combine them, but we should monitor these side effects
- **Contraindications:**
  - **Liver and kidney damage, pregnancy, lactation**

Effects of statins and fibrates on lipid:

	Statins	Fibrates
↓ LDL	+++	+
↓ Triacylglycerols	+	+++
↑ HDL	+	++
↓ Postprandial lipemia	-	++

- **Statins** are better in decreasing of LDL and cholesterol
- On the other hand, **fibrates** are better in decreasing triacylglycerol
  - Fibrates are better in increasing HDL than statins
  - And also, the effect of fibrates on postprandial lipemia is better

Pharmacological therapy of hyperlipidemia

Isolated ↑LDL (hypercholesterolemia)	Statin + ezetimibe/niacin
Isolated ↑TAG (hypertriacylglycerolemia)	Fibrate + niacin
↑LDL + ↑TAG = Combined hyperlipoproteinemia	Statin + fibrate (be careful → rhabdomyolysis)
Dyslipoproteinemia ↓HDL	Fibrate/niacin + other hypolipidemics (statins)

30. Antianemics (57)

Anemia is defined as a below normal plasma hemoglobin concentration, either due to decreased number of circulating RBCs or an abnormally low total Hb content per unit of blood volume.

Etiology

- Chronic blood loss, bone marrow abnormalities, incresed hemolysis, infections, malignancy, endocrine deficiencies, renal failure and other diseases
- Anemias that are due to chronic bleedings can temporarily be corrected by transfusion of whole blood
- Nutritional anemias are due to dietary deficiencies of metabolites such as iron, folic acid, or vitamin B_{12} which are necessary for normal erythropoiesis
- A large number of drugs can cause toxic effect on blood cells, Hb production or erythropoetic organs which may cause anemia

Treatment

Iron deficiency

Results from acute/chronic blood loss, insufficient intake during periods of accelerated growth in children or in heavy menstruation and pregnancy. This leads to a negative iron balance due to depletion of iron storages/inadequate intakeà*hypochromic microcytic anemia*
Supplementation with **ferrous sulfate** is required
Adverse effects: GI disturbances caused by local irritation
Dextran (Parenteral iron) may be used

Folic acid deficiency

May be caused by increased demand (pregnancy, lactation), poor absorption (pathology of small intestine), alcoholism, treatment with drugs that are dihydrofolate reductase inhibitors (eg. Methotrexate)
This leads to *megaloblastic anemia*
Treatment: **Oral folic acid** administration, non-toxic, no serious SE

Vit B12 deficiency

Can result from low dietary level, poor absorption due to failure of gastric parietal cells to produce intrinsic factor, loss of activity of the receptor needed for intestinal uptake, malabsorption syndromes or gastric secretion

Treatment:

- Vitamin B_{12} (**cyanocobalamine**) administered orally, intramuscularly or deep s.c.
- Oralfordietarydefiencies
- Intramuscularly or deep subcutaneously for *pernicious anemia*
- Folic acid administration alone reverses the hematologic abnormality and masks the vitaminB_{12} defiency à may proceed to severe neurologic dysfunction - therefore, megaloblastic anemia has to be treated with a combination of folate and vitamin B_{12}
- Therapy must be continued for the remaining life if the patient has pernicious anemia
- Adverse effects: non-toxic even in large doses, rarely headache, nausea, vomiting

Eryhropoetin and darbepoetin

Erythropoietin is a glycoprotein normally made by kidneys that regulates the RBCs proliferation and differentation in the bone marrow. Human erytropoietin that is produced by recombinant DNA technology are effective in the treatment of:

- Anemia caused by end-stage renal disease
- Anemia associated with HIV–infected patients
- Anemia in some cancer patients

Darbepoietin is a long-acting version of erythropoietin: due to delayed onset of action - no value in acute anemia Supplemention with iron may be required
Administration: i.v, s.c
Adverse effects: generally well tolerated, but may elevate BP and arthralgia

8. CNS

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18. **Pharmacology and toxicology of nicotine (44)**

1. Neurotransmitters of CNS (64)

Neurotransmitters – General:

- *Endogenous chemicals released by presynaptic terminals and produce rapid excitatory or inhibitory response in postsynaptic neurons*
- So, they transmit signals from neuron to target cell across a synapse
- Neurotransmitters can be fast or slow:
  - Fast NT → ionotropic → operate through ligand-gated ion channels (e.g., GABA)
  - Slow NT → metabotropic → operate mainly through G-protein receptors (e.g., Dopamine)
- Most drugs that affect CNS act by altering some step in neurotransmission
  - May act presynaptically (effect **synthesis**, **storage**, **release**, **termination** of NT) or on postsynaptic receptors
- CNS have more synapses and are more complex, they have many NT, while ANS only uses 2 (ach + NE)

Neurotransmitters – Classification acc. action:

1 **Excitatory** → Glutamate, Aspartate, Homocysteine (depolarize = Na, Ca, G_q)
2 **Inhibitory** → GABA, Glycine (hyperpolarize = Cl, K, G_i)
3 **Both** → Norepinephrine, Dopamine, Acetylcholine

Synaptic Potentials in CNS:

- Most synapses are coupled to ion channels. Binding of NTs on postsynaptic membrane receptors results in opening of ion channels → producing depolarization or hyperpolarization depending on ions

1 **Excitatory pathway:**
  - Movement of ions causing **depolarization** of postsynaptic membrane
  - EPSP (excitatory postsynaptic potentials) are generated by stimulation of excitatory neurons that release NTs (e.g., Glutamate), which bind to receptors on postsynaptic membrane → ↑ Na permeability → ↑ generation of action potential

2 **Inhibitory pathway:**
  - Movement of ions causing **hyperpolarization** of postsynaptic membrane
  - IPSP (inhibitory postsynaptic potential) are generated by ⊕ of inhibitory neurons that release NTs (e.g., GABA), which binds to receptors on postsynaptic membrane → ↑ of K, Cl permeability → ↓ generation of action potential

- Most neurons in CNS have combined effect (both EPSP + IPSP), thus several NTs may act on the same neurons, but bind to its own specific receptors

GABA (GABA = most common inhibitory NT of CNS – GABA produces calming effect in the brain)
- ↓ in anxiety (BNZ to ↑ GABA)
- ↑ in Parkinson's disease

Serotonin
- Disrupted function in anxiety (Buspirone)
- ↓ in depression

Norepinephrine
- ↑ in anxiety (BBs = ↓NE)
- ↓ in depression

Dopamine
- In schizophrenia → ↑ dopamine = positive symptoms, ↓ dopamine negative symptoms
- ↑ = mania, ↓ = depression
- ↓ in Parkinson's disease

Acetylcholine
- ↑ in Parkinson's disease

2. Anxiolytics (18)

Anxiety is one of the most common psychiatric disorders (still increasing)

- **Anxiety** = normal reaction to stress (adaptive warning system) → **normal**
- **Anxiety disorder** = excessive anxiety → **abnormal**

- Symptoms – muscular tension, tachycardia, sweating …

(Different types of anxiety disorder – General anxiety disorder (GAD), panic disorder, social anxiety disorders, phobias, OCD, PTSD)

Anxiolytics:

- *Decrease anxiety*
- *Decrease tension*
- *Decrease aggression*

The significant mediators of anxiety in the CNS are *GABA*, *serotonin* and *norepinephrine*

- Reduced activity of GABA receptors (hypofunction of GABA) can be a part of the pathomechanism
  - For treatment of anxiety, we use **drugs that stimulate GABA function**
    - **(= Benzodiazepines)**
- A second one can be not reduced, but *changed*, disrupted regulatory function of serotoninergic neurons, arising from dorsal raphe nucleus
  - For treatment of anxiety, we use **drugs that manage serotoninergic metabolism** and pathways
    - **(= Buspirone)**
- Furthermore, overactivity of noradrenergic neurons, arising from the locus coeruleus may produce excessive excitation in the brain and are implicated in anxiety disorders
  - For treatment of anxiety, we use **drugs that inhibit norepinephrine**
    - (= **beta blockers** have very good anxiolytic effect)

Anxiolytics - Classification

1. Benzodiazepines	2. Non-benzodiazepines	3. Others
- Benzodiazepines (Agonists of GABA receptor) → **Short acting:** **- Triazolam** **- Midazolam** → **intermediate acting:** **- Alprazolam*** **- Lorazepam*** **- Bromazepam*** → **Long acting:** **- Diazepam*** **- Clonazepam***	**- Buspirone** **- Guaiphenesin** **- (Barbiturates)**	**Drugs recommended for other diseases, but are helpful in treatment of anxiety:** **- Antihistaminics** **- β-blockers** **- Antidepressants** **- Antipsychotics** **- Anticonvulsants**

- Anxiolytics can be categorized into **benzodiazepine** and **non-benzodiazepine** groups

1. Benzodiazepines

- **Agonists of GABA receptors** (= stimulate the inhibitory function of GABA)
  - → GABA = most common inhibitory NT of CNS
  - GABA produces calming effect in the brain
- Widely used drugs with very wide spectrum of therapeutic effects:
  - Used for treatment of **anxiety** (anxiolytic effect)
  - Decrease tone of skeletal muscles (**cause relaxation of muscles**)
  - **Anticonvulsive effect** (→ Especially diazepam for status epilepticus)
  - **Premedication before surgery** (induction into general anesthesia
  - **Hypnotic effect**
  - Management of **alcohol detox**

2. Non-benzodiazepine anxiolytics

- Buspirone:

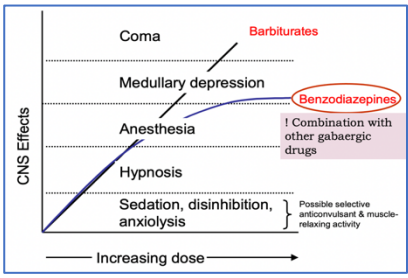
- **<u>Indicated to relieve of symptoms of generalized anxiety disorder</u>**
  - Has anxiolytic effects without myorelaxant and anticonvulsive effects
- = ***Serotonin partial agonist***
  - = Affects the metabolism of serotonin
  - A) Full agonist of presynaptic regulatory serotonin receptors type 1A
    - → 1A receptors are inhibitory and reduce levels of serotonin
  - B) Stimulates postsynaptic receptors
- Do not combine with other serotoninergic drugs!! (MAO-I or SSRIs)

- Guaiphenesin:

- Used for the management of stage fright

- Barbiturates:

- Obsolete, very rarely prescribed
  - Because they have high potential for addiction
  - Also have high risk of inhibition of medulla → respiratory depression
- However very effective as anxiolytics, hypnotics and anticonvulsants
  - But have been replaced by other less toxic drugs



Effects of BNZ vs. barbiturates (Dose – Response Curve)

- The mechanism of action of benzodiazepines and barbiturates is relatively the same
- **Benzodiazepines are currently preferred over barbiturates**
- Benzodiazepines are generally **well tolerated** and are **relatively safe** when they are used **short-term** at recommended doses
- **Barbiturates strongly bind to <u>beta</u> (β) subunits of GABA-A receptors** → hardly dissociated from the receptor
  - Therefore, **their effect is linear**, and they have **higher ability to produce depression of the medulla and produce respiratory failure**
- Benzodiazepines bind to the **alpha subunit (and gamma)**
  - They reach **anxiolytic**, **sedative**, **hypnotic effect**
  - However, **saturation of GABA receptors binding sites** at normal doses **don't increase the CNS effect**
    - So, they **don't cause depression of the medulla**
  - The risk of CNS depression after benzodiazepines administration is potentiated by combination with other GABA-ergic drugs – Such as combination with alcohol, barbiturates, opioids → can be fatal

3. Other anxiolytics

- H1 receptor antagonists (Hydroxyzine → 1st generation, lipophilic = CNS effects)

- Lipophilic 1st generation H1 antihistaminic drug → inhibits ***H1 histaminic***, ***muscarinic*** and ***alpha1 receptors***
- Very good anxiolytic and sedative effects
- May be used to treat anxiety disorders and sleep disorders

- Beta blockers

- Have to be ***lipophilic BBs*** in order to cross BBB and have CNS effects
- For example, **propranolol**
- Beta blockers inhibit the **noradrenaline secretion from locus coeruleus** = anxiolytic effects
- And in the periphery, BBs reduce anxiety symptoms
  - Such as tachycardia, palpitations, sweating…

- Antidepressants – SSRI, SNRI

- Antipsychotics

- In low doses → anxiolytic effects

- Antiepileptics

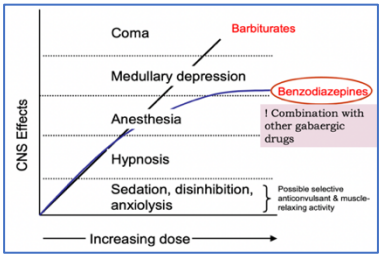
3. Benzodiazepines (26)

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  - **Hypnotic effect**
  - Management of **alcohol detox**
- Benzodiazepines = **Agonists of GABA receptors** (= stimulate the inhibitory function of GABA)
  - → GABA = most common inhibitory NT of CNS – GABA produces calming effect in the brain

GABA receptors:

→ **GABA-A** (ionotropic receptors) = the target of benzodiazepines

- Pentameric receptors (2 α, 2 β and 1 γ subunits)
  - Barbiturates bind to β subunit
  - Alcohol binds to α subunit
  - **Benzodiazepines bind to alpha (α) and gamma (γ) subunits**
- When GABA-A receptors are activated (by BNZ for example)
- → They increase **chloride** entry into the cells
- → Causing **hyperpolarization** of the membrane



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  - The risk of CNS depression after benzodiazepines administration is potentiated by combination with other GABA-ergic drugs – Such as combination alcohol, barbiturates, opioids → can be fatal

Pharmacokinetics:

- Way of administration

- Can be administered via **intramuscular**, **intravenous**, **oral**, **sublingual**, **intranasal** or **rectal form**
- For **acute** states → **Rectal** or **intravenous** administration!

Other pharmacokinetic parameters of benzodiazepines:

- **↑ Lipid solubility – ↑ transport into CNS**
  - (Accumulates in fatty (lipid-rich) tissue)
- **↑ Bound to plasma proteins → interactions**
- **Biotransformation – Cytochrome P-450**
  - **Short-acting derivatives → Non-active metabolites**
  - **Long-acting derivatives → Active metabolites**
- **Elimination – by kidney**

Members:

→ Short-acting benzodiazepines

- **Midazolam**
- **Triazolam**
  - Short half-life (4-6 hours)
  - Most frequently used = midazolam → potent anxiolytic and sedative drug
    - Primarily used before surgeries as an anxiolytic, sedative and hypnotic agent

→ Middle-acting benzodiazepines

- **Alprazolam**
- **Lorazepam**
  - These agents are recommended to be used as anxiolytics

→ Long-acting benzodiazepines

- **Diazepam**
- **Clonazepam**
  - Produce active metabolites = long acting
  - Most frequently used = diazepam
    - Anticonvulsant used for the treatment of anxiolysis, sedation and as myorelaxant

Side effects

- **Common side effects: (all benzodiazepines cause) → Drowsiness, lethargy, and fatigue**
- **At higher dosages, impaired motor coordination, dizziness, vertigo, slurred speech, blurry vision…**
- **Short-acting BNZ: paradox reactions**
  - Don't forget, paradoxical reaction is typical for **short-acting derivates** → e.g., aggression
- Benzodiazepines cause **impairment of long-term memory**
  - In surgical operations, BNZs are used specifically for they **amnestic properties (Anterograde amnesia)**
  - But in nearly all other incidences, amnesia is an undesirable side effect of benzodiazepines
- **Delirium**
  - Other side effects are that benzodiazepines may cause delirium, especially in older patients
  - Delirium is a syndrome encompassing disturbances in attention, consciousness, and cognition

All benzodiazepines can cause dependence

- **Tolerance → Dependence → Withdrawal syndrome (Rebound phenomenon!)**
- **The dose of benzodiazepines should be tapered slowly**
- ❖ Suddenly stopping therapy after few weeks of daily therapy may be associated with withdrawal syndrome
  - ➢ Which causes the typical symptoms, grand mal seizures, long-term insomnia, delirium, muscle spasms, anxiety panic attacks and more
- **! Combination with other medications with synergic effects ↑ Risk of respiratory depression:**
  - **Barbiturates, opioids, alcohol!**
- **! Drug interactions – Cytochrome P450**
- ❖ Do not forget the interactions with cytochrome P450 metabolism
- ❖ Drugs that either attenuate or potentiate cytochrome P450 enzyme will either increase or decrease the elimination half-life of benzodiazepines
- ❖ It is necessary to control the interactions

BZD – Contraindications

- **Myasthenia gravis →** Due to relaxation of skeletal muscles
- **Syndrome of sleep apnea →** Due to risk of suppression of medulla
- **Respiratory insufficiency →** COPD and some other respiratory disorders can be a risk
- **Intoxication with alcohol, hypnotics →** Due to synergic effects on GABA receptors
- **! Pregnancy (Pregnancy is an absolute contraindication for the use of BNZs)**
  - **BZD – teratogenic – benzodiazepine syndrome**
  - **Neonatal withdrawal syndrome**
- **Lactation**
  - Benzodiazepines are excreted in breast milk, so they are contraindicated in breast-feeding mothers
- **Risk patient! (patient with drug dependence)**
  - GABA receptors control this reward pathway which causes benzodiazepines to be absolutely contraindicated for patients with risk of dependence or with history

4. Symptoms and therapy of benzodiazepine poisoning (2)

→ Byrjaðu á að tala um grafið – BNZ vs. barbs of comination contraindications!

- Intoxication with BNZ can be **lethal when combined with other CNS depressants** (e.g., alcohol)
- Fortunately, the toxic dose is relatively high:
  - **Toxic dose = 20x therapeutic dose** (= its relatively hard to accidentally be intoxicated by benzodiazepines)

Symptoms:

- Somnolence
- Impairment of coordination, hyporeflexia
- Confusion
- Hypotension
- Respiratory depression (very high doses) – followed by coma and death

- Patients initially present with mild to moderate impairment of CNS function (diplopia, impaired balance, impaired motor function, anterograde amnesia, ataxia, and slurred speech).
- Most patients with pure benzodiazepine overdose will usually only exhibit these mild CNS symptoms.
- Paradoxical reactions such as anxiety, delirium, combativeness, hallucinations, and aggression can also occur.
- GI symptoms such as nausea and vomiting have also been occasionally reported.
- In severe overdose have been reported symptoms including prolonged deep coma, apnea, respiratory depression, hypoxemia, hypothermia, hypotension, bradycardia, cardiac arrest, and pulmonary aspiration, with the possibility of death.
- The duration of symptoms following overdose is usually between 12 and 36 hours in the majority of cases.

Treatment

- **Supportive and symptomatic care:**
  - ***Gastric lavage***
  - ***Activated charcoal***
  - i.v. hydration and maintain airway
- Antidote: **Flumazenil** – competitive antagonist of GABA-A
  - Rapid response 1-2 min max. up to 10 min
  - Duration 1-5 h - Short half-time (<1hr)
  - Dose 0,2 mg i.v. during 30 sec., followed by 0,5 mg in 1 min intervals up to maximal dose 3 mg

5. Hypnotics (5)

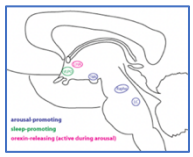
Hypnotic drugs are a class of psychoactives whose primary function is to **induce sleep**, in the **treatment of insomnia**

Areas of the brain – Regulation of sleep

- 5 important centers participate in the regulation of sleep and arousal:

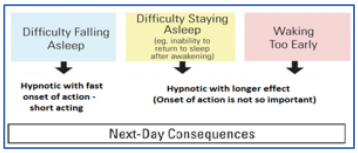
Category	Nucleus	Neurotransmitter	Level of activity	
			During arousal	During sleep
Sleep-promoting	Ventrolateral preoptic area	GABA	0	++
Arousal-promoting	Locus coeruleus	Norepinpehrine	++	0
Arousal-promoting	Raphe nuclei	Serotonin	++	0
Arousal-promoting	Tuberomammillary nucleus	Histamine	++	0
Orexin-releasing	Lateral hypothalamic area	Orexin	++	0

- Drugs used as hypnotics have different mechanism of action, they can act as:
  - GABA **agonists**
  - **Antagonists** of histaminergic, norepinephrine and serotonin receptors
  - **Antagonists** of orexin
- Don't forget these neurotransmitters and areas which control sleeping and arousal
  - We can use drugs with different mechanism of action to induce sleep



Insomnia

- Insomnia is a very common sleep disorder, approx. 50% of adults experience insomnia and 10% of adults have chronic insomnia
- **Hypnotics should be selected according to type of insomnia**
  - Insomnia with **difficulty falling asleep** → Choose **short-acting** hypnotics with **fast onset**
  - Insomnia with **difficulty staying asleep** → Choose **long-acting** hypnotics



a. Benzodiazepines as hypnotics

- Benzodiazepines with the stronger hypnotic effect and weak anxiolytic effect
- **They can only be used for some short-term treatment of insomnia due to side effects**
- **Side effects:**
  - **Prolong Non-REM sleep** and **reduce the REM sleep**
- **1. Short-acting: Triazolam**
- **2. Intermediate-acting: Nitrazepam, flurazepam**
- **Long-term BZD – residual effects (sleepiness) in the morning and the possibility of cumulation**

b. Selective agonists of BZ_1 → Z-hypnotics (zopiclone, eszopiclone, zolpidem and zaleplon)

- **Hypnotic effect only**! – bind on BZ1 binding-site of GABA receptor
- Rapid onset of the action, shorter effect
- They influence the sleep pattern less (especially REM phase)
- ↓ risk of drug dependence
- Same antagonist as BNZ– **Flumazenil**

Z-hypnotics

- **Zopiclone** also has mild anxiolytic effects (because it is an antagonist of muscarinic receptors)
- **Zopiclone** and **eszopiclone** have **longer half-life** than **zolpidem** and **zaleplon**
  - Thus, zopiclone and eszopiclone are recommended for the **introduction to sleep** and they **also increase the duration of sleep**
  - Because the **onset is relatively short**, they can be used for the **introduction to sleep**
  - And because of their **long half-life**, they can **increase the duration of sleep**
- On the other hand, **zolpidem** and **zaleplon** are strongly recommended **only for the introduction to sleep**
  - Because their **onset of action is very fast**, and their **half-life is very short**

Z-Hypnotics – Side effects

- **Headache, drowsiness, nausea, dizziness, nightmares, and agitation**
- **Extensively metabolized by CYP3A4, except for zaleplon**
- **Next-day impairment of driving and other activities (zopiclone, eszopiclone)**
  - But less than in comparison with benzodiazepines

Drug	Long/short acting	Side effect	Clinical use	Indication
Zolpidem	Short acting	Amnesia	- Introduction to sleep	Insomnia with difficulty falling asleep
Zaleplon				
Zopiclone + Mild anxiolytic	Long-acting	+ Anti-muscarinic effects	- Introduction to sleep - Increase duration of sleep	Insomnia with difficulty staying asleep
Eszopiclone		Depression		

c. Orexin antagonists (hypocretin)

❖ Another group of hypnotic drugs are antagonists of orexin (Orexin is also known as hypocretin)
❖ Orexin is a neuropeptide that regulates arousal, wakefulness and appetite
  ➢ It is produced in the lateral hypothalamus

- **Orexin plays a role in keeping people awake and alert, a medication that blocks its action has the potential to promote sleep**

Orexin receptor antagonist (DORA)

- Suvorexant

- **DORA – dual orexin receptor antagonist OX1, OX2**
- **Induce sleep faster (within 1 hour) and extended the duration of sleep (T½ 12 h)**
- **Side effects:**
  - **Nightmare, abnormal dreams…**

d. Melatonin

1. Natural melatonin

- Helps induce sleep, especially in older patients
- Substance with low toxicity
  - Only in high doses it can cause – drowsiness, headache, dizziness, slower reaction time

2. Prolonged-release melatonin (Circadin)

❖ It is indicated for the treatment of primary insomnia in patients older than 55 years old
❖ Circadin is the first prescribed trade product which contain melatonin

3. Melatonin receptor agonists (MT1, MT2)

❖ We can also use agonists of melatonin receptors:

- Ramelteon

- Ramelteon is a receptor agonist for mentation 1 and 2 (MT 1 and 2) receptors
- It is recommended for the management of insomnia characterized by difficulty of sleep onset
  - Because its onset of action is very fast, and its half-life is short
- **BENEFIT: Reduced potency to dependence, abuse, withdrawal and rebound insomnia**
- **Ramelteon → Contraindicated in Pregnancy**

- Tasimelteon

❖ It is approved for the treatment of non-24 hours sleep-wake disorder in blind people
  ➢ This is the only indication for Tasimelteon

e. H1 receptor antagonists (1st generation)

- Diphenhydramine, Hydroxyzine, Alimemazine

- **Effects**
  - **Anxiolytic**
  - **Sedative**
  - **Antiemetic**

- **Pediatric use**

- **Side Effects**
  - **Anticholinergic**
  - **Hypotension**
  - **Tachycardia**

❖ The benefit of these substances is that they can be used as hypnotics and sedatives in pediatric practice

f. Dexmedetomidine – PRECEDEX inj.

- Dexmedetomidine is not a hypnotic, but a drug which induces sedation
  - It is able to provide sedation without the risk of respiratory depression
- **Increases GABA activity (GABA agonist) + alpha2 adrenergic agonist**
  - **Decreases the activity of noradrenergic neurons in the locus coeruleus in the brain stem**
- **Achieves its effects without causing respiratory depression**
- **Used in the intensive care setting to produce sedation** → For example during colonoscopy

6. Antipsychotics – (Overview, mechanism of action) (56)

- ❖ Antipsychotics are a class of medication primarily used to manage psychosis
- ❖ Approx. 60% of antipsychotics are used in different diagnosis, such as schizophrenia, sedatives, anti-vomiting, antidepressants, hypnotics, resistant insomnia and other indications

Schizophrenia – A serious mental disorder characterized by disordered thoughts, delusions, hallucinations and mood disturbance

Positive symptoms
- Hallucinations
- Delusions (bizarre, persecutory)
- Disorganized thought
- Perception disturbances
- Inappropriate emotions

(Positive symptoms generally respond very well to medication)

Negative symptoms
- Blunted emotions
- Anhedonia - Lack of feeling
- Loss of motivation
- Social withdrawal
- Demoralization
- Suicide

(They are less responsive to medication and therapy)

The role of Dopamine in schizophrenia

- **Positive symptoms** are due to **hyperreactivity of dopamine** transmission in **mesolimbic pathway**
- **Negative and Cognitive** symptoms are due to **hypoactivity of dopamine** transmission in **mesocortical pathway**

Other Dopamine pathways in CNS → effects

- **Extrapyramidal syndrome** (resting tremor, bradykinesia, muscle stiffness…) is due to **hypofunction** of **nigrostriatal pathway**
  - Antipsychotics inhibit dopaminergic receptors and can cause these symptoms
- **Tuberoinfundibular pathway**
  - Dopamine release from this pathway **inhibits the release of prolactin** from the pituitary gland
  - So, if there is **antidopaminergic** activity → **hyperprolactinemia**

Summary:

- **Hyperactivation of the mesolimbic pathway → positive symptoms of schizophrenia**
- **Hypofunction of the mesocortical pathway → cognitive and negative symptoms of schizophrenia**
- **D2 blockade of the nigrostriatal pathway →extrapyramidal syndrome**
- **D2 blockade of the tuberoinfundibular pathway increases prolactin blood levels → hyperprolactinemia**

Antipsychotic agents

- **1st Generation – Typical**
  - **D receptor antagonists (D_2 receptors)**
  - **More significant: Anti M, anti H_1, anti-alpha**

- **2nd Generation – Atypical**
  - **D2 receptor antagonists in some areas of brain**
  - **5-HT_{2A} receptor blockade (+ other 5HT receptors)**
  - **Mild Anti-M, anti-H_1, anti-alpha**

- ❖ The goal of the treatment by antipsychotics is to manage signs and symptoms at the lowest possible dose
- ❖ We have 2 classes of antipsychotics
  - ➢ The **1st generation**, or **typical**
  - ➢ And **the 2nd generation**, or **atypical**
- ❖ The main essential distinction between typical and atypical antipsychotics agents is the capacity to inhibit different types of receptors
  - ➢ The **1st generation** are generally **antagonists of D-receptors** – highly selective to **D2 receptor**
    - And they have other activities such as **anti-muscarinic**, **anti-histaminic** and **anti-alpha**
  - ➢ The **2nd generation**, atypical, agents are antagonists of D2 receptors but **only in some areas of brain**
    - And if we compare them to 1st generation, 2nd generation modulates the activity of serotonin receptors
    - They have the same other activity, but **only mild** anti-muscarinic, anti-histaminic and anti-alpha
  - ➢ These differences are necessary to know because we have to recognize different activities and different spectrum of side effects of 1st and 2nd generations of anti-psychotics

(D2 receptors = inhibitory receptors!)

7. Typical antipsychotic (17)

Antipsychotic agents

- **1st Generation – Typical**
  - **D receptor antagonists (D_2 receptors)**
  - **More significant: Anti M, anti H_1, anti-alpha**

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Mechanism of action of typical antipsychotics:

<u>Dopaminergic</u> → D2 blockade:

- Typical anti-psychotics block the dopamine receptors in **all areas of the brain** (in contrast to 2nd generation)
  - **D2 blockade in mesolimbic system** – for antipsychotic effect (**reduces positive symptoms**)
  - **D2 blockade in mesocortical system** in high doses – **can induce negative symptoms**
  - **D2 blockade in nigrostriatal system** – **induces extrapyramidal syndrome**
  - **D2 blockade in tuberoinfundibular system** - increases prolactin levels – **hyperprolactinemia**

Anti-Adrenergic: Alpha 1, alpha2

Anti-Muscarinic: M1-M3

Anti-Histamine: H1

- But they also inhibit adrenergic receptors, muscarinic receptors and histaminic receptors

→ These other activities may determine the additional actions and profile of **side effects**

Classification:

<u>Incisive antipsychotics</u> (Piperazine)

→ they have **high affinity to D2 receptors** and **low affinity to other types of receptors**.

- They affect **positive symptoms** of schizophrenia mainly.
- They have *higher frequency of extrapyramidal side effects* (EPS).
- ↑ Affinity to D2 → ↑ extrapyramidal syndrome, ↑ prolactin, ↓ affinity to H1 receptors, α1 M1, 5-HT, antiemetic action

<u>Sedative antipsychotics</u> (Aliphatics)

→ they have **lower affinity to D2 receptors** and **higher affinity to other receptor types**

- They have sedative effects, they cause anticholinergic, antihistaminic and cardiovascular side effects
  - And extrapyramidal symptoms are less frequent.
- ↓ Affinity to D2 → ↓ extrapyramidal syndrome, ↓ antipsychotic effect, ↑ blockade of H1, M1, α1, ↑ **hypno-sedative activity** (atropine-life effects)

1st generation – typical/conventional antipsychotics:

a. Phenothiazines

- **Piperazine derivates** (**incisive**):
  - Perphenazine
  - Prochlorperazine
  - Fluphenazine

Piperazine (incisive)
- **Higher potency for D2 receptors**
- **= Higher frequency of extrapyramidal side effects**

- **Aliphatic derivates** (**sedative**):
  - Promethazine
  - Chlorpromazine
  - Levomepromazine

Aliphatic (sedatives)
- **Higher Anticholinergic, antihistaminic efficiency**
- **= Higher sedative, atropine-like effects**

b. Butyrophenones (**more incisive**)

- Haloperidol
- Droperidol

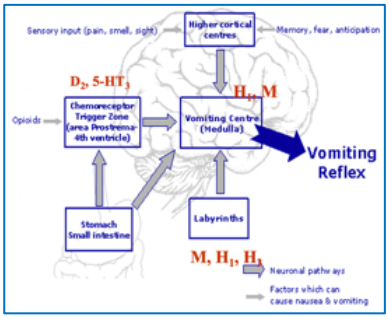
c. Thioxanthenes (**more sedative**)

- Chlorprothixene
- Zuclopenthixol
- Flupentixol

❖ **Haloperidol** is the most frequently used among the typical antipsychotics
- ➢ It exists in parenteral and peroral forms
- ➢ It is recommended for the treatment of schizophrenia, acute treatment of delirium, treatment of moderate to severe manic episodes, acute psychomotoric restlessness associated with bipolar disorder, it is also recommended for some ticks, including Tourette syndrome and many other indications

Therapeutic uses of typical (1st generation) antipsychotics

- **Psychosis, schizophrenia**
- **Agitation, aggressiveness**
- **Nausea and vomiting**
- **Intractable hiccups, stuttering (haloperidol)**



Phenothiazines as antiemetics

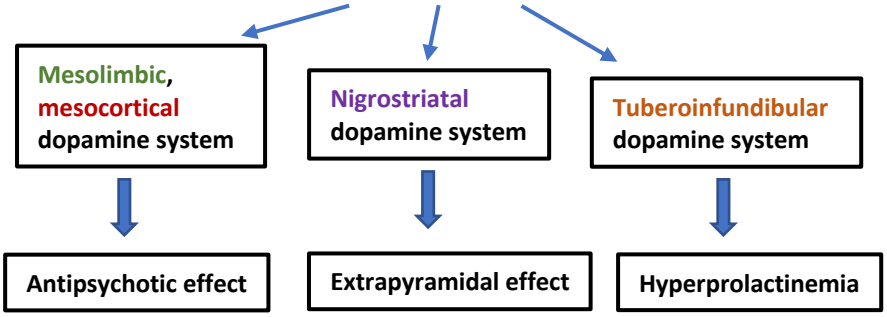
- Cancer chemotherapy, Meniere's disease, Postoperative emesis, …

❖ Most antipsychotics also have antiemetic effect

❖ They can interact with the central dopaminergic receptor in the chemoreceptor trigger zone in area postrema and thus, effect the vomiting center in medulla

❖ This center is under the control of histaminergic and muscarinic receptors
- ➢ Both mechanisms can be suppressed with phenothiazines as antiemetics
- ➢ Because they block dopaminergic, histaminergic and muscarinic receptors
- ➢ So, they can be recommended as anti-vomiting drugs for patients after chemotherapy, post-operative emesis, after intoxication of some drugs

Typical Antipsychotics – Side effects

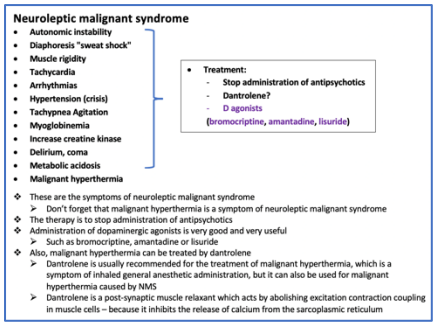


- ❖ When explaining the spectrum of side effects of typical antipsychotics, we must return to the individual dopaminergic pathways
- ❖ Don't forget that clinical effect of typical antipsychotics is related to non-selective inhibition of dopaminergic receptors in all mentioned dopaminergic pathways
- ❖ Logically, typical antipsychotics are more active on positive symptoms than negative, they can even cause worsening of positive symptoms
- ❖ Typical antipsychotics block dopamine in tuberoinfundibular pathway, so they can cause increase in the amount of prolactin in blood → hyperprolactinemia
- ❖ They also inhibit the nigrostriatal neurons so, they can be responsible for extrapyramidal syndrome

- **Extrapyramidal syndrome (EPS)**
  - **Parkinsonian syndrome**
  - **Dystonia**
  - **Akathisia**
- **Neuroleptic malignant syndrome**

} **Early**

- **Tardive dyskinesia** } **Late**



- **Neuroleptic malignant syndrome (NMS)**
- ❖ Neuroleptic malignant syndrome is a rare, but very dangerous medical situation, it requires immediate medical attention
  - ➢ The mortality is about 20%
- ❖ This reaction has been associated with various types of antipsychotics
  - ➢ But its prevalence may be more significant when high doses of typical antipsychotics are used
  - ➢ And especially when they are administered parenterally in depot forms of injections
- ❖ It can also be a symptom of some atypical antipsychotics, clozapine, olanzapine and risperidone
  - ➢ But it is rarer, more frequently this syndrome is related to typical antipsychotics

Other side effects of typical antipsychotics

- **Antiadrenergic (α_1):**
  - **Orthostatic hypotension**
  - **Reflex tachycardia**
  - **Problems with ejaculation**

- **Antiadrenergic (α_2):**
  - **Sedation**

- **Antihistaminic effect: anti H_1**
  - **Sedation**
    - Sedation is considered as a desirable effect in restless or aggressive patients, but generally it is counted as a side effect of antipsychotics
  - **Weight gain**
    - Weight gain can occur by extended treatment of most antipsychotics
    - Can be paradoxical, some patients lose weight, but only low percentage of patients

- **Anticholinergic (antimuscarinic) side effects:**
  - **Dry mouth...**
  - **Blurred vision, mydriasis**
  - **Tachycardia**
  - **Constipation**
  - **Urinary retention...**
  - **CNS anticholinergic effects – worsening of cognitive functions!**

8. Atypical antipsychotic drugs (61)

- Atypical antipsychotics – also known as 2nd generation antipsychotics
- Atypical antipsychotics intergrade with **serotonin**, **norepinephrine** and **dopamine** receptors
  - So, they have a different spectrum of receptor influence in comparison with typical antipsychotics

- Here is a list of the 2nd generation antipsychotics
  - The oldest are **selective antagonists of dopaminergic receptors**
  - Then, the **serotonin and dopamine antagonists** (**SDA**)
  - And lastly, **multi-acting receptor targeted agents** (**MARTA**)

D_2, D_3 selective antagonists
Sulpiride
Tiapride
Serotonin and dopamine antagonists (SDA)
Risperidone
Ziprasidone
Sertindole
MARTA
Clozapine
Olanzapine
Quetiapine
Zotepine

Benefit of atypical antipsychotics vs. typical

- **Low tensity to cause neurological side effects**
  - Extrapyramidal side effects or tardive dyskinesia
- **More effective on negative symptoms** of schizophrenia
- Improve cognitive function, antidepressant effect, anxiolytic...
- **Wider therapeutic index**
- However, at the cost of acting on different spectrum of receptors, the atypical antipsychotics have higher incidence of other side effects
  - Specifically ***metabolic side effects*** are a consequence of their administration

A. D_2, D_3 Selective antagonists

Mechanism of action

- **Biphasic regulation of dopamine system**
  - **In low Doses:**
    - **They inhibit presynaptic D_2/D_3 auto-receptors in mesocortical pathway**
    - **= Causes transient increase in dopamine release**
      - **→ So, in low doses, they can treat negative symptoms of schizophrenia!!**
  - **In high Doses**
    - **Classic antipsychotic activity (= decrease dopamine release in mesolimbic pathway)**
    - **Treating positive symptoms of schizophrenia**
- **Benefit: Effect on positive and negative symptoms**
- **BUT: hyperprolactinemia can be a consequence of their use**
  - **Also, mild extrapyramidal syndrome**

Agents:

- **Tiapride (alcohol withdrawal only)**

- The drug of choice from this group is tiapride
  - Tiapride is recommended for the management of alcohol withdrawal
    - Because dopamine hyperactivity has been linked with alcohol withdrawal syndrome, tiapride's antidopaminergic effects are the most likely mechanism for its clinical efficacy
  - Studies show that alcoholic patients treated with tiapride show reduced psychological distress and improve abstinence from alcohol
    - However, these are only experimental studies, at present time, tiapride is recommended only for acute 2 weeks alcohol withdrawal detox
      - Treatment to prevent hallucinations and to prevent extrapyramidal symptoms during alcohol withdrawal

Risperidone
Ziprasidone
Sertindole

B. SDA – Serotonin, Dopamine Antagonists

- These substances interact with dopamine, but they also manage some serotoninergic pathways
  - They are **very effective** in the management of schizophrenia

Serotonin and dopamine antagonists (SDA) – Mechanism of action

- The difference between SDA and typical antipsychotics is that SDA don't lower dopamine in all areas of the brain
- Firstly, they **inhibit the dopamine receptors in mesolimbic pathway**
  - So, they are very effective in the treatment of positive symptoms of schizophrenia
- However, SDA **increase the level of dopamine** in the **mesocortical region**
  - So, they can also treat negative symptoms of schizophrenia
- They also **increase dopamine** levels in **tuberoinfundibular** and **nigrostriatal** pathways
  - Thereby, **reducing** the extrapyramidal syndrome and hyperprolactinemia incidences
- This is the difference of SDAs in comparison with typical antipsychotics

- How do SDAs achieve these effects?
- → **Act on regulatory serotonin (2A) receptors and increase dopamine concentrations in MC, TI, NS pathway!**
  - By affecting the **regulatory receptors of serotonin,** SDAs inhibit the **presynaptic serotonin receptors which regulate the dopamine release**
  - So, they have the opposite effect in comparison with typical antipsychotics
  - → they increase dopamine concentration in mesocortical, tuberoinfundibular and nigrostriatal pathways!!

C. MARTA – Multi Acting Receptor Targeted Agents

Clozapine
Olanzapine
Quetiapine
Zotepine

- There is not such a big difference between SDA's and MARTA's
  - The structure of receptor modification is the same
  - They **inhibit dopaminergic receptors** in the **mesolimbic pathway**, treating the **positive symptoms**
  - They inhibit the **presynaptic serotonin receptors type 2A**
    - **Increasing dopamine concentration** in the **mesocortical**, **nigrostriatal** and **tuberoinfundibular** pathways
    - So, MARTA's **treat both positive** and **negative symptoms**, and **reduce** the occurrence of **extrapyramidal** syndrome and **hyperprolactinemia**
  - They stimulate serotonin receptor 1A, causing **anxiolytic effect**
- So, these are the same effects as in SDAs
- The differences between MARTAs and SDAs:
  - MARTA's **inhibit serotonin receptors 2C**
    - This type of serotonin receptor **regulates the appetite** and **satiety**
    - Therefore, **MARTAs cause significant weight gain**
  - They also inhibit the histaminergic receptors
    - Also increasing the weight gain
  - They may have **antidepressant** activity because they induce serotonin reuptake inhibition and norepinephrine reuptake inhibition
    - So, they are **very good antidepressants in case of resistant depression**

Indications of atypical antipsychotics

- **Schizophrenia and schizoaffective disorder (first line therapy)**
  - Both typical and atypical antipsychotics are used to treat schizophrenia and schizoaffective disorders
    - However, at present time, atypical antipsychotics are first-line therapy
- **Depressions (resistant forms) - MARTA**
- **Bipolar disorders**
  - Atypical antipsychotics rapidly control acute mania and mixed episodes, often in conjunction with mood stabilizers such as lithium or valproate
- **Psychic symptoms of dementia (aggression, agitation…)**
- **Anxiety disorders (panic)**
  - Atypical antipsychotics have very good anxiolytic effect
    - Anxiety disorders and especially panic disorders can be managed with atypical antipsychotics
- **Psychosis induced by antiparkinsonics**



Auka info um clozapine + olanzapine

Clozapine

- An example of MARTA is clozapine
- Clozapine is the main stone of atypical antipsychotics
- The limitation of clinical use of clozapine is the bone marrow suppression and **agranulocytosis**
  - The incidence is about 1% within several months of treatment and is independent of dose
  - So, it is recommended to control the blood count if clozapine is used in therapy
  - Some other drugs increase the risk of agranulocytosis, especially antiepileptics, carbamazepine, analgesic metamizole
- Clozapine has very good antipsychotic activity, however, today it is not the first-line drug
  - Despite its excellent effect, clozapine is only used in resistant forms of schizophrenia
- Except for agranulocytosis, it can cause cardiac side effects such as myocarditis

Olanzapine

- **Clozapine without agranulocytosis**
- **Paradoxical reactions: unusual changes in personality, thoughts or behavior; hallucinations and suicidal ideation**

- The second type of frequently used MARTA antipsychotic is olanzapine
- Olanzapine is known as “modern clozapine” – or clozapine without agranulocytosis
- The spectrum of side effects is similar as for clozapine, olanzapine can cause some paradoxical reactions and unusual changes in personality, thoughts or behavior can be a consequence of olanzapine administration

Atypical antipsychotics – side effects

- Metabolic syndrome is more significant after administration of atypical antipsychotics, especially MARTA’s
  - MARTA’s have higher incidences of metabolic syndrome than SDA’s

- Metabolic syndrome: MARTA > SDA

- Metabolic syndrome is defined as:
  - **Hyperglycemia (inhibition of insulin release)**
  - **Insulin resistance (insensitivity of ins receptors in periphery)**
  - **Worsening of pre-exist diabetes**
  - **Hyperlipidemia**

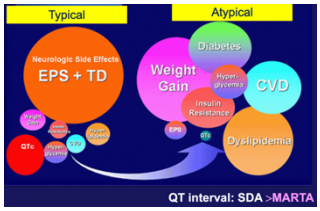
- + anti-M, anti-alpha1, anti-H1

- MARTA antipsychotics (clozapine, olanzapine, quetiapine) are associated with the most significant weight gain and decrease insulin sensitivity
  - Followed by risperidone (SDA) and other groups of antipsychotics

Side effects of atypical antipsychotics:

- Shift in risk perception

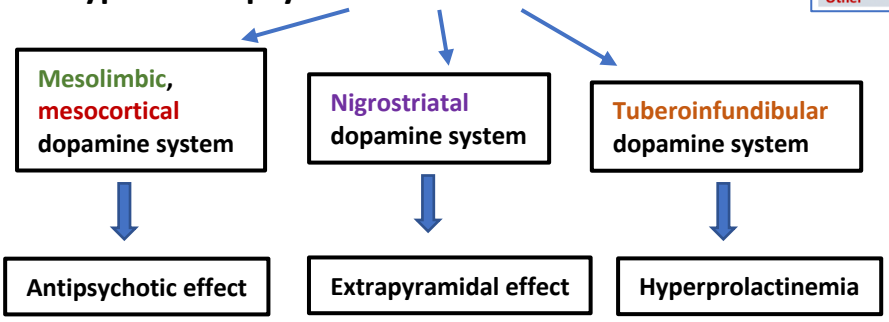
- This picture is a good comparison of the frequency of occurrence of side effect between typical and atypical antipsychotics
- Dominant side effects of typical antipsychotics are neurological side effects
  - Extrapyramidal and tardive dyskinesia
- And in the case of atypical, the side effects spectrum is shifted to metabolic side effects
  - Hyperglycemia, hyperlipidemia, cardiovascular disorders, weight gain, insulin resistance
  - Extrapyramidal syndrome and tardive dyskinesia are less significant



Autonomic nervous system	Dry mucous membranes, problems with accommodation, urination, obstipation	Anti-muscarinic effect
	Orthostatic hypotension, impotence, ejaculation problems	Anti-adrenergic effect
Central nervous system	EPS, Parkinson syndrome, akathisia, dystonia	Anti-dopaminergic effect
	Tardive dyskinesia	Dopaminergic receptors hypersensitivity
	Toxic – confusional state	Anti-muscarinic effect
Endocrine system	Amenorrhea Infertility, impotence	Hyperprolactinemia
Other	Weight gain	H_1-blockade

9. Side effects of antipsychotics – (25)

a. Typical Antipsychotics – Side effects

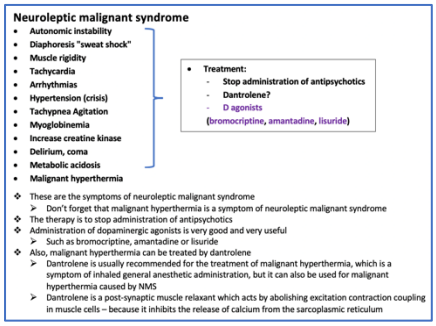


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  - **Parkinsonian syndrome**
  - **Dystonia**
  - **Akathisia**
- **Neuroleptic malignant syndrome**

} **Early**

- **Tardive dyskinesia** } **Late**



- **Neuroleptic malignant syndrome (NMS)**
- ❖ Neuroleptic malignant syndrome is a rare, but very dangerous medical situation, it requires immediate medical attention
  - ➢ The mortality is about 20%
- ❖ This reaction has been associated with various types of antipsychotics
  - ➢ But its prevalence may be more significant when high doses of typical antipsychotics are used
  - ➢ And especially when they are administered parenterally in depot forms of injections
- ❖ It can also be a symptom of some atypical antipsychotics, clozapine, olanzapine and risperidone
  - ➢ But it is rarer, more frequently this syndrome is related to typical antipsychotics

Other side effects of typical antipsychotics

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  - **Sedation**
    - Sedation is considered as a desirable effect in restless or aggressive patients, but generally it is counted as a side effect of antipsychotics
  - **Weight gain**
    - Weight gain can occur by extended treatment of most antipsychotics
    - Can be paradoxical, some patients lose weight, but only low percentage of patients

- **Antiadrenergic (α_1):**
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  - **Problems with ejaculation**
- **Antiadrenergic (α_2):**
  - **Sedation**
- **Anticholinergic (antimuscarinic) side effects:**
  - **Dry mouth...**
  - **Blurred vision, mydriasis**
  - **Tachycardia**
  - **Constipation**
  - **Urinary retention...**
  - **CNS anticholinergic effects – worsening of cognitive functions!**

b. Atypical antipsychotics – side effects

❖ Atypical antipsychotics have absolutely different spectrum of side effects
❖ Metabolic syndrome is more significant after administration of atypical antipsychotics, especially MARTA's
  ➢ MARTA's have higher incidences of metabolic syndrome than SDA's

- Metabolic syndrome: MARTA > SDA

- Metabolic syndrome is defined as:
  - **Hyperglycemia (inhibition of insulin release)**
  - **Insulin resistance (insensitivity of ins receptors in periphery)**
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- + anti-M, anti-alpha1, anti-H1

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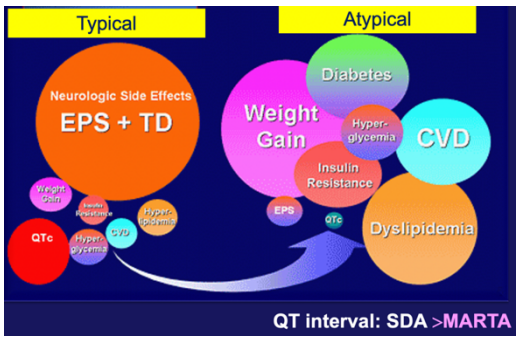
Estimated mean weight gain at 10 weeks

❖ This picture compares estimated mean weight gain after 10 weeks of treatment with antipsychotics
❖ The MARTA's have the highest incidences, clozapine and olanzapine
  ➢ Their average weight gain is 5 kg per 10 weeks
❖ Interestingly, primarily obese patients gained less weight before they started treatment
❖ This side effect is very undesirable and limits the clinical use if atypical antipsychotics

Side effects of atypical antipsychotics:

- Shift in risk perception

❖ This picture is a good comparison of the frequency of occurrence of side effect between typical and atypical antipsychotics
❖ Dominant side effects of typical antipsychotics are neurological side effects
  ➢ Extrapyramidal and tardive dyskinesia
❖ And in the case of atypical, the side effects spectrum is shifted to metabolic side effects
  ➢ Hyperglycemia, hyperlipidemia, cardiovascular disorders, weight gain, insulin resistance
  ➢ Extrapyramidal syndrome and tardive dyskinesia are less significant



10. Nootropic drugs (4)

- **Memory enhancers, cognitive enhancers, and intelligence enhancers**
- **Delayed onset of action (2-3 months!)**
- **They work by altering the availability of the brain´s supply of neurochemicals, by improving the brain's oxygen supply, or by stimulating nerve growth.**
- **However, the efficacy of nootropic substances, in most cases, has not been conclusively determined!!!**

- Nootropic agents are drugs that ***improve memory***, they are known as ***cognitive enhancers*** and ***intelligence enhancers***
- Nootropics are not psychostimulants; they have delayed onset of action and their effect appears after approx. 2 or 3 months
- Their mechanism is different, they can improve the brain supplies of neurochemicals, they can improve the circulation of brain, they can scavenge oxygen radicals
- Indications for their use is memory and intellectual disorders, such as senile dementia, cerebrovascular circulation disorders caused for example by atherosclerosis of the brain or after stroke
- But the efficiency of nootropic agents in most cases has not been conclusively determined
  - We haven't got any long-term studies that confirm the benefit of nootropic therapy

Nootropics

Indication: Organic disturbances of memory and intellect, senile dementia… Efficacy after 2-3 months		
Pyritinol	**ENERBOL ENCEPHABOL**	**Oxygen radicals scavenger, glucose brain metabolism, ...**
Piracetam	**NOOTROPIL, PYRAMEM, KALICOR**	
Nootropics – Vasodilators (Improve rheologic blood quality and cerebral perfusion)		
Cinnarizine	**STUGERON**	**Calcium channels blockers**
Vinpocetine	**CAVINTON**	
Flunarizine	**SIBELIUM**	
Naftidrofuryl	**ENELBIN DUSODRIL**	**Antagonist of $5HT_2$**
Nootropics – Ergot alkaloids vasodilators (alpha antagonists)		
Dihydroergotamine	**SECATOXIN**	
Nicergoline	**SERMION**	

- Nootropics can be vasodilators, calcium channel blockers, antagonists of serotonin receptors, phosphodiesterases, they can be alpha antagonists, ergot alkaloids, dehydro-derivates, dihydroergotoxine, or pyritinol and piracetam – these members of nootropics are scavengers of oxygen radicals and they improve the glucose metabolism in the brain, but the precise mechanism of action is not fully explained

11. Antidepressants action – (Overview, mechanism of action) (33)

Intro – Depression:

- *A persistence of low mood and aversion to activity that can affect person thoughts, behavior, feelings and physical well-being*
- **Symptoms:**
  - Moodiness, anger, irritability, anhedonia, sadness, guild, low self-confidence, social isolation, changes in sleep + appetite, somatic complaints

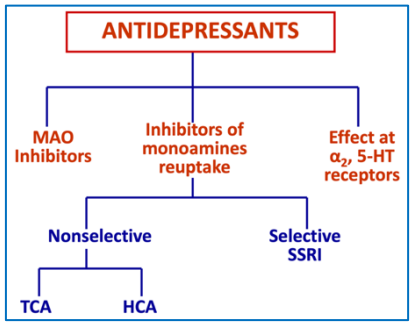
Monoamine theory of depression

- **Pathogenesis:**
  - **Reduced levels of Serotonin**
  - **Reduced levels of Norepinephrine**
  - **Dopamine** ↑ = mania – ↓ = depression

Therapeutic use of antidepressants

- **Depression**
- Expect for depression, we can also use antidepressants for:
  - **Panic, generalized anxiety, social phobia (SSRIs)**
  - **Obsessive-compulsive disorders (SSRIs)**
  - **Enuresis**
    - Some of the drugs, like imipramine for example, can be used for the therapy of enuresis and nocturia (urination during night)
- **Bulimia nervosa, anorexia nervosa, gambling**
- **Chronic algic syndromes – neuropathic, myofascial pain (TCA, SSRI, SNRI)**
- When we use antidepressants, the major mechanisms are coupled with some way to increase neurotransmitters (mainly serotonin, but also norepinephrine) in the synaptic clefts
- There are different ways how to do that:

Antidepressants – Classification:



1 **Inhibition of monoamine reuptake**
   - Mechanism of action → ↓ transport of neurotransmitters
   a) **Selective → SSRI**
   b) **Nonselective → TCA + HCA**

2 **MAO-Inhibitors**
   - Mechanism of action → Inhibit degradation of neurotransmitters

3 **Effect at α_2 + 5-HT receptors (antidepressant with the influence at receptors)**
   - ↓ density of receptors → ⊖ overexpressed receptors

1. Inhibitors of monoamine reuptake:

a) SSRI (selective serotonin reuptake inhibitors)

- SSRIs block the reabsorption (reuptake) of serotonin into neurons
- They inhibit ***serotonin transporters***, which remove serotonin from the synaptic cleft back into the cells
  - = We will have higher amount of serotonin available in the synaptic cleft
- Serotonin receptors will be activated, and by prolonged activation it will lead to downregulation to the normal levels of these receptors
- SNRIs are drugs which inhibit the reuptake of both serotonin and norepinephrine

b) TCA (tricyclic antidepressants)

- Inhibitory reuptake of both norepinephrine and serotonin = non-selective
- TCAs are also antagonists of other receptors, especially histamine (H1), adrenergic receptors (α1 and α2) and also muscarinic receptors = many and frequent side effects
- Currently TCAs are not considered as drugs of first choice → SSIRs = 1st choice

2) MAO-I (monoaminoxidase inhibitors)

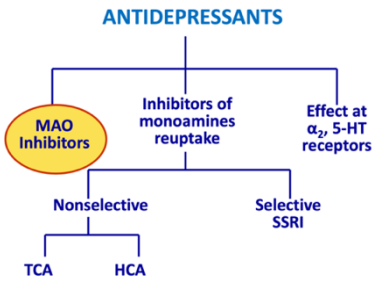
- They inhibit the degradation of monoamines, like serotonin and norepinephrine
- This can be done by inhibition of the enzyme ***monoaminoxidase (MAO)***
- We have different isoforms of MAO, MAO-A and MAO-B
  - The role of MAO-B is to degrade **dopamine**
  - MAO-A are involved in the degradation of **norepinephrine** and **serotonin**
- By inhibiting MAO-A we increase the concentration of norepinephrine and serotonin in the synaptic cleft
- Unfortunately, MAOs act very non-selectively
  - When we inhibit MAO-A, we inhibit them in the whole body
  - Thus, it is associated with quite many side effects
  - And what is worse, it is associated with the risk of interactions
    - We should ***never co-administer SSRIs together with MAOs***, because it can lead to dramatic increase of serotonin in synaptic clefts, not only in the brain, but all around the body
      - This may lead to hypertensive crisis which may be fatal for the patient

3) Antagonists of "bad" serotonin receptors + agonists of "good" serotonin receptors

- Another way how to treat depression is to somehow influence these receptors which are overexpressed
- How to antagonize these overexpressed receptors? (we don't want overexpressed receptors)
  - We can antagonize them; we can use antagonists of certain receptors, especially serotoninergic receptors
  - In this situation, we talk about antagonists of serotonin receptors
  - Or we don't only have negative receptors, we also have positive receptors which are called "good" receptors, there we use more often agonists

- Also, there are molecules which may combine a triple effect
- There is a drug called vortioxetine, which may:
  - Inhibit reuptake of serotonin
  - Antagonize these bad serotonin receptors
  - And at the same time, it can be an agonist on these good serotonin receptors
- It is not easy to call this drug by some uniform name, that's why we call this drug "multimodal drugs" or "drugs with multimodal activity"

- These are the basic ways how to increase neurotransmitters in the synaptic cleft
  - The lack of neurotransmitters in synaptic cleft and there are certain ways how to increase them, and to help us to influence the upregulation of "bad" serotoninergic receptors
  - And by this way, we can influence the production and secretion of BDNF leading to increased neuroplasticity



12. Antidepressants – MAO inhibitors (62)

Inhibitors of monoaminoxidase - (Thymoeretics)

❖ ***Monoaminoxidase*** is an enzyme which has a role in **degradation of monoamines**:
- ➢ MAO-A: **Serotonin**, **norepinephrine**, **epinephrine** and **tyramine**
- ➢ MAO-B: **Dopamine**

MAO-Inhibitors

- **For *atypical depression***
- **As a last line of treatment when other classes have failed**
- The position of MAO-I in therapy of depression is that they are **last line of treatment, when other classes have failed**, why?
  - It is not because they are not effective, it is because they have ***very high risk*** and ***high frequency of adverse effects***
- **Rapid, good GIT absorption → Can be administered perorally**
- **Good distribution**
- **Liver metabolism**
- **T½ – short relatively**

MAO-A

- Inhibition of MAO-A **reduces the breakdown** of serotonin, epinephrine, **norepinephrine**
  - So, MAO-A inhibitors can be used for the therapy of depression
  - When we use MAO-A inhibitors, there will be ↑ **serotonin** and ↑ **norepinephrine** available in synaptic cleft
- **→ a higher risk of serotonin syndrome and/or a hypertensive crisis**
  - Inhibition of MAO-A may lead to accumulation of serotonin, epinephrine and norepinephrine, and this leads to a special problem called cheese reaction – or serotoninergic effect
- **Tyramine** is also broken down by MAO-A
  - **Therefore, inhibiting MAO-A may result in excessive build-up of tyramine**
  - **So, diet must be monitored for tyramine intake. This risk is generally not present with RIMAs**

MAO-B

- **Inhibition reduces the breakdown mainly of dopamine**
  - **= Used for the therapy of Parkinson's disease!**
- **Two such drugs, selegiline and rasagiline**

MAO inhibitors (MAO-I)

- Phenelzine
- Isocarboxazid
- Tranylcypromine

→ **Non-selective (irreversible)**

- Moclobemide
- Pirlindole

→ **MAO-A selective (reversible RIMA)**

- Selegiline
- Rasagiline

→ **MAO-B selective**

❖ Moclobemide is the only MAO-A inhibitor which is available on market
- ➢ The others are not used anymore

❖ Moclobemide belongs to the RIMAs
- ➢ We only use reversible MAO-A inhibitors to prevent cheese reaction

❖ These irreversible and non-selective agents have dramatic side effects

The side effects associated with reduced degradation of norepinephrine and serotonin are postural hypertension, dry mouth, blurred vision and urinary retention
- These are atropine-like effects

Also, weight gain, which is partly associated with histaminergic activity

MAOI – adverse effects

- **Tremors**, **confusion**, **memory impairment**, **headache**, **tremors**, **anxiety**, **insomnia** etc.
- **Sexual dysfunction** due to **higher concentration of serotonin available**
- And of course, due to **norepinephrine**, **heart palpitation** can also be a problem
- Blurred vision, xerostomia,

- **Hypertensive crisis ("cheese reaction")**
  - **Tyramine (↑ BP) – metabolized by MAO in GIT**

- Hypertensive crisis (cheese reaction) is due to presence of tyramine in food
  - So, the patient should follow a low tyramine diet when being administered MAO inhibitors
- Also, we should be careful when co-administering monoaminoxidase inhibitors with other drugs
  - An example can be when you have a patient who is being treated with **SSRIs**, and the therapy is not successful, and you decide to switch the patient to MAO-I
    - We should **wait several days up to a week** until we start the treatment with MAO-I
    - Otherwise, they can lead to hypertensive crisis
    - The reason for that is that some SSRIs, like fluoxetine for example, has extremely long half-life, more than 30 hours (Prozac is the brand name for fluoxetine)
    - Furthermore, it also has active metabolites, which means that when we stop medication of SSRIs, we can start with MAO-I after several weeks, with fluoxetine it is after 6 weeks, in order to prevent this hypertensive crisis or cheese reaction

- **Moclobemide does not cause the cheese reaction because it is a reversible selective inhibitor of MAO type A, which inactivates noradrenaline and 5-HT**

- When using moclobemide the risk of causing cheese reaction is much lower, but it still exists

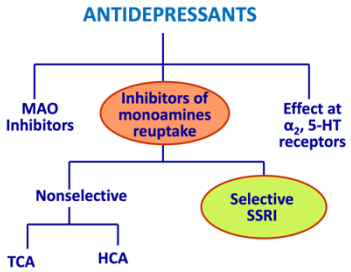
Note! patients must wait for 14 days following discontinuation of MAO inhibitor before they can safely consume any of these foods or drugs enhancing NE

- It also works oppositely; patients must wait for 14 days following discontinuation of MAO-I
- MAO have short duration of action, but we should be careful

MAOI - drug interactions

- **Sympathomimetics**
- **Dopamine agonists (Bupropion)**
- **SSRIs, Venlafaxine, TCA**
- **L-Tryptophan**
- **Analgesics (tramadol, dextromethorphan...)**

- The drug interactions are with sympathomimetics of course
- With dopamine agonists, like bupropion
- SSRIs, venlafaxine is a SNRI and also tricyclic antidepressants
  - Venlafaxin belongs to the group of serotonin and norepinephrine reuptake inhibitors
- All of these have something to do with serotonin
  - That's why they are contraindicated to be used together with monoaminoxidase inhibitors



13. Antidepressants - SSRI, SNRI (57)

- Inhibitors of monoamine reuptake

❖ They are classified to 2 subgroups → **Non-selective** and **selective**

❖ From **non-selective** we have **tricyclic antidepressants** and **heterocyclic antidepressants**

➢ Non-selective means that they inhibit the reuptake of more than one monoamine

▪ Either **serotonin** and **norepinephrine** or **norepinephrine** and **dopamine**

▪ Or maybe **all 3 together**, norepinephrine, serotonin and dopamine

➢ Tricyclic antidepressants inhibit all 3 monoamines

❖ From selective we have SSRIs

➢ Selective means that they inhibit the reuptake of only one monoamine

a. SSRI = Selective Serotonin Reuptake Inhibitors

❖ SSRIs can be thought of as a subgroup of heterocyclics

➢ Only difference between them is that SSRIs are selective

❖ We must remember this group, why?

➢ Because SSRIs are currently the **drugs of choice in the therapy of depression**

- **Citalopram**
- **Fluoxetine (PROZAC)**
- **Fluvoxamine**

❖ Remember **citalopram**, **fluoxetine**

❖ We also have available fluvoxamine

➢ It is used to treat depressive symptomatology in patients who are dependent on alcohol for example

➢ It can also be used in the treatment of patients with anxiety

Mechanism of SSRI action

- **The mechanism Is BLOCKADE of the serotonin transporter**

❖ The principle of the mechanism of SSRIs is to inhibit the reuptake of serotonin, so there will be more serotonin available in the synaptic cleft

- **↑ of postsynaptic 5-HT1A sensitivity**

❖ The target of SSRIs is to **increase the sensitivity of postsynaptic 5-HT1a receptors**

❖ If there is already increased expression due to upregulation of 5-HT2a and 5-HT2c receptors, they should be blocked

➢ By longer duration of exposure to serotonin, they will be downregulated = good thing

❖ If we need faster action, it is good to use a drug which combines inhibiting of reuptake and at the same time antagonizes these "bad" serotonin receptors →5-HT2a + 5-HT2c, using multimodal drugs

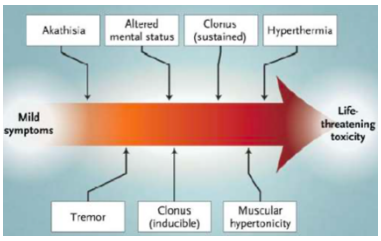
SSRIs – pharmacokinetics

- **Inhibition of cytochrome P-450**
  - **Fluoxetine** is a ***very potent inhibitor of cytochrome P450***
  - If patient is taking a drug which is also metabolized via cytochrome P450, **fluvoxamine** is considered as a safer alternative of fluoxetine
    - Because the inhibition of cytochrome P450 is lower compared to fluoxetine
- **↑ protein binding**

SSRIs – adverse effects

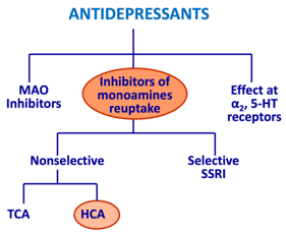
❖ The side effects of SSRIs are mostly associated with serotonin

- **Nausea, vomiting, diarrhea**
- **Tremor, muscle rigidity, myoclonus**
- **Disturbances of the sexual functions** (serotonin!)
- **Anorexia**
- **Agitation, insomnia**
- **Hyperthermia**
- **Risk of bleeding – antiplatelets**
- **Rapid changes in mental status and vital signs**
- **Suicide as an adverse effect?**



Serotonin syndrome

- ❖ Serotonin syndrome can happen due to SSRI overdose
  - ➢ Especially if you combine SSRIs with drugs which also inhibit cytochrome P450
  - ➢ Or if you combine SSRIs with drugs which increase serotonin levels in the brain
- ❖ This life-threatening complication can lead to ***hyperthermia***, ***muscular hypertonicity***, clonus etc.
- **It is important to wait up to 6 weeks after medication is stopped, before starting with another drug**
- **Treatment → Cyproheptadine 5-HT$_2$ antagonist = antidote for serotonin syndrome**
  - ➢ This antidote is an antagonist of 5-HT2 receptors
  - ➢ Cyproheptadine can be used
- ❖ Importantly, when we stop medication with SSRIs, we should wait for up to 6 weeks before we start using another drug
  - ➢ Especially this goes for fluoxetine – it is crucial



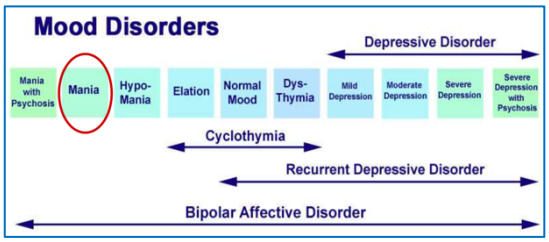
b. SNRI (Serotonin and Norepinephrine Reuptake Inhibitors)

- ❖ SNRIs belong to the group of **heterocyclic antidepressants** (HCAs)
- **Venlafaxin**
- **Duloxetine** (also milnacipran) → neuropathic pain
- **Effective in the patients resistant to SSRI or for SSRI side effects**
- **More rapid onset of the action**
- ❖ A very important group which can inhibit both **serotonin** and **norepinephrine** reuptake (SNRI)
  - ➢ More serotonin and norepinephrine available in the synapse
- ❖ In case we need to treat **anxiety**, or we need to **neuropathic pain** then drugs from the group of SNRI would be the dugs of choice
  - ➢ For example, **milnacipran** is only registered for the therapy of neuropathic pain
  - ➢ **Venlafaxin** and **duloxetine** can be used in the **therapy of anxiety**

SSRI/SNRI Discontinuation Syndrome

- **F.I.N.I.S.H.**
- **Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbance, Hyperarousal**
- ❖ Oppositely, whenever we have in a drug a serotonin reuptake inhibitor, which means there are high levels of serotonin, if we stop the medication too quickly, it can lead to discontinuation syndrome
  - ➢ It means that we will have some symptoms ones the body senses that we are suddenly missing this serotonin previously provided by SSRIs/SNRIs

- ❖ Why are SSRIs preferred over TCAs?
  - ➢ They have similar efficacy, similar price and similar pharmacokinetics
  - ➢ But the reason is the higher risk of side effects of TCAs
  - ➢ SSRIs have much fewer anticholinergic and cardiovascular side effects
    - ▪ Because SSRIs do not influence so dramatically histaminic and muscarinic receptors
- ❖ However, ***SSRIs have more sexual and gastrointestinal side effects*** compared to TCAs
  - ➢ But generally, SSRIs are better tolerated due to fewer side effects
- ❖ SSRIs are associated with less frequent treatment discontinuation compared to TCAs
  - ➢ Except for the side effects of TCAs, another reason for this can be increased body weight due to TCAs
- ❖ Also, importantly, SSRIs are generally considered as a safer alternative in overdose compared to TCAs
  - ➢ This means that if you have patient who has suicidal tendencies, then it would be much wiser to treat him with SSRIs rather than TCAs
  - ➢ Because the risk of cardiovascular toxicity which can be induced after taking 5x the daily dose of TCAs can lead to death of the patient
- ❖ However, in case of SSRIs, it was discovered in recent studies that in children and adolescents, especially in the beginning of treatment, may trigger suicidal tendencies
  - ➢ So, before the treatment they have no suicidal tendencies and then suddenly after being treated with SSRIs they might have it
  - ➢ Luckily, the intoxication with this drug is not as risky as with the TCAs
  - ➢ But of course, these patients can find other ways how to end ther lifes
  - ➢ So, the therapy with SSRIs in children and adolescents should be very carefully monitored
    - ▪ Especially in the beginning of treatment
    - ▪ It is recommended to keep them in the hospital for the first 2-3 week to observe the effect of the drug



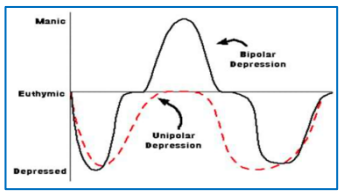
14. Antimanics (55)

Anti-manics or Mood Stabilizers

- We use 2 groups of drugs for treating mania
  - One is **lithium**
    - An element which is normally found in nature, it is relatively cheap and has good bioavailability
    - Unfortunately, it is relatively toxic
      - It can interfere with other ion channels
  - The other possibility is to stabilize the membranes by using **antiepileptics**
    - Mostly, we don't use antiepileptics which influence GABA receptors, but we use drugs which ***antagonize especially sodium channels***

Antimanics

- **Are used to treat bipolar disorder**
- **Mood stabilizers – decreases not only the manic phase but also the depressed phase of bipolar disorder**
- **For many years – lithium**
- **More recently – some antiepileptics, e.g., carbamazepine and valproic acid**
  - The main role of these is to block sodium channels



a. Lithium

- The target of therapy is to keep the patient at or under the normal levels
- We will still have some waves, recurrent depression
  - But ***no manic bipolar phases***

- **Lithium - as a *mood stabilizer* or an *antimanic* rather than an antidepressant because it will relieve manic symptoms and block both mania and depression, but it cannot treat depression**
- The problem of lithium is that its mechanism is not completely clear, and it is associated with many side effects (***cardiovascular*** and ***urinary tract*** side effects)
  - Also, the problem with them is their **toxicity** which is associated with their concentration in plasma
  - ***The therapeutic index is very small*** (Therapeutic index is the ration between the toxic dose and the effective dose)
    - If this ratio is big, then the drug is relatively safe
    - Small therapeutic index = small difference between effective dose and toxic dose, we must be careful when using the drug, because only a small increase in concentration may lead to severe side effects

Lithium – Pharmacokinetics

- **Rapid absorption – can be a problem**
- **Peak 30 min-2 hours**
- **Most Li is now in a slow-release forms**
- **A low therapeutic index – blood levels need to be carefully monitored**
- **Is excreted unchanged**
- **Half-life of 12-21 hours (36 hours)**

- The problems of lithium can only be solved by monitoring the blood levels in order to prevent toxicity

Possible mechanisms of Li action

- **More Cl- and K+ inside the cell = hyperpolarization = less excitable = stabilization of membrane**

- This is the "possible" mechanism of action – because it is not 100% known
- Alteration of balance of chlorine and potassium
- So, the major target of lithium is to stabilize membranes
  - Similarly, like anti-epileptics
- Many other mediators and receptors can be involved, downregulation of norepinephrine receptors etc.
- But their major effect is stabilization of cell membranes

Lithium – Toxic drug

- **Adverse reactions are dose- and concentration-dependent**

Lithium – adverse effects

- Lithium is a toxic drug, so it leads to adverse reactions
- Its adverse effects are mostly associated with gastrointestinal tract and motility
    - Its use also leads to weight gain

- **Hand tremors**
- **Increased thirst**
- **Nausea and vomiting**
- **Diarrhea**
- **Swelling**
- **Weight gain**
- **Fatigue**
- **Muscle weakness**
- **Hypothyroidism**
- **Strong teratogen**
- **Long-term use – kidney damage or failure**

b. Anticonvulsants

- **Valproic acid**
- **Carbamazepine**

Skrifa eitthvað um anticonvulsants!

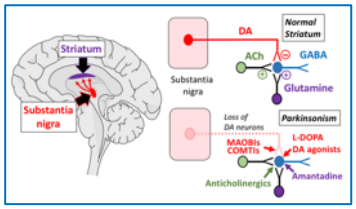
<u>Lamotrigine</u>

15. Antiparkinsonics – (50)

Parkinson's disease = neurodegenerative disorder that affects both motor and cognitive function

Pathogenesis of Parkinson's disease

- Parkinson's disease affects nerve cells in the basal ganglia and the substantia nigra
- Nerve cells in the substantia nigra produce the neurotransmitter **dopamine** and control the body movements
  - In Parkinson's disease, **dopamine-producing nerve cells of the substantia nigra begin to die**
- Control of GABA release in substantia nigra:
  - ***Dopamine inhibits GABA release***
  - ***Acetylcholine increases GABA release***
- But Parkinson's disease, due to loss of dopaminergic neurons, dopamine is not inhibiting GABA release
  - So, the **GABA release** is **increased** because it is in the control of **acetylcholine** in absence of dopamine
  - = There is an imbalance between dopaminergic and cholinergic neuronal transmission, in favor of the cholinergic



- **↓ Dopamine**
- **↑ Acetylcholine**
- **↑ GABA**

Symptomatology of Parkinson's disease

- Symptoms can take years to develop, most people live for many years with the disease
- Non-motoric symptoms: ***fatigue, constipation, depression…***
- Motoric symptoms: ***Resting tremor, bradykinesia, akinesia, muscle rigidity, postural instability***
- Clinical symptoms: typical symptoms of Parkinson's disease when ***80% of dopamine is lost***

Antiparkinsonics

- Medications that can replace dopamine are the mainstay of the treatment
- **1. Dopaminergic drugs**
  - **A. Dopamine replacement therapy**
  - **B. Catechol-O-methyltransferase inhibitors (COMT inhibitors)**
  - **C. Dopamine agonists**
  - **D. Monoamine oxidase inhibitors (MAO-B inhibitors)**
  - **E. NMDA-receptor antagonists**

Inhibitors of dopamine metabolism

- **2. Anticholinergic/Acetylcholine-blocking drugs**



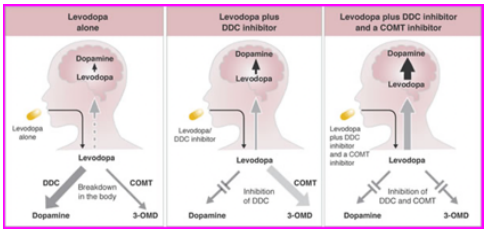
a. Dopamine replacement therapy

Levodopa (L-DOPA)

- **Levodopa** (L-DOPA) is used as a **prodrug** to **increase dopamine levels** *(Tyrosine → Levodopa → Dopamine)*
  - **L-DOPA** is able to **cross the blood brain barrier very easily** (***dopamine is not able to cross BBB!***)
- Once levodopa has entered the CNS it is metabolized to dopamine by ***amino acid decarboxylase***

Pharmacokinetics – L-DOPA given orally has several disadvantages

- Levodopa is absorbed in proximal part of small intestines
- L-DOPA shares the same active transport system (competes) with **large neutral amino acids** (LNAA)
  - Therefore, a high amount of dietary proteins decreases the uptake of L-DOPA
- Another disadvantage is **fast L-DOPA metabolism in the periphery**
  - Result of this is less L-DOPA available to cross the intestinal mucosa and then to cross the BBB and in turn, higher levels of L-DOPA metabolites in the periphery which cause adverse effects
- **= Only about 1-3% of administered levodopa actually enters the brain unaltered**
  - **Therapy with L-DOPA alone is not effective**



How to manage these disadvantages?

- Combination with L-amino acid (DOPA) decarboxylase inhibitors

- Levodopa is always given together with **DOPA decarboxylase inhibitors**
  - Either **carbidopa** or **benserazide** (they do not penetrate the blood-brain barrier!!)
  - Combining levodopa with these inhibitors nearly triples the oral bioavailability of levodopa
  - They markedly reduce both the required level of levodopa to reach therapeutic dose and severity of dopamine mediated gastrointestinal and cardiovascular side effects

- Combination with COMT inhibitors

- In addition, in the presence of **amino acid decarboxylase inhibitors**, the metabolism of levodopa can be predominantly shifted to formation of **methyldopa** by the **COMT** enzyme which has its highest activity in the liver and kidney
- In such conditions, we can use triple therapy
  - That means**: L-DOPA** + **amino acid decarboxylase inhibitors** (carbidopa or benserazide) + **COMT inhibitor**

Levodopa = Platinum therapy for Parkinson's disease (the most effective of all drugs used for symptoms of PD)

- **PD progression is not altered → *symptomatic treatment***
- **After 5 years of L-dopa therapy ↓ efficacy (nearly 80% of young patients or 44% in older patients develop motor complications)**
  - Early use L-DOPA may predispose patients to develop long-term motor complications
    - → "Wearing off" phenomenon – when effects diminish before its time for next dose
    - → "On-off" phenomenon – switch between mobility and immobility
- **+ bradykinesia, rigidity**

Side effects of L-DOPA:

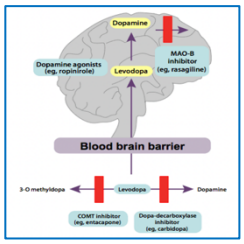
- **GIT → nausea + vomiting**
- **CVS → arrhythmia + orthostatic hypertension**
- **Psychotic disorders**
- **Motor complication (dyskinesia)**
- **Others…**

Contraindications

- **Drug-Drug Interactions (DDI):**
  - **MAO inhibitors (can lead to hypertensive crisis), antipsychotic drugs, pyridoxin (B6)**
- **Active peptide ulcer**
- **CVS disease**
- **Psychosis**
- **Glaucoma** (L-DOPA can increase intraocular pressure)
- **Melanoma** (because L-DOPA can be metabolized via melanogenic pathway to melanin

b. COMT inhibitors

- COMT inhibitors are only **adjunctive therapy to L-dopa therapy**
- Why are they used?
  - **DOPA-decarboxylase inhibition** (to decrease peripheral side effects) **COMT → ↑methyldopa**
    - **= ↓ Therapeutic response**



- Entacapone

- Opicapone

Entacapone and **opicapone** are unable to cross the BBB

- Thus, they prevent the metabolism of L-DOPA to dopamine only in the periphery due to DOPA decarboxylase inhibition

- Tolcapone

Tolcapone is able to act in the periphery, as well as in the CNS

- Tolcapone inhibits metabolism of L-DOPA to dopamine in the periphery
- And also, it increases the synthesis of dopamine in the brain from L-DOPA
  - Because amino acid decarboxylase inhibitors do not cross the BBB

a. **L-dopa**

b. **+ carbidopa** (***decarboxylase inhibitor*** → decreases peripheral formation of dopamine)

c. **+ entacapone** (***COMT inhibitor*** → decreases formation of methyldopa → more L-DOPA available for CNS)

} Triple therapy

Adverse effects

- Because the final effect of triple therapy is roughly the same as for L-DOPA, the adverse effects are very similar
- **– dyskinesias, nausea, confusion**
- **Entacapone** can cause **orange discoloration of the urine**
- **In rare cases tolcapone** can lead to liver failure **(Hepatotoxicity)**

Drug	Dopamine receptor interaction	Interaction with other receptors		Half-life (h)
		NA	5-HTP	
Non-ergot				
Pramipexole	D2	±	-	10
Ropinirole	D2	-	-	6
Rotigotine	D2 > D1	+	+	5-7 (t.d.)
Apomorphine	D2/D1	-	-	0,5 (s.c.)
Ergot				
Bromocriptine	D2	+	+	3-6
Pergolide	D2 > D1	+	+	15
Cabergoline	D2	+	+	65

c. Dopamine agonists

- Although levodopa is the most effective symptomatic treatment for Parkinson's disease, its relationship to the onset of motor complications causes limits on its use, especially in patients younger than 70 years old with mild symptoms
  - Therefore, dopaminergic agonists provide a safe and effective alternative option to L-DOPA in younger patients
    - Dopamine agonists = **first choice drugs in young, newly diagnosed PD patients**
      - Postpones L-DOPA treatment
  - These drugs are associated with lower incidences of motor complications at the 5 year mark
  - They are effective both as monotherapy in early stages of the disease, as well as in combination with L-DOPA in advanced stages

Advantages:

- **Safe and effective alternative to L-dopa in younger patients**
- **The effect persists for long period of time**
- **↓ Incidence of motor complications at the 5-year mark**

- They are effective both as monotherapy in early stages, as well as in combination with L-DOPA in advanced stages of the disease

Disadvantages:

- **Less effective than L-DOPA**
- **Dopamine agonists have a greater risk of psychosis than levodopa**

Dopamine agonists → Ergot alkaloids

- Ergot derivatives (***bromocriptine***, ***pergolide*** and ***cabergoline***) were the first dopamine agonists available
  - But the use of these drugs is currently restricted due risk of fibrotic valvular heart disease
  - They should never be considered as first-line treatment

Non-ergot alkaloids

- Non-ergot alkaloids (***pramipexole***, ***ropinirole, rotigotine***) are more selective for dopaminergic receptors
  - They bind to bind to dopamine 1 and 2 subtypes of receptors, which play a critical role in producing smooth voluntary movement

Adverse effects

- Gastrointestinal

- **Anorexia, nausea, vomitus, constipation, dyspepsia, symptoms of reflux esophagitis, peptic ulcer bleeding**

- Cardiovascular

- **Postural hypotension, painless digital vasospasms, cardiac arrhythmia**

- Behavioral!!!

- **Confusion, hallucination, delusion, impulsive and compulsive behaviors and other psychiatric complications**

- Dyskinesia

- **Abnormal movements**
- **- Others →** Risk of tissue and organ fibrosis is associated with ergot derivatives
  - **Pleural, retroperitoneal, cardiac and valvular fibrosis, pulmonary infiltrates, headache, nasal congestion, irritability, tendency to fall asleep**

Contraindications

- **Psychiatric diseases**
- **CVS diseases (MI)**
- **GIT– active peptic ulcer**
- **PVD – peripheral vascular diseases**

MAO-A
- Degrades: Norepinephrine, serotonin, tyramine
  - MAO-A inhibitors are used for the treatment of depression

MAO-B
- Degrades: Dopamine
  - MAO-B inhibitors are used for the treatment of Parkinson's disease

d. Monoamine oxidase inhibitors (MAO-B inhibitors)

- They cause increased **availability of dopamine (↑effect + ↓dose of L-dopa)**
  - MAO-B inhibitors can extend the duration of action of L-DOPA by inhibiting the metabolism of dopamine
- They can be used as monotherapy at the early stages of Parkinson's, or as adjunct therapy in more advanced stages
- **Selegiline**
- **Rasagiline**

Adverse effects:

- **↑ AE of L-dopa**
- **Insomnia, excitation, anxiety**
- **Hypertensive crisis**
- **serotonin syndrome**

- MAO-B inhibitors can increase serotonin levels when used at higher doses and in various combinations
  - Serotonin syndrome is associated with severe CNS toxicity leading to hyperpyrexia, myoclonus, hyperreflexia, diaphoresis, tremor, shivering, hallucinations
  - It can be fatal if it is not identified and treated promptly

e. NMDA-receptor antagonists

- **Amantadine** (antiviral drug)
  - In the treatment of Parkinson's disease, amantadine acts on dopamine neurons as a weak non-competitive antagonist of the NMDA receptor, it **increases dopamine release** and **prevents dopamine reuptake**
- Amantadine has become a useful adjunctive medication in people with advanced Parkinson's disease and motor fluctuations
- It is less potent than L-DOPA and its benefits may be short-lived, often disappearing after only weeks of therapy

Adverse effects:

- The most frequent side effect of amantadine are:
  - **Nausea**, **dry mouth**, cardiovascular – **heart failure**, **orthostatic** hypotension and those from the CNS

2. Anticholinergic drugs/*tertiary amine parasympatholytics*

- = Drugs that block the effect of acetylcholine have the potential to restore the normal balance between dopamine and acetylcholine
  - Thereby, reducing the symptoms of Parkinson's disease
- The anticholinergics can provide modest benefits, mainly for tremor
  - But they can also cause significant mental and physical side effects
- **Biperiden**
- **Procyclidine**

Indications:
- Younger patients, when dopaminergic therapy is not effective + tremor, rigidity, hypersalivation

Adverse effects of PSL

- **Dry mouth, dry skin**
- **Mydriasis, cycloplegia, ↑ IOP, ↓ lacrimation**
- **Tachycardia**
- **GIT paralysis – constipation, UGT- urinary retention**
- **CNS disturbances – confusion, hallucination, restlessness, excitation, disorientation, delirium, coma, apnea**
- **Dementia, Alzheimer´s disease!**

Contraindications – PSL

- **Glaucoma**
- **CVS – cardiac diseases**
- **Prostate hypertrophy**
- **GIT obstruction – pyloric stenosis, paralytic ileus**
- **Dementia, elderly > 65yrs**

Conclusion:

- **Therapy of PD is only symptomatic → does not affect progression of disease**

In conclusion, the therapy of Parkinson's disease is only symptomatic and does not affect the progression of the disease

- For in the management of Parkinson's disease, we can use either dopaminergic drugs or anticholinergic drugs
- Don't forget, dopamine is unable to cross the BBB, which is why we use its precursor, L-DOPA
  - L-DOPA undergoes extensive metabolism in the periphery, therefore it is used together with inhibitors of its metabolism, such as carbidopa, benserazide or COMT inhibitors such as entacapone and tolcapone
    - Remember Tolcapone is also active in the brain! – others are active in the periphery
- Other options are dopaminergic receptor agonists, such as bromocriptine, pramipexole and ropinirole
  - But these drugs are associated with high-risk CNS side effects
    - Because they interact directly with dopamine receptors
  - Their main adverse effect is risk of compulsive behavior and sleepiness

16. Antiepileptics (Overview, mechanism of action) (49)

- **Epilepsy is a disorder of the brain** characterized by **constant predisposition** to generate **epileptic seizures** and by the **neurobiological, cognitive, psychological, and social consequences of this condition.**
- **A "seizure" is a paroxysmal alteration of neurologic function caused by the excessive, hypersynchronous discharge of neurons in the brain.**

Antiepileptics aim to ***inhibit the abnormal neuronal discharge*** rather than to correct the underlying cause
→ They do this by stabilizing the cell membrane

Membrane stabilization

❖ Antiepileptic pharmacotherapy is driven to create membrane stability via inhibiting ion channels or neurotransmitters:

Ion channels
- **Blocking voltage-gated sodium channels**
- **Blocking voltage-gated calcium channels**
- **Enhancing voltage-gated potassium channels**

Antiepileptic drugs – according to mechanism of action:

- Ca2+channel blockers
  - ***Valproate***, ***Gabapentin***, *Pregabalin*

- Sodium channel blockers
- Voltage-gated sodium channels are responsible for depolarization of the nerve cell's membrane and conduction of action potential across the surface of neuronal cells
  - ***Phenytoin***, *Carbamazepine*, *Oxcarbazepine*, *Lamotrigine*, *Zonisamide*, *Lacosamide*

- Potassium channel enhancers
- Voltage-gated potassium channels are primarily responsible for repolarization of the cell membrane, and they regulate the balance between input and output in individual neurons
  - ***Retigabine***

- GABA agonists (drugs enhancing inhibitory transmission)
- ***Barbiturates*** and ***benzodiazepines*** potentiate GABA at GABA-A receptor
  - They either increase the frequency or duration of chloride ion channel opening, leading to hyperpolarization
- ***Tiagabine*** inhibits GABA reuptake
- ***Vigabatrin*** inhibits GABA metabolism
- And ***valproate*** increases GABA turnover

Neurotransmitters
- **Inhibiting excitatory neurotransmitter glutamate**
- **Promoting inhibitory neurotransmitter GABA**

- Glutamate antagonists (drugs inhibiting excitatory neurotransmission)
  - ***Topiramate***, *felbamate* and *perampanel*

Pharmacokinetics of antiepileptic drugs

Routes of drug administration

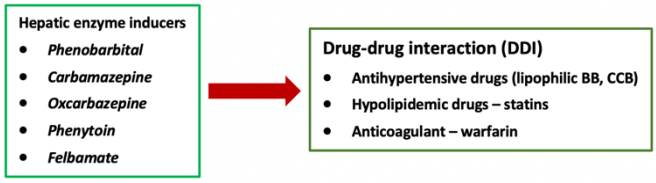
❖ Most antiepileptic drugs are administered ***orally*** since epilepsy is a chronic condition
❖ Antiepileptic drugs also exist for intravenous, intramuscular, rectal, intranasal or buccal administration
❖ Rectal administration, for example with **diazepam**, is useful to terminate repetitive seizures
  ➢ It can be administered by family members at home = advantage
❖ ***i.v. route is generally used in emergencies***, such as status epilepticus, since the absorption phase is avoided
❖ Intramuscular midazolam can be considered when i.v. route is not available

Absorption

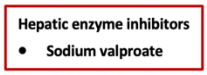
❖ With oral formulations, the rate of absorption and bioavailability generally varies widely by drug formulation used, patient characteristics, concomitant drugs and food
  ➢ For example, calcium containing antacids may interfere with phenytoin, phenobarbitals, carbamazepine and gabapentin absorption
    ▪ Because they decrease the acidity of the stomach and also by formation of insoluble complexes that cannot be absorbed

- The pharmacokinetics of newer antiepileptic drugs is more favorable because they are minimally, or not bound to albumin and they are **not metabolized by cytochrome enzymes**
  - In contrast to the hepatic metabolism of the older antiepileptic drugs
  - Newer antiepileptic medications undergo more extensive renal elimination in unchanged form and may be susceptible to interactions affecting the expression process
  - For example, agents that cause alkalization of urine increase the elimination of phenobarbitals by reducing the reabsorption of this acidic drug from the renal tubuli

Interactions at level of metabolism



- Certain antiepileptic drugs act as ***hepatic enzyme inducers***
  - Concomitant treatment with cytochrome inducers, such as ***carbamazepine*** and ***phenytoin***, can result in **substantial reduction** of the oral bioavailability of beta blockers, calcium channel blockers, statins or warfarin → these drugs will ***have less effects*** (because they are metabolized faster)
- In contrast, ***valproate*** is the only medication from this group which is ***hepatic enzyme inhibitor***
  - This will lead to high plasma concentrations of the affected drug and the possibility of clinical toxicity



Dose-dependent side effects of antiepileptic drugs

- Because of their mechanism of action, all seizure medications have CNS side effects
  - These are common side effects of almost all epileptic drugs
    - **Sedation, drowsiness**
    - **Vestibulocerebellar symptoms – nystagmus, diplopia, tinnitus, ataxia, vertigo**
    - **Psychological changes**

Toxic effects of long-term use of antiepileptic drugs

- **Hepatic enzyme inducers,** if used for a long period of time **osteopenia, osteoporosis**
- **Phenytoin – gingival hyperplasia, hirsutism**
- **Valproate – prolonged bleeding**

Antiepileptics – indications

Seizure type	Monotherapy 1st choice
Generalized-onset tonic-clonic seizures	Valproate
Myoclonic seizures	Valproate
Focal-onset seizures	Carbamazepine Lamotrigine Levetiracetam
Absence seizures	Ethosuximide Valproate

- The choice of antiepileptic drug depends on the patient's seizure type, age, sex, childbearing potential, comorbidities and concomitant medications, and the drug's adverse effects and interaction profile
- For **generalized-onset tonic-clonic seizures**, ***valproate*** = **drug of first choice**
  - With exception of women of childbearing potential
  - Valproate is also approved for **myoclonic** seizures
  - And together with ***ethosuximide***, ***valproate*** is approved for the management of ***absence seizures***
- **Carbamazepine, lamotrigine and levetiracetam are drugs of first choice for focal-onset seizures**
- **Ethosuximide is the drug of first choice for absence seizures**

!!!
- **Valproate**
- **Phenytoin**
- **Phenobarbital**

Epilepsy and pregnancy

- Prior to conception and during pregnancy is necessary:

- Detail information (risk/benefit of AEDs)
- Switch to drugs with low potential to fetal adverse effects
- Assure treatment adherence and take antiepileptic serum concentrations
- **Lamotrigine** and **levetiracetam** are the ***first-choice treatment options in pregnant women***
  - Because they carry the lowest risk of major congenital malformations and have no impact on neurobehavioral development
- Folic acid → prevention of spina bifida

Status epilepticus

- **When a convulsive seizure continues for a prolonged period (longer than 5 minutes), or when convulsive seizures occur one after the other with no recovery between**
- **Convulsive status epilepticus is an emergency and requires immediate medical attention**

- **Benzodiazepines**
  - **i.m. midazolam, i.v. diazepam or i.v. lorazepam**
- **Phenytoin/fosphenytoin**
- **Phenobarbital**
- **Valproate**
- **Levetiracetam**
- **Lacosamide**
- **Anesthesia**
- **(thiopental, propofol, midazolam)**

- Status epilepticus is defined as either continuous seizure, lasting for at least 5 minutes, or 2 or more separate discrete seizures between which there is incomplete recovery of consciousness
- As a medical emergency, it requires prompt and aggressive treatment
- After stabilization phase, benzodiazepines are the initial therapy of choice
  - We have 3 options, we can use intramuscular midazolam, i.v. diazepam or i.v. lorazepam
- But if the seizures continue, we can choose one of the second-line options
  - Including, i.v. fosphenytoin, valproate or levetiracetam
- In resistant cases, we can consider anesthesia with thiopental, midazolam, phenobarbital or propofol with continuous electroencephalograph monitoring

17. Antiepileptics modulated GABA metabolism (16)

Membrane stabilization

❖ Antiepileptic pharmacotherapy is driven to create membrane stability via inhibiting ion channels or neurotransmitters:

Antiepileptic drugs - according to mechanism of action:

- Ca^{2+} channel blockers

– *Ethosuximide*, ***Valproate***, **Gabapentin**, *Pregabalin*

- Sodium channel blockers

– ***Phenytoin***, *Carbamazepine*, *Oxcarbazepine*, *Lamotrigine*, *Zonisamide*, *Lacosamide*

- Potassium channel enhancers

– ***Retigabine***

- GABA agonists (drugs enhancing inhibitory transmission)

- ***Barbiturates*** and ***benzodiazepines*** potentiate GABA at GABA-A receptor
  - They either increase the frequency or duration of chloride ion channel opening, leading to hyperpolarization
- ***Tiagabine*** inhibits GABA reuptake
- ***Vigabatrin*** inhibits GABA metabolism
- And ***valproate*** increases GABA turnover

- Glutamate antagonists (drugs inhibiting excitatory neurotransmission)

– *Topiramate*, *felbamate* and *perampanel*

Drugs that enhance GABAergic (inhibitory) transmission, this may be achieved by:

– ***Enhanced postsynaptic action of GABA***
– ***Inhibiting GABA transaminase***
– Or by drugs with ***direct GABA agonist properties***

↑ GABA → ↓ neuronal excitability

a. Sodium valproate

- **Mechanism of action:**
  - The enzyme ***glutamic acid decarboxylase*** (GAD) converts glutamate into gamma-aminobutyric acid (GABA)
    - Valproate affects this enzyme by **increasing the synthesis of GABA**
  - Valproate also Inhibits GABA transaminase
- **Indications:**
  - Generalized seizures (myoclonic s., absence, tonic-clonic s.)
  - Partial seizures
  - Bipolar affective disorder
  - Migraine prophylaxis
  - Neuropathic pain
- **Pharmacokinetics:**
  - **High PPB!!!**
  - **INHIBITOR of CYP450!**
- **Adverse effects:**
  - **GIT (nausea, vomitus, abdominal pain, ...), reversible alopecia, ↑ appetite and weight gain, severe hepatotoxicity (rare)!, thrombocytopenia, teratogenicity (spina bifida, CVS, orofacial, digital abnormalities)**

❖ Valproate has relatively low toxicity
❖ However, it has **teratogenic potential** – causing a variety of birth defects
  ➢ Including neural tube defects and other congenital malformation

- **Allosteric modulation of GABA-A receptors**
- **↑ channel open duration**

b. Barbiturates

- **Mechanism of action:**
  - Enhancement of GABA-mediated inhibition (GABA-A receptor)
  - Blockade of AMPA receptors
  - Blockade of voltage gated Na+ and T-type voltage gated Ca 2+ channels (↑c)
- **Indications:**
  - Some partial s., recurrent generalized tonic-clonic s., recurrent s. in children (ineffectiveness - absence, atonic s., infantile spasms)

❖ Whilst **barbiturates increase the duration of chloride ion channel opening**, benzodiazepines increase their frequency

- **INDUCTOR of CYP450! UGT**

Adverse effects

- Dose-dependent:
  - Sedation, drowsiness, ↓ cognitive and motor ff., ↑ doses – agitation, confusion, respiratory depression, CVS (alcohol, CNS depressive)
- Dose-independent:
  - Skin allergic reaction

- **Allosteric modulation of $GABA_A$ receptors**
- **↑ Frequency of $GABA_A$ opening**

c. Benzodiazepines

- **Mechanism of action:**
  - **Facilitates GABA-mediated inhibitory neurotransmission ($GABA_A$ receptor)**
- **Indications:**
  - **All types of epilepsy including SE**
- **i.v., per rectum, p.o. (i.m., b.c., i.n.)**
- **Adverse effects:**
  - **Sedation, drowsiness, lethargy, tolerance, paradoxical hyperreactivity – children**
- **Diazepam**
- **Lorazepam**
- **Clonazepam**
- **Clobazam**
- **Midazolam**
- **Clorazepate**
- **Nitrazepam**

- Both barbiturates and benzodiazepines are only used for limited period of time, due to strong sedative properties, risk of tolerance with need to increase the dose to reach the same therapeutic effect associated with risk of psychological and physical dependence and respiratory depression
  - This is the reason for why these drugs are only recommended in emergency situations
    - Such as status epilepticus

Tiagabine

- Inhibits GABA uptake and thereby enhances the action of GABA as an inhibitory neurotransmitter.
- Indications: adjunctive therapy, monotherapy – partial seizures in patients at least 12 years old
- Adverse effects: dizziness, fatigue, depression, tremor, ataxia etc.

Vigabatrin

- Acts by inhibiting the enzyme GABA transaminase, which is responsible for inactivating GABA
- Indications: partial seizures, bipolar affective disorder, spastic pain, West´s syndrome ‘
- Adverse effects: dizziness, visual field narrowing (40%), psychosis

Felbamate

- Potentiates GABAA receptor responses
- Indications: partial seizure. Adverse effects: aplastic anemia, severe hepatitis, GIT upset

Topiramate

- Potentiates the inhibitory effect of GABA-A receptor
- Indications: monotherapy – partial & generalized tonic-clonic seizures, West syndrome, absence seizures, migraine
- Adverse effects: fatigue, dizziness, glaucoma, teratogen etc.

Stiripentol

- Increases GABAergic transmission due to prolonged opening of Cl- channels in GABA-A
- Adjunctive therapy – pharmacoresistant epilepsy, generalized tonic-clonic seizures.
- Adverse effects: GIT upset, CNS disturbances

18. Pharmacology and toxicology of nicotine (44)

- From the group of CNS stimulants, the most common drug dependence is on nicotine
  - It is estimated that 18% of world population are smokers, the number rapidly increases in the third-world countries, while it has been slowly declining in developed countries

Nicotine is an agonist of ***nicotinic acetylcholine receptors***, ligand gated channel type which are widely expressed in brain, cortex

- The main molecular structure which is responsible for the development of drug dependence is a nicotinic receptor which consists of the combination of subunits **α4** and **β2**
  - →The α4β2 is the principal mediator of nicotine dependence.
- Nicotine is a drug which acts very promptly, this receptor is associated with sodium ion channels so, the activation leads to very fast neuronal excitation and facilitation of the neurotransmitter release

Nicotine – Mechanism of rewarding and addictive effects

- Nicotine is a prototype **direct stimulator of dopamine release in ventral tegmental area**
  - However, the **GABAergic interneuronal modulation**, as well as **glutamatergic mediation enhancement**, are also strongly involved in the development of the drug dependence
- In terms of the dopaminergic enhancement, the alpha4 subunit is the most effective

Pharmacokinetics of nicotine

- Nicotine is a small lipophilic molecule which is very rapidly absorbed during smoking through airway mucosa, leading to prompt increase in plasma levels
- This prompt increase is followed by similarly prompt drop in plasma concentration because of 2 reasons:
  - 1. Because of the **rapid distribution from the blood to tissues**, due to the **lipophilicity**
  - 2. And also due to the **intensive metabolism in the liver**
- **In smokers there is an induction of liver and intestine CYP450s → decreased effects of some drugs (e.g., beta blockers)**
  - The liver enzymes involved in nicotine metabolism are inducible
    - **Nicotine is a strong inducer of CYP450**, and this can be a problem in terms of other medications
    - Smokers have decreased response to specific medications that are metabolized by CYP450
      - Such as general anesthetics, methylxanthines, anti-thrombotic agents
      - This is the reason for why before general anesthesia, it is very important to obtain accurate history of the patient, including history of smoking

Effects of nicotine:

CNS effects
- Combination of excitatory and inhibitory effects
- ↑ Vigilance
- ↑ Ability to concentrate
- Cognitive enhancement
- Suppression of anxiety and nervousness
- ↓ Appetite (lower average weigh of smokers – 4 kg

Peripheral effects
- ↑ Blood pressure
- ↑ Heart rate (tachycardia)
- ↑ Cardiac output
- ↑ Sweating
- ↑ Tremor
- ↑ GIT motility
- Nausea and vomitus after first exposure to cigarette

- Nicotine poses combination of central and peripheral effects
- Peripheral effects are mostly stimulatory because it is mediated stimulation of vegetative ganglia
  - We can observe effects such as **cardiovascular stimulation**, **increased sweating**, **increased activity of striatal muscles** and **increased GIT motility**
  - This combination of effects is experienced as unpleasant responses
    - However, the desensitization of the peripheral ganglia is relatively prompt and after repeated use of nicotine, we can observe very rapid adaptation and development of tolerance

- In the CNS, we can distinguish a combination of excitatory and inhibitory effects
  - It is associated with localization of nicotinic receptors
  - Increased vigilance, ability to concentrated and cognitive enhancement
    - These are effects stimulated after application of nicotine
  - On the other hand, we can also observe suppression of anxiety and decreased appetite
    - The tolerance of these effects is also developed during time, but it is less rapid in comparison with the desensitization of the peripheral ganglia and thus, peripheral effect

Withdrawal symptoms of nicotine

Withdrawal symptom	How long they last
Cravings	2 weeks
Increased appetite	10 weeks
Depression	4 weeks
Restlessness	4 weeks
Poot concentration	2 weeks
Irritability/anger	4 weeks
Disturbed sleep	1 week
Light-headed	2 days
Chesty cough	2 weeks

- Withdrawal syndrome after stopping of nicotine intake is very intensive, it as psychological and very strong physical symptomatology
  - It approx. lasts for **4 weeks** – 4 weeks is equal to the **lifecycle of nicotinic α4β2 receptors**
- During the withdrawal syndrome we can observe depression lasting for 4 weeks, restlessness, irritability and the intensive craving lasts for 2 weeks

General principles of pharmacologic treatment:

- Reduce physical symptoms of withdrawal

- Eliminate, through desensitization of nicotinic receptors, the immediate, reinforcing effects of nicotine

Nicotine replacement therapy:
- **Patch**
- **Gum**
- **Spray**
- **Inhaler**

Non-nicotine pharmacotherapy:
- **First-line therapy:**
  - **Bupropion**
  - **Varenicline**
- **Second-line therapy**
  - **Nortriptyline**
  - **Clonidine**

- The treatment of nicotine addiction can be either **nicotinic** or **non-nicotinic** pharmacotherapy
- Nicotinic replacement treatment is the mostly used in clinical practice
  - We replace the nicotinic effect by drug-forms which pose prolonged release of the molecule
    - This way, they lead to limited dopaminergic enhancement
- Non-nicotinic mediation is much more logical
  - The first line agents are **bupropion** and **varenicline**
    - They have similarities in their mechanism of action

- Varenicline

- **Varenicline** is a **partial agonist-antagonist** of **nicotinic receptors**
  - So, it is able to activate these receptors partly, producing moderate dopaminergic effects
  - On the other hand, the type of their bond is irreversible, leading to the conformational changes of these receptors, so they become less sensitive to nicotine itself
    - This is the reason why they cause breaking of association build up during the activation of reinforcing cycle

- Bupropion – atypical antidepressant

- **↓ Craving for cigarettes**
- **↓ symptoms of nicotine withdrawal (depression)**

- Bupropion is an atypical antidepressant which leads to very similar effects as varenicline
- It's a dual norepinephrine and dopamine inhibitor (NDRI), which also acts as antagonist on nicotinic receptors
- The dopaminergic effect is associated with the inhibition of dopamine active transporter and the antagonizing activity against nicotinic receptor prevents their activation by nicotine itself
- Both varenicline and bupropion decrease the craving and strongly decrease the symptoms of nicotine withdrawal, especially the very severe depression

9. Anesthetics

1. **Inhalational general anesthetics (60)**
2. **Intravenous general anesthetics (1)**
3. **Complications and side effects of general anesthesia (38)**
4. **Local anesthesia (44)**
5. **Local anesthetics – ester type (24)**
6. **Local anesthetics – amide group (64)**
7. **Myorelaxants (centrally, peripherally acting) (31)**

Intro – Types of anesthetics
1. **General anesthetics**
   a. **Inhaled**
   b. **Intravenous**
2. **Local anesthetics**
   a. **Esters**
   b. **Amides (preferred!)**
3. **Skeletal muscle relaxants**
   a. **Peripheral → they act at the endplate**
      i. Depolarizing
      ii. Non-depolarizing
   b. **Central (spasmolytics)**

1. Inhalational general anesthetics (60)

General anesthetics intro

- = Reversible state of CNS depression, causing loss of response to perception of stimuli
- General anesthetics can be administered either **inhaled** or **intravenously**
  - When they are inhaled, using the absorption in lungs → blood → brain
- Generally, general anesthetics lead to unconsciousness kind of anesthesia
  - Their mechanism is mostly involved in stabilizing the cell membranes, inhibiting action potentials

***Analgesia*, *relaxation of skeletal muscle*, *suppression of reflex reactions* = narcosis**

- The most important aspect for us is **analgesia**
- Additional benefit from this point of view is the **relaxation of skeletal muscles**
  - Because it makes surgical intervention easier
  - And we suppress the reflex reactions as well, so the patient is unresponsive, which is why we call these drugs **narcotics**

Different effects in different agents (necessary to use combinations)

- In some situations, anesthetics don't have all the properties we need, which is why we can combine them
  - For example, **barbiturates** are quite good in regards of suppressing the reflex reactions, but the analgesic and myorelaxant effect is not as good as in for example some fluorinated alkanes

Classification of general anesthetics:

1. Route of administration:

a) Inhaled
- Mainly used for maintenance of anesthesia

b) Intravenous
- Usually used for induction of anesthesia
- The difference between them is the **100% bioavailability** of intravenous anesthetics

2. Effect on CNS:

a) Associative – Completely suppress CNS (suppress all parts of the brain!)

b) Dissociative – stimulation in some areas of CNS (*ketamine*)

- In contrast to associative, dissociative suppress some parts of the brain, but some areas can be either intact or stimulated

4 levels of anesthesia:

- 1. Level of analgesia
- Decreased activity of neurons in substantia gelatinosa in dorsal spinal roots – *up to losing consciousness*

- 2. Level of excitation (atropine)

(1^{st} level – up to unconsciousness → 2^{nd} level of excitation *tachycardia*, *irregular breathing*, *irritation of vagus nerve*, *emesis* & *aspiration*)

- To prevent this level of excitation, **atropine** is recommended before surgical intervention
  - Atropine is usually a part of the premedication if you expect excitatory problems in anesthesia

- 3. Level of surgical anesthesia (the level we want to reach)

- 4. Level of medulla oblongata depression (the level we don't want to reach)

- Blocking of breathing and cardiovascular system → risk of death of the patient

Mechanism of action of general anesthetics

- In anesthesia we want to ***suppress neuronal activity***
  - We do this by inducing ***hyperpolarization***
- Inducing hyperpolarization can be done by:
  - **Increasing intracellular chloride** (Cl^-) + **potassium** (K^+) or **decrease inward flow** of **Na^+** and **Ca^{2+}**
  - Or **agonizing GABA-A receptor** (benzodiazepines + barbiturates)

Pharmacokinetics

- Inhaled air must first go the lungs → bloodstream → brain
- In case we administer them intravenously, then of course, we will skip this absorption from the lungs, and will be directly available in bloodstream (only depends on the lipophilicity of the agent how fast it is transported to brain)
- **Rate of reaching the concentration in brain depends on:**
  - Properties of anesthetics – **Blood/air dissociation coefficient:**
    - Higher = more dose is required to reach target tissue (more gases are kept in blood = slow onset of action)
      - Nitrous oxide = low blood/air dissociation coefficient = fast onset of effect
      - Halothan = high blood/air dissociation coefficient = slow onset of effect
  - Minimum alveolar concentration (MAC)
    - *Concentration of anesthetics causing effects in 50% of patients*
  - Intensity of pulmonary ventilation + solubility
    - **↑ ventilation + high solubility → ↑ effects**
  - Blood flow through lungs
- **Distribution** – of Different tissues:
  - **Arteriovenous concentration gradient:**
    - Concentration of drug in arteries and veins
  - Brain, heart, liver, kidney, endocrine glands → highly perfused and have fast onset of action
  - Fat → poorly perfused and have the ability to store the drug (because most inhaled anesthetics are liposoluble)
- **Elimination:** By lungs + liver metabolism

Effects of inhaled anesthetics

- CVS → Decrease of middle arterial pressure – can be accompanied by **tachycardia**

- Except for of **halothan**, which leads to bradycardic activity
- But **enflurane** and **sevoflurane** may lead anti-muscarinic activity, which leads to tachycardic responses

- **Decrease of myocardial contractility** and **decreased myocardial oxygen consumption**
  - = protective action on the heart, sometimes we induce patients to intentional sleep on order to reduce oxygen demands of the heart

- Respiratory system → Suppression of breathing

- → which is why during the 3rd level of anesthesia, we apply **artificial ventilation**
- **Bronchodilation** is induced by **halothan**

- Brain → Slower brain metabolism + ↑ Cerebral blood flow

- Kidney → ↓ glomerular filtration + ↓ blood flow to kidneys

- So, the elimination process can be a little bit reduced

- Liver → ↓ Liver blood flow

- Uterus smooth muscle → Relaxation → Important, similarly to the airways, there will be **relaxation uterus smooth muscle** (and generally smooth muscles)

Adverse effects of inhaled anesthetics

- As for toxicity, we should mention the **hepatotoxicity** typical for repeated doses of ***halothan***
- Another on very typical is **malignant hyperthermia**
  - These 2 are the most frequent
- (But also, nephrotoxicity and chronic toxicity)

→ Malignant hyperthermia (hyperpyrexia)

- **Serious complication during inhaled narcosis (or in *combination with myorelaxant drugs*)**
- Malignant hyperthermia = **heat production** due to **overactivity of skeletal muscles**, due to excessive release of calcium from sarcoplasmic reticulum (released without impulses)
  - Skeletal muscles start to show fasciculation and rigidity, leading to myopathy afterwards
  - This muscle destruction is present at the later stages, not at the beginning
- **Clinical symptoms:**
  - **Trismus (one of the first signs), Tachycardia, Dysrhythmia, Fever,**
  - **Skeletal muscles rigidity – myopathy – increased serum levels of creatin kinase with K^+ (muscle destruction)**
- **Therapy:**
  - **Cooling** (symptomatic treatment) **+ DANTROLENE** (blocker of ryanodine receptors in SR)

Prevention of risk during anesthesia and increasing the narcotics efficiency

- **a) Premedication** (to ***increase effectiveness of anesthesia*** and to ***reduce the need of anesthetics***)
  - **Atropine (excitation), analgesics, hypnotics-anxiolytics**
    - **Atropine** will **prevent this excitatory phase** (2^{nd} level)
    - **Analgesics** will **reduce the dose necessary for anesthesia**
    - **Hypnotics-anxiolytics** may reduce the fear and overactivity of sympathetic nervous system
- **b) Initial (basal) narcosis**
  - **Quick and short acting anesthetics (i.v. or i.m.)**
- **c) Myorelaxation**
  - **Peripheral myorelaxant agents (tubocurarine) – requires intubation for artificial ventilation by paralysis of intercostal breathing muscles**

Inhaled anesthetics (vapors vs gases)

A. Vapors:

- Liquids in room temperature, very effective also in low concentration

→ **Halothan**

- **Induces deep unconsciousness with quick onset and recovery**
- **Very weak analgesic and myorelaxant effects – occurring in 3rd level**
  - The analgesic and myorelaxant effects of halothan is ***not sufficient***
    - So, premedication with opioid painkillers is needed
    - And they also have to be combined with some myorelaxant agents
- **Malignant hyperthermia** (risk = increased if we use myorelaxants)
- **No irritation of airways → bronchodilation**
- What you should remember about halothan is that there is a **risk of hepatic function impairment**
  - This was the ***reason why it has been discontinued***
- **Transport through placenta (CI in 1st trimester of gravidity)**
- **Vasodilation in cerebral circulation – ↑ intracranial pressure**

→ **Ether**

- Induces **central anesthesia with myorelaxation**
- **Explosive agent** (disadvantage)
- Adverse effects:
  - Problem with ethers is **significant 2^{nd} (excitatory) level** of anesthesia (***reason why it is not used***)
    - (Emesis, misbalance of BP, irritation of n. vagus)

Halogenated ethers:

→ **Isoflurane**

- **Most frequent inhalational anesthetic**
  - The benefit of them is that they act faster compared to halothan
- **More significant depression of breathing**
  - We should remember that desflurane has problems with possible irritation of respiratory system
    - So, bronchoconstriction, bronchospasms, cough etc.
- **No hepatotoxicity**

→ **Desflurane and sevoflurane – less toxic, less soluble in blood and fat – faster onset and recovery**

→**Desflurane – higher MAC – possible irritation and bronchospasm**

→ **Enflurane – older agent, less used (convulsions is contraindication!)**

B. Gases

Nitrous oxide – N_2O

- The **narcotic effect** of nitrous oxide is insufficient – **necessity to combine with other narcotics (often with i.v. anesthetics)**
  - **For anesthesia with appropriate blood oxygenation is administered in mixture with O_2**
    - **(85 % N_2O + 15 % O_2)** → The maximum concentration we can use is 85% (because minimally 15% should be oxygen)
- **Weak myorelaxation – necessity of myorelaxant agent**
- **Administration of high concentration (over 50%) replaces nitrogen from tissues - barotraumas**
- **Interference with metabolism of vitamin B12 – risk of megaloblastic anemia**

Intro – Types of anesthetics
1. **General anesthetics**
   a. **Inhaled**
   b. **Intravenous**
2. **Local anesthetics**
   a. **Esters**
   b. **Amides (preferred!)**
3. **Skeletal muscle relaxants**
   a. **Peripheral → they act at the endplate**
      i. Depolarizing
      ii. Non-depolarizing
   b. **Central (spasmolytics)**

2. Intravenous general anesthetics (1)

General anesthetics intro

- = Reversible state of CNS depression, causing loss of response to perception of stimuli
- General anesthetics can be administered either **inhaled** or **intravenously**
  - When they are inhaled, using the absorption in lungs → blood → brain
- Generally, general anesthetics lead to unconsciousness kind of anesthesia
  - Their mechanism is mostly involved in stabilizing the cell membranes, inhibiting action potentials

***Analgesia*, *relaxation of skeletal muscle*, *suppression of reflex reactions* = narcosis**

- The most important aspect for us is **analgesia**
- Additional benefit from this point of view is the **relaxation of skeletal muscles**
  - Because it makes surgical intervention easier
  - And we suppress the reflex reactions as well, so the patient is unresponsive, which is why we call these drugs **narcotics**

Different effects in different agents (necessary to use combinations)

- In some situations, anesthetics don't have all the properties we need, which is why we can combine them
  - For example, **barbiturates** are quite good in regards of suppressing the reflex reactions, but the analgesic and myorelaxant effect is not as good as in for example some fluorinated alkanes

Classification of general anesthetics:

1. Route of administration:

a) Inhaled

– Mainly used for maintenance of anesthesia

b) Intravenous

– Usually used for induction of anesthesia

– The difference between them is the **100% bioavailability** of intravenous anesthetics

2. Effect on CNS:

a) Associative – Completely suppress CNS (suppress all parts of the brain!)

b) Dissociative – stimulation in some areas of CNS (*ketamine*)

- In contrast to associative, dissociative suppress some parts of the brain, but some areas can be either intact or stimulated

4 levels of anesthesia:

- 1. Level of analgesia

- Decreased activity of neurons in substantia gelatinosa in dorsal spinal roots – *up to losing consciousness*

- 2. Level of excitation (atropine)

(1st level – up to unconsciousness → 2nd level of excitation *tachycardia*, *irregular breathing*, *irritation of vagus nerve*, *emesis* & *aspiration*)

- To prevent this level of excitation, **atropine** is recommended before surgical intervention
  - Atropine is usually a part of the premedication if you expect excitatory problems in anesthesia

- 3. Level of surgical anesthesia (the level we want to reach)

- 4. Level of medulla oblongata depression (the level we don't want to reach)

- Blocking of breathing and cardiovascular system → risk of death of the patient

Mechanism of action

- Most intravenous anesthetics act on GABA-A receptor
  - Increase of inwards flow of chlorine inside the cell → hyperpolarization

Intravenous anesthetics:

- Induce **narcosis without classical schema as in inhaled anesthetics**
- They are usually **ultra-short acting (prolongation of administration is possible)**
- **Weak myorelaxant effect**

Indications:

- **Short-term surgical interventions, Burnings, Diagnostic procedures, Painful bandaging, *Initial narcosis***

Pharmacokinetics of intravenous anesthetics

- As soon as we administer thiopental by intravenous administration, we have 100% bioavailability so immediately 2 processes start
  - First, there is **elimination** (metabolism and excretion)
  - And secondly is **redistribution to other compartments**
    - So, from blood, general anesthetics, will go to some other organs
      - First it will go to well perfused and lipophilic organs (**brain** and viscera)
      - Then less lipophilic but well perfused (**lean tissues**)
      - And lastly, low perfused but high fat containing organs (**fat**)
    - And of course, afterwards, the compartment will also slowly release the anesthetic

Intravenous anesthetics – Most commonly used Drugs:		
Propofol	***Thiopental* (*Barbiturate*)**	***Etomidate***
• **Associative action** • Quick onset and very quick recovery **Indication:** • Drug of choice for 1 day surgery • Most common induction agent of anesthesia **Characteristics:** • Has antiemetic activity • Risk of hypotension	• **Associative action** • Quick onset + quick recovery (bolus) + slow recovery (infusion) **Indication:** • I.v. anesthesia induction - Especially short procedures **Characteristics:** • Risk of respiratory depression	• **Associative action** • Quick onset + recovery **Indication:** • I.v. anesthesia for patients w. hemodynamic instability **Characteristics:** • Little or no effect on CVS
***Midazolam* (short-acting BZD)**	***Fentanyl* (opioid analgesics)**	***Ketamine***
• **Associative action** • Slow onset + recovery **Indication:** • i.v. anesthesia induction + preoperative sedative **Characteristics:** • Has anterograde amnesia effect • CVS stability	• **Associative action** • Slow onset + recovery **Indication:** • Analgesia during induction and maintenance anesthesia **Characteristics:** • Significant analgesia	• **Dissociative action** • Mild onset + recovery **Indication:** • Emergency anesthesia for polytrauma • Short procedures **Characteristics:** • Sympathomimetic effect - ⊕ CVS, no depression of resp. • ↑ cerebral blood flow → worsens recovery

3. Complications and side effects of general anesthesia (38)

Adverse effects of inhaled anesthetics

- ❖ As for toxicity, we should mention the **hepatotoxicity** typical for repeated doses of ***halothan***
- ❖ Another on very typical is **malignant hyperthermia**
  - ➢ These 2 are the most frequent
- ❖ (But also, nephrotoxicity and chronic toxicity)

→ Malignant hyperthermia (hyperpyrexia)

- **Serious complication during inhaled narcosis (or in *combination with myorelaxant drugs*)**
- Malignant hyperthermia = **heat production** due to **overactivity of skeletal muscles**, due to excessive release of calcium from sarcoplasmic reticulum (released without impulses)
  - Skeletal muscles start to show fasciculation and rigidity, leading to myopathy afterwards
  - This muscle destruction is present at the later stages, not at the beginning
- **Clinical symptoms:**
  - **Trismus (one of the first signs), Tachycardia, Dysrhythmia, Fever,**
  - **Skeletal muscles rigidity – myopathy – increased serum levels of creatin kinase with K^+ (muscle destruction)**
- **Therapy:**
  - **Cooling** (symptomatic treatment) **+ DANTROLENE** (blocker of ryanodine receptors in SR)

Risk factors of General Anesthesia – General:

- ❖ Usually safe and risk of long-term complication or death is very small
- ❖ Risk of complication is more related to type of procedure undergoing and general health status of patient
- ❖ **Factors increasing the risk of complication:**
  - ➢ Smoking, COPD, Obesity, Hypertension, DM, liver + kidney + resp failure
- ❖ **Patient factors needed to be taken into account when selecting general anesthetics:**

1. Liver + kidney status → for metabolism + clearance of drug
2. Respiratory system → Because anesthetics depress resp. system + bronchodilators
3. CVS → Some of anesthetics have CV depression
4. Nervous system → Neurological disorders influence the selection of anesthetics
5. Pregnancy → some anesthetics can cause complication during pregnancy

Properties of intravenous anesthetic agents

Drug	Induction and recovery	Main unwanted effects	Notes
Thiopental	**Fast onset** (**accumulation** occurs, giving slow recovery) Hangover	**Cardiovascular and respiratory depression**	Used as induction agent declining ↓ CBF and O2 consumption Injection pain
Etomidate	Fast onset, fairly fast recovery	Excitatory effects during induction **Adrenocortical suppression**	Less CVS and resp depression than with thiopental Injection site pain
Propofol	Fast onset, very fast recovery	CVS and resp depression Pain at injection site	Most common induction agent Rapidly metabolized; possible to use as continuous infusion Injection pain **Antiemetic**
Ketamine	Slow onset, after-effects common during recovery	**Psychotomimetic effects** following recovery, Postop. Nausea, vomiting, salivation	Produces good **analgesia** and amnesia. No injection site pain
Midazolam	Slower onset that other agents	Minimal CVS and resp effects	Little resp or CVS depression No pain. Good amnesia

- **Thiopental** is a barbiturate
  - It has fast onset
  - In case you use it in from of infusion, there is a **risk of accumulation**
  - Also, there is a **risk of suppression of cardiovascular and respiratory centers**
- With propofol, the benefit is fast onset and extremely fast recovery
  - There is partial euphoria
  - And another benefit is antiemesis
  - So, there is no need for monitoring after anesthesia
- Ketamine is a dissociative anesthetic
  - It means that there will be no problems regarding suppression of respiratory and cardiovascular centers
  - Unfortunately, it **may lead to psychotomimetic effects, vomiting and salivation**
- Midazolam belongs to the group of benzodiazepines
  - The benefit is good amnesia
  - So, if you need patients to not remember what happened during anesthesia, it is recommended to either use an anesthetic from the group of benzodiazepines or to use benzodiazepines as premedication

4. Local anesthesia (44)

- It's a drug that causes **reversible local anesthesia and a loss of nociception**
- They reversibly block impulse generation and conduction along nerve axons & other excitable membrane
- **Methods of administration:**
  - Surface, infiltration, nerve-block, epidural, spinal anesthesia
- **Clinical use:**
  - Locally used for symptomatic therapy of pain – neuropathic pain, hemorrhoids
  - Systemic use as antiarrhythmic agents e.g., **Lidocaine**, **Trimecaine**

Mechanism of the action

- Their mechanism is not in the brain, but in peripheral neuronal axons
  - **= The loss (reversible) of the sensation by blockade of impulse conduction along nerve axons**
- Their purpose is to **block the initiation and propagation of action potentials of Na^+ channels**
  - ***The sodium channels must be blocked from the inside*** = they have to enter the cells
- Their activity is **pH**-dependent (local anesthetics are **weak bases**!!)
  - Local anesthetics should be administered in **non-ionized form** in order to get into the cytoplasm
  - In the cytoplasm it is ionized and there it will block the inward flow of sodium
- If the area in which we administer local anesthetics has *low pH* (which can be for example in **inflammatory area**, where the pH is about 3-4) then then the **proportion of ionized form will be much higher**
  - It means that the local anesthetic cannot pass through membranes, which means that there will be resistance to local anesthetics in inflamed tissues
  - = **inflamed tissues are resistant to local anesthetics** (To solve this problem, we can use **nerve block anesthetics**)

Susceptibility to block of types of nerve fibers

- Bigger diameter = stronger resistance to blocking – The **sensitivity increases with smaller diameter**
  - C-fibers, and those related to pain are relatively thin = the response will be relatively potent
  - And the last fiber to be blocked will be the thick motoric neurons

Method of administration

- **Surface (topical)** → Gel or patches impregnated with local anesthetics
- **Infiltration anesthesia** → injected into the area where we want the anesthetic effect
- **Nerve-block anesthesia** → not administered where we want the effect, but where the pain is propagated!
- **Epidural anesthesia**
- **Spinal (subdural) anesthesia**

  - Epidural and subdural anesthesia can partly be considered as nerve block anesthesia
  - Because they block the roots coming to the brain
  - But it is important to understand the density of the local anesthetics
    - Because especially by spinal anesthesia it can move in the spinal cord
      - If the density is too high, then it will have tendency to go downwards
      - Good positioning can prevent some complications

Pharmacokinetics

- Absorption

- **Depends on – the concentration of local anesthetic**
- Depends on the blood flow through the area in which we administered local anesthetics
  - Higher blood flow = faster absorption → Faster absorption = shorter and weaker effect → also higher risk of adverse effects
- This is the reason for why we combine local anesthetics very often with some vasoconstrictors (mostly epinephrine)
  - The benefit of epinephrine is that is activates alpha1 receptors → vasoconstriction of area = slower blood flow
    - **Prolongation the duration of the action of LA**
    - **Increase of the effect of LA**
    - **Decrease of the toxicity of LA**
    - **Reduce of the consumption of LA** (due to reduced need of LA)

Esters are destroyed by plasma pseudocholinesterases
Amides are metabolized in the liver (by *amidase*)
➢ You should remember this

- Breakdown

- **Esters** are rapidly hydrolyzed by *plasma pseudocholinesterase* → short half-life **(1-2 hours)**
  - So, **they don't need the activity of the liver for their metabolism**
  - Because they are **rapidly** hydrolyzed by the ***plasma pseudocholinesterase***, their **onset of action is quite fast**, and their duration is generally shorter (= shorter half-life)
  - This is the reason for why we don't currently use esters so often – almost never
- **Amides are** metabolized in the liver
  - We use amides more often → Their effect is more predictable
  - Their **pharmacokinetic properties are better (= they have longer plasma half-life)**
  - As they are amides, they **must be destroyed by amidase in the liver**

- Excretion by urine

Effects

On nerve fibers

- The loss of the function in the order: **Pain** > **temperature** > **touch** > **skeletal muscle tone** (opposite in recovery)

On the central nervous system

- **Lower concentrations** – there will be some irritation → tremor, seizures
- **Higher concentrations** – depression → respiratory, cardiovascular system
  - If liver is not working or if there is not sufficient additive vasoconstrictor, or there is some intravenous administration of the agent, it can lead to depression of CNS
    - Suppression of respiratory and cardiovascular centers – leading to heart arrest and to death of the patient

On the cardiovascular system

- Normally, most local anesthetics have indirect **vasodilatory** action on vessels
  - Because they block the conduction of vasomotoric nerves → **vasodilation** → ↓ **Blood pressure**
- Heart – expressive antiarrhythmic effect **(lidocaine + trimecaine)**
  - These are the 2 drugs form the group of local anesthetics which are also used as antiarrhythmics (***group 1b***)
  - But for this indication, we expect the systemic action, so we will administer them **intravenously**

Adverse effects

- **Acute intoxication**
  - **Cardiotoxicity, tremor, salivation, convulsion, excitation, hypotension, depression of the breathing**
  - **Treatment of the intoxication**
    - Restoration of the cardiovascular system
    - Inhalation of oxygen
    - Inhibition of the seizures – diazepam, thiopental
- **Sudden collapse and death**
  - **Deep hypotension**
  - **Fibrillation and arrest of the heart**
- **Allergies** (mostly esters)
  - **Skin rashes**
  - **Bronchospasm**
- **Other**
  - **Laryngospasm**
  - **Adverse effects of the vasoconstrictor (epinephrine)**
    - **Local – hypoxia, necrosis**
    - **Systemic – ↑ blood pressure, tachycardia etc.**

Esters
- **Cocaine**
- **Procaine**
- **Tetracaine**

Amides
- **Trimecaine**
- **Lidocaine**
- **Bupivacaine**
- **Articaine**
- **Cinchocaine**
- **Ropivacaine**

A helping tool to remember which drugs belong to which group:
➢ All local anesthetics end with "-caine"
➢ And in those which belong to the group of amides have another "i" in the first part of the word
  - Except for Oxetacaine, but this is the only exception
➢ Whereas the esters don't have any "i" in the first part of the word
"i" in the first part of the word = amide

Esters are destroyed by plasma pseudocholinesterases
Amides are metabolized in the liver (by *amidase*)
➢ You should remember this

5. Local anesthetics – ester type (24)

Esters vs. amides:

- Local anesthetic molecules consist of an aromatic part linked by an **ester** or **amide** bond to a ***basic*** sidechain
  - They are ***weak bases***, which is important in relation to their ability to penetrate the axon membrane in order to block Na channels from the inside (have to be in non-polar form!)
- The presence of the ester or amide bond in local anesthetic molecules is important because of its susceptibility to metabolic hydrolysis.
  - The ester-containing compounds are fairly rapidly inactivated (hydrolyzed) in the plasma and tissues (mainly liver) by non-specific esterases (**pseudocholinesterase**).
- **Esters** are rapidly hydrolyzed by *plasma pseudocholinesterase* → short half-life **(1-2 hours)**
  - So, **they don't need the activity of the liver for their metabolism**
  - Because they are **rapidly** hydrolyzed by the ***plasma pseudocholinesterase***, their **onset of action is quite fast**, and their duration is generally shorter (= shorter half-life)
  - This is the reason for why we don't currently use esters so often – almost never
- **Amides are** metabolized in the liver
  - We use amides more often → Their effect is more predictable
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  - As they are amides, they **must be destroyed by amidase in the liver**

Drugs:

a. Cocaine

- A **natural alkaloid**
- **CNS stimulant → euphoria, psychic dependence**
- **Vasoconstriction – sniffing → ischemia, necrosis, perforation of the nasal septum**
- Local anesthetics lead to vasodilation, but ***cocaine is an exception***! → Cocaine leads to ***vasoconstriction***
  - This is why cocaine sniffers have very often perforation of nasal septum
- **Only rarely used → only surface anesthesia in ORL, ophthalmology**
  - Cocaine is only used rarely nowadays, it used in ophthalmology and otorhinolaryngology in form of eye drops to induce anesthesia, when we do not want to add some vasoconstricting additive

b. Procaine

- **Poorly penetrates** across mucous membranes
- Quickly broken down by ***plasma pseudocholinesterases***
- **Metabolite → spasmolytic and analgesic effect**
- For all types of injection local anesthesia – 0.2 % - 1% concentration
- **Currently not registered**, amide anesthetics are preferred
  - (Currently it is not used, it has very short action and is allergenic)

c. Tetracaine

- Slower onset of the action, longer duration, greater potency than procaine
- **Adverse effects** after systemic administration → for topical administration
- Nowadays it is not registered

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6. Local anesthetics – amide group (64)

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Amides = safer and preferred local anesthetics

Drugs:

a. Trimecaine

- **A very popular drug** (exists in infiltration, nerve block and topical gels)
- **For all types of the anesthesia - solution 0.5% - 2%**
- **Also, for the treatment of the arrhythmias!! (group 1b)**

b. Lidocaine

- **LIDOCAINE, XYLOCAINE inj. and other medicinal form for topical administration (gel, supp., ung.)**
- **Produces the sedation along anesthesia**
- **Metabolism - in the liver to active metabolites → toxic reactions of the central nervous system**
- **Also, for the treatment of the arrhythmias!! (group 1b)**

→ Trimecaine and lidocaine are the 2 mostly used agents

c. Bupivacaine

- The benefit of it is quite long duration of action – so, repeated dosing is not so frequent
- **Long-acting anesthetic – it is preferred for spinal and epidural anesthesia (0.5%)**
- **Adverse effects – cardiotoxicity – hypotension, bradycardia → suitable pre-treatment with atropine**
  - This is the biggest problem of the use of bupivacaine is its potential to cause cardiotoxicity
    - We must be sure that their administration is **not intravenously**
      - Because if it is intravenously, then the cardiotoxic effects can be much faster

d. Articaine

- **Mainly in the stomatology**
- **Quick the onset of the action (1-3 minutes), duration 45 minutes**
  - Its duration of action is relatively long, so there is no need of reapplication
- **Less cardiovascular disturbances** (not a high risk of systemic complications)
- **Suitable for risk patients**
- **Usually with epinephrine**
  - It is combined with epinephrine (additive vasoconstrictor)
  - The benefit is not only stronger action, but it also ***reduces the bleeding from wounds***

e. Cinchocaine

- **Very toxic after systemic administration → only for topical administration**
  - Cinchocaine is only used locally in form of ointments or suppositories to treat hemorrhoids in dermatology
  - We never use it subcutaneously, only local topical administration
- **In the dermatology, for the treatment of hemorrhoids**

f. Oxetacaine

- **Stable and active in the acidic conditions (lower pKa)**
  - Which means that **it also works at acidic environment**
- **Historically it was used in combination with antacids for the treatment of ulcer disease and gastropathy with hyperchlorhydria**
  - **Currently less used**

7. Myorelaxants (centrally, peripherally acting) (31)

A muscle relaxant = ***a drug which affects skeletal muscle function and decreases the muscle tone***.
It may be used to treat symptoms such as muscle spasms, pain, and hyperreflexia.

The role of skeletal muscle relaxants is to block contraction of smooth muscle, even though the neurons are sending impulses

- ❖ They act either:
  - ➢ **Peripherally** = neuromuscular blockers
    - Which means they act in ***endplates***
    - They act by influencing the ***Nm receptors*** → muscle form of nicotinic receptors at the endplates
  - ➢ **Centrally** = spasmolytics
    - Which means that they act in the CNS
    - They mostly act by changing the activity of alpha2 receptors and GABA-B receptors

A. Central acting neuromuscular-blocking drugs – spasmolytics

- **The reduction of the spasticity of the skeletal muscles**
- **<u>The improvement of the spasticity symptoms</u>**

Mechanism of action:

- ❖ They are called central acting because they act at the level of the **cortex**, **brain stem** or **spinal cord**, or **all three areas**
- ❖ **Not all agents however have CNS activity**
  - ➢ **They can also interfere with skeletal muscle excitation–contraction coupling**
    - This goes for ***dantrolene*** for example (treatment of malignant hyperthermia)
- ❖ The generation of the neuronal signals in motor neurons that cause muscle contractions are dependent on the balance of synaptic excitation and inhibition the motor neuron receives.
  - ➢ Spasmolytic agents generally work by either:
    - Enhancing the level of inhibition (GABA)
    - Or reducing the level of excitation of motor neurons
- ❖ Indications:
  - ➢ Spasticity in cerebral palsy, cerebral paresis spasticity, MS
  - ➢ Lower back pain, neck pain, fibromyalgia, tension headache

Representatives

- **Benzodiazepines: Diazepam**
- **Tolperisone**
- **Mephenoxalone**
- **Tizanidine**

> ❖ The mostly used are these 3 red ones
> ➢ They are very often prescribed by neurologists and orthopedists to block the spasms around the back

- **Baclofen → *GABA-B agonist***
  - It is an inhibitor of adenyl cyclase, leading to increased potassium conduction
  - **↑ K^+ conductance → hyperpolarization of the membrane**
  - **Reduction of the calcium influx**
  - **↓ the release of the excitatory neurotransmitters**
  - **In the spinal cord and in the brain**
  - **Less sedation than diazepam**
    - Sedation is not typical for baclofen because it doesn't influence GABA-A receptors, only GABA-B
- **Dantrolene**
  - Interferes with the release of Ca^{2+} the activator from sarcoplasmic reticulum
    - Dantrolene acts peripherally on the release of calcium from sarcoplasmic reticulum
  - Is used in the **<u>treatment of malignant hyperthermia</u>**

B. Peripheral neuromuscular-blocking drugs

- Neuromuscular blockers which act by interfering with transmission at the neuromuscular end plate and have no CNS activity
- They are often used during surgical procedures and in intensive care and emergency medicine to cause temporary paralysis - paralysis of skeletal muscles
    - So, they produce the paralysis of the skeletal muscles

Peripheral neuromuscular blocking agents are divided into

- **a) Non-depolarizing blocking agents**
- **b) Depolarizing blocking agents**

Depolarizing:

- The typical depolarizing agent which is registered is **suxamethonium**
- Succinylcholine consists of 2 molecules of acetylcholine, which means that they have very **high affinity to all cholinergic receptors** (also muscarinic receptors → side effects)
- Depolarizing agents are not competitive antagonists – they are agonists which stay connected and desensitize the receptors!
- The Nm receptor is coupled with sodium channel, so first → it will open this channel
    - The consequence of this is that at the beginning of using depolarizing agents, there will be **fasciculations**
- Normally, if there is acetylcholine, automatically this acetylcholine will be destroyed by acetylcholine esterase and the channel will close again
    - But in this case, **it stays open** because suxamethonium is different from acetylcholine
        - It is destroyed by **pseudocholinesterase** – which is not present physiologically in our body, has to be made – so it takes time to work
    - There is no way how to destroy them or to inhibit their activity
        - We don't have the possibility to give the patients some pseudocholinesterases, so we must simply wait until the effect will stop
- Because the sodium channels stay open, there is no more responding, there is no depolarization at the endplate → this is the desensitization
    - So, at the beginning of the use of depolarizing agents, we will have some fasciculations, because there is opening of the channels
        - But then the membrane will remain desensitized and will not respond to further stimulation = Paralyzed
- As succinylcholine is metabolized by plasmatic pseudocholinesterase, the duration of action is not so long, usually less than 10 minutes (about 8 minutes)
    - But there can be a problem if the patient has some genetic deficiency of pseudocholinesterase
        - In that case, the duration of action can last for several hours

→ Suxamethonium (or succinylchloride or succinylcholine)

- **Breakdown by pseudocholinesterase**
- **Effects – very rapid and short**
    - Its duration of action is normally up to 8 minutes
- **Crosses placental barrier and into milk**
- **Stimulates all types of muscarinic receptors → adverse effects**
    - The problem of its use is that it stimulates all types of muscarinic receptors, leading to adverse effects

Non-depolarizing

- The non-depolarizing agents also contain molecules of acetylcholine
- That means that they will also have affinity to these receptors, but their structure is much bigger
    - That means that if it connects to the receptors, there is no place to open the sodium channels, so there will be no depolarization at the beginning
        - = **no fasciculation at the beginning** either
    - This is the reason why they are called non-depolarizing agents
- They are **competitive antagonists of acetylcholine at Nm receptors**
    - There is similarity with acetylcholine which is sufficient for Nm receptors
        - But they will not be active at Nn receptors, because they are too different
        - Also, **they will never stimulate muscarinic receptors**
            - Oppositely, some non-depolarizing agents (especially pancuronium) can block muscarinic receptors
    - And because they are competitive antagonists, **we have a possibility to stop this blockade** by increasing the concentration of acetylcholine (we can use stigmines – acetylcholinesterase inhibitors = ↑ AcH)

- Isoquinoline derivatives:

→ Tubocurarine

- We currently don't use Tubocurarine
- **The order of paralysis of muscles – jaw, eye, limbs, trunk, diaphragm**
  - **The recovery in the opposite order**

→ Atracurium

- **More potent than tubocurarine, widely used**
- **The function of the liver and kidney without effect on its activity**
- **Crosses the blood-brain barrier → ↑ doses – seizures**
- Atracurium can be used, but the problem is that it can lead to seizures
  - So, it is not used very often

- Steroids:

→ Pancuronium (remember this one → widely used)

- **Synthetic steroid**
- **More and rapidly active than tubocurarine**
- **↑ doses – tachycardia from antimuscarinic effect**

→ Pipecuronium

→ Vecuronium

- **Without effects on the CVS, ganglia and histamine**
- **Small cumulation**
- **Occasionally causes prolonged paralysis – probably active metabolite**

Rocuronium

- **Similar – faster onset, mostly used currently in Slovakia**

Adverse effects

- **For all skeletal muscle relaxants:**
  - **Arrest of the ventilation** (logically, because you block the breathing muscles)
- **For non-depolarizing**
  - **↓ Of the blood pressure**
  - **Release of histamine – allergy, asthma**
  - There is mostly no effect of block of M receptors
    - Pancuronium blocks Muscarinic receptors → can lead to tachycardia
  - **Hypergic reaction – in myasthenia gravis**
- **For depolarizing**
  - **Direct Muscarinic effects – bradycardia**
  - **↑ in K+ level in the blood – heart arrest!**
  - **↑ intraocular pressure**
  - **↑ intragastric pressure – emesis**
  - **Postoperative muscle pain**
  - **Malignant hyperthermia – rare (Suxamethonium!) – especially when combined with halothan**
  - **Prolonged paralysis from – abnormality of CHE**
  - **Interactions - ATB, LA**
  - **↓ Activity of CHE**

Antidote

- **Non-depolarizing**
  - **Inhibitors of acetylcholinesterase (neostigmine)**
  - **Atropine** is used to protect muscarinic receptors in the heart from overactivation
- **Depolarizing**
  - **Without antidote (we just have to wait) → control of the ventilation**

10. Cancer

1. **Immunosuppressants (26)**
2. **Cytostatics – mechanism of action (27)**
3. **Cytostatics – side effects (6, 18)**

1. Immunosuppressants

Immunosuppressant – General:

- *Immunosuppressants are class of drugs that suppress strength of body immune system*

Indication:

1. Suppress rejection of transplanted organs and tissues
2. Suppress graft-versus-host disease in BM transplants
3. Treat variety of conditions that are believed to have an important autoimmune component in their pathogenesis
   - E.g., idiopathic thrombocytopenia purpura, some hemolytic anemia, myasthenia gravis…

Classification of immunosuppressants:

1. **Calcineurin inhibitors** – selective ⊖ of cytokine production and function
2. **Antiproliferative cytostatic** – ⊖ purine synthesis (DNA synthesis)
3. **Antibodies** – block IL2 receptors
4. **M-TOR inhibitors** – ⊖ cell proliferation
5. **Corticosteroids**

1. Calcineurin inhibitors

- Selective ⊖ of cytokine production
- **Normally:**
  - Calcineurin dephosphorylates **NFAT** (nuclear factor of activated T cells) → NFAT travels into the nucleus and ⊕ production of cytokines → ↓ activation of T cells
    - by ⊖ calcineurin → ⊖ production of cytokines
- Indication → prevention of transplant rejection, autoimmune disorder, inflammatory bowel disease
- Side effects:
  - They have narrow therapeutic window
    - Levels to low = transplant rejection, levels to high = nephrotoxicity

A. *Cyclosporine:*

- Drug that binds to **cyclophilin** → complex binds to calcineurin and cause ⊖

B. *Tacrolimus:*

- Drug that binds to **FK binding protein** → complex binds to calcineurin and cause ⊖
- Much more potent than *cyclosporine*

2. Antiproliferative Cytostatic:

- ⊖ purine synthesis (DNA synthesis) → cytostatic (⊖ cell division) of T and B cells
  - They ⊖ enzymes important in purine synthesis (IMP dehydrogenase + PRPP aminotransferase)
- Indication → Prophylaxis of acute rejection, autoimmune disease
- Side effects → GIT disturbances, pancreatitis, pancytopenia
- **Drugs:**
  - ***Azathioprine + Mycophenolate mofetil***
    - *Mycophenolate mofetil* has replaced *azathioprine* because of its safety and effectiveness

3. Antibodies – *Basiliximab + Daclizumab*

- They are monoclonal antibodies that block IL-2 receptor → ⊖ IL-2 activity → ↓ WBC activity
- Indication → treatment of acute rejection + prevent transplant rejection
- Side effect → Severe allergic reaction

4. M-TOR inhibitors - *Sirolimus*

- *Sirolimus* binds to **FK binding protein** (same as *Tacrolimus)* → complex will ⊖ m-TOR (mammalian target of rapamycin) → ⊖ cell proliferation
  - M-TOR is an protein that is important for cell proliferation
- Indication → prophylaxis of acute and chronic organ rejection, autoimmune diseases
- Side effects → Metabolic disorders:
  - Hypercholesterolemia, hyperglycemia, hepatotoxicity, pancytopenia

5. Corticosteroids:

- First line immunosuppressive therapy for both transplantation + autoimmune disorder
- Immunosuppressive corticosteroids → ***Prednisolone, hydrocortisone, dexamethasone***
- Mechanism of action:
  - ⊖ of intracellular NF-κB → ⊖ of multiple inflammatory and immune mediators → ↓ B and T cell activity
- Main clinical uses:
  - Transplant rejection prophylaxis, autoimmune disease, atrophy + asthma, adrenal insufficiency
- Side effects:
  - Many… e.g., weight gain, peptic ulcer, hypertension, diabetes, infection…

2. Cytostatics – mechanism of action

Cytostatics – General:

- Cytostatic = *Inhibition of cell growth and multiplication*
- **Chemotherapy** is treatment of cancer with more cytotoxic antineoplastic drugs as a part of a standardized regimen
- **Cytostatics** = Chemotherapeutic agents
- Cytostatics have also role in treatment of other conditions (e.g., MS or chron disease)
- Aim of therapy:
  - Remission, eradication (kill?), minimal toxicity, prevention of resistance to cytostatics, prevention of relapse of cancer

Factors influencing effectivness of treatment:

- Pharmacodynamics of cytostatics
- Sensitivity of cancer cell
- Time of starting chemotherapy
- Dose
- Combination of agents

General info – Cancer:

- *Excessive uncontrolled proliferation of tumor cells, clonal cells, invasive, ability to metastasize, immortality*
- Early detection → better survival rate

General rules of chemotherapy:

1. Aggressive high-dose chemotherapy
2. Combination of agents with different mechanism of action (to ↓ resistance)
3. Supportive therapy (e.g. antiemetics)
4. Different agents for different type of cancer

Cytostatics – classification of drugs acc. Mechanism of action:

1. Direct damage of DNA in the nucleus – Antimetabolites:

A. Antifolates:

- *Methotrexate:*
  - Methotrexate = a folic acid analog
  - Competitive inhibition of dihydrofolate reductase → ↓ formation of nucleotides (dTMP) → ↓ DNA synthesis
  - Can be used for the treatment of leukemias, lymphomas, solid cancer
  - Also, methotrexate can be used for conditions where there is abnormal proliferation of trophoblastic tissue
  - Major site effect = bone marrow suppression + megaloblastic anemia
    - Bone marrow suppression can be reversed with leucovorin → leucovorin rescue
      - Leucovorin is a reduced form of folic acid and thus, doesn't requires dihydrofolate reductase to get activated
    - Liver toxicity → steatosis
    - Pulmonary fibrosis
- *Pemetrexed*:
  - ⊖ of thymidylate synthase → ↓ nucleotide (dTMP) → ↓ DNA synthesis

B. Pyrimidine antagonists: - Pyrimidine pathway

- 5-fluorouracil (5-fu) is converted to 5-FdUMP → 5-FdUMP competes with thymidylate synthase → ↓ nucleotide (dTMP) → ↓ DNA synthesis
- 5-Fu also incorporate into RNA + DNA → ↓ DNA + RNA synthesis

C. Purine antagonists: - Purine pathway

- 6-mercaptopurine (6-MP):
  - ⊖ enzymes (PRPP synthetase + AMP deaminase) → ↓ purine synthesis → ↓ DNA synthesis
  - Also incorporate into DNA → ↓ DNA synthesis

D. Inhibitors of ribonucleoside reductase:

- Inhibition of ribonucleotide reductase → ↓ DNA replication → massive cytoreduction

2. Genotoxic drugs – Alkylating agents:

- They stop tumor growth by cross-linking **guanine** in DNA strands
  - By alkalization
- This will cause the strands unable to separate (necessary in DNA replication) → ⊖ DNA synthesis

3. Plant derived inhibitors of mitosis:

- Bind to tubulin → block ability to polymerase and form microtubules → ⊖ mitotic spindle formation → Cell is stuck in metaphase → ↓ cell division

4. Plant derived Topoisomerase inhibitors:

- ⊖ Topoisomerase → ⊖ DNA unwinding. → ↓ DNA replication + DNA degradation

5. Cytotoxic Antibiotics:

- Intercalation between bases of DNA

6. Others:

- **Hormones agonist/antagonists**
- **Protein kinase inhibitors**
  - ⊖ of kinase involved in growth factor receptor transduction
- **Monoclonal antibodies**
  - Block cell proliferation

Factors influencing effectivness of treatment:

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3. Cytostatics – side effects

Cytostatics – General:

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4. Different agents for different type of cancer

General info – Cancer:

- *Excessive uncontrolled proliferation of tumor cells, clonal cells, invasive, ability to metastasize, immortality*
- Early detection → better survival rate

Side effects – General:

- Main side effect or limiting factor for cytostatics are that they have rather high toxicity
- Side effect are very common
- Side effect can occur at any time:
  - Immediate (hours), early (days-several weeks), delayed (months), late (months, years)
- Side effects mostly effect tissues that are **rapidly proliferating**:
  - **Skin, hair follicles, GIT mucosa, germinative cells, bone marrow, lymphatic tissue**

1. **Hemopoiesis:**
   - BM suppression → Myelosuppression, granulocytopenia, thrombocytopenia, anemia
   - Occurs in majority of cytostatics
2. **GIT Disturbances:**
   - Malabsorption, diarrhea, nausea + vomiting
3. **Infertility and impairment of spermatogenesis:**
   - Germinative cells
4. **Skin disturbances:**
   - Pigmentation, rashes, palmoplantar erythema
5. **Hair loss** (alopecia)
6. **Nephrotoxicity + Urotoxicity**
7. **Neurotoxicity:**
   - Symptoms include → peripheral, autonomic, central neuropathy
8. **Cardiotoxicity:**
   - Arrhythmias, bradycardia
9. **Lung toxicity:**
   - Interstitial lung fibrosis
10. **Teratogenic, mutagenic and cancerogenic effects:**
    - Causes underdevelopment of fetus + mental retardation
11. **Secondary cancers** (e.g., leukemia)

11. Pharmacology of pain

1. **Opioid analgesics (6)**
2. **Opioid analgesics – agonists of opioid receptors (20)**
3. **Atypical opioid analgesics (9)**
4. **Opioid analgesic: Agonists-antagonists (27)**
5. **Symptoms and therapy of opioid analgesics poisoning – (47)**
6. **Non-selective NSAiD (37)**
7. **Preferential and selective NSAiD (64)**
8. **Symptoms and therapy of NSAiD poisoning (63)**
9. **Analgesic - antipyretic drugs (52)**

Therapy of pain

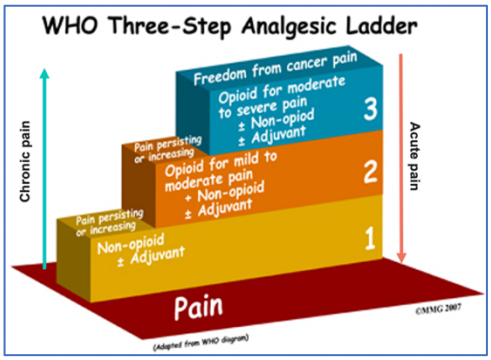
Management of the pain

- **Pharmacological**
  - **Non-opioid analgesics**
  - **Opioid analgesics**
  - **Adjuvants (antidepressants, anticonvulsants, sedatives, anxiolytics, local anesthetics…)**

Conventional

- **Non-pharmacological**
  - **Neurosurgery**
  - **Electrostimulation (TENS)**
  - **Physiotherapy**
  - **Psychotherapy, acupressure, acupuncture**

Unconventional



Categorization of analgesics

- **Opioid analgesics**
  - **Opioid receptors stimulation**
  - **In CNS – pain suppression**
  - **In periphery – side effects**
- **Non-opioid analgesics: Analgetic – antipyretics**
  - **Inhibition of peripheral nociceptors + PB in CNS (paracetamol, metamizol)**
- **Non-opioid analgesics: NSAIDs**
  - **COX inhibition**
  - **+ Significant anti-inflammatory effects**

WHO 3-step analgesic ladder:

1) **Non-opioids ± adjuvant (mild pain)**
2) **Opioids (mild to moderate pain)**
   ± Non-opioid
   ± Adjuvant
3) **Opioids (moderate to severe pain)**
   ± Non-opioid
   ± Adjuvant

- For **chronic pain**: (pain lasting for more than 3 months)
  - **Start from step 1** and work your way **up** to step 3 according to severity
- For **acute pain**:
  - **Start from step 3** and work your way **down** to step 1 as pain gets less severe

1. Opioid analgesics (6)

Opioid analgesics

- Opioid analgesics have been used for centuries for their **analgesic effects**
- They are *the most commonly used pharmacological agent for the management and treatment of* ***moderate-to-severe pain***
- The word "opium" is derived from the Greek word oppos – which means juice from pops
  - Opium is an extract of the juice of the poppy heads of ***Papaver somniferum*** that contains morphine and other related alkaloids

- Opioids are divided according to their origin into:
  - **Natural alkaloids (from poppy heads) – morphine, codeine**
  - **Synthetic – fentanyl, sufentanil**

Opioid receptors:

	μ (Mu)	δ (Delta)	κ (Kappa)
Analgesia			
- Supraspinal	**+++**	**-**	**-**
- Spinal	**++**	**++**	**++**
Respiratory depression	**+++**	**++**	**-**
Pupil constriction (miosis)	**++**	**-**	**+**
Reduced GI motility	**++**	**++**	**+**
Euphoria	**+++**	**-**	**-**
Dysphoria	**-**	**-**	**+++**
Sedation	**+**	**-**	**+++**
Physical dependence	**+++**	**-**	**+**

- Opioid analgesics exert their pharmacological effects by binding to opioid receptors, both **within** and **outside the CNS**
- Opioid receptors are a group of **inhibitory G-protein (Gi) coupled receptors** (*metabotropic)*
  - When activated → ↓ *GABA secretion* = ↑ *dopamine release*!
- The endogenous opioids are for example dynorphins, endorphins, endomorphins, nociceptins

- Opioids act on 3 major subtypes of opioid receptors: **mu,** delta and **kappa**
- **Mu receptors**:
  - **Spinal** and **supraspinal analgesia**, **respiratory depression**, **miosis**, **constipation** (reduced GI motility), **euphoria** and **physical dependence** is under the control of Mu receptor
  - ***Mu2 receptor is associated with antitussive effect and depression of repository center*** (***Codeine***!!!!)
- **Kappa receptors:**
  - Stimulation of kappa receptors leads to **spinal analgesia**
  - Respiratory function, miosis, constipation is **not** affected by the stimulation of kappa receptors
  - However, stimulation of kappa receptors cause **sedation**, **dysphoric** effect, **hallucinogenic** effect

Drugs influenced opioid receptors

- Active substances affecting the opioid receptors are divided according to their **selectivity** into:
  - 1. Pure agonists (or *morphine-like opioids*) of opioid receptors
    - These are ***very strong agonists of mu receptors*** and ***mild agonists of kappa*** receptors
  - 2. Substances with mixed activity (**agonists-antagonists**)
    - **Pentazocine** is an *antagonist of Mu* and *agonist of Kappa*
    - **Buprenorphine** is an agonist of Mu and antagonist of Kappa
  - 3. Antagonists of opioid receptors
    - **Naloxone** and **naltrexone** are examples of **competitive antagonists of opioid receptors**
    - They block the activity of opioid agonists and these receptors

Drugs	μ (Mu) receptor	κ (Kappa) receptor
1. Pure agonists	**Agonist**	**Agonist**
2. Agonist-Antagonist		
Pentazocine	**Antagonist**	**Agonist**
Buprenorphine (partial agonist)	**Agonist**	**Antagonist**
3. Antagonists	**Antagonist**	**Antagonist**

Routes of administration of opioid analgesics

Chronic pain
Peroral (extended release tbl.)
Transdermal (fentanyl, buprenorphine)
i.v. infusion or s.c. (~~i.m.~~)
Rectal

- For different types of pain (acute vs chronic), different administration of opioids is used

Chronic:

- The **peroral** way of administration of opioids is commonly used as extended-release tablets
  - However, due to first-pass effect in the liver and very low bioavailability, oral doses of opioids may need to be **much higher** when compared with parenteral doses, to achieve to same therapeutic effect
- **Transdermal patches** provide stable drug plasma levels → *fentanyl patches*
  - It is thought to provide better pain control
- **Rectal suppositories** of morphine are sometimes used when oral or parenteral way of administration are contraindicated
- Intramuscular way of administration is not recommended → because it is very painful

Acute:

- For acute pain (or breakthrough pain), the **intravenous** way is commonly used
- Other ways for acute pain include **transmucosal**
  - Currently, fentanyl and sufentanil are the major opioids available for **intranasal**, **sublingual**, **buccal** administration
- Opioids may also be given **epidurally** and **intrathecally** in surgery

Acute pain
Parenteral (i.v.)
Intranasal spray (fentanyl)
Sublingual tablets (fentanyl)
Buccal film (fentanyl)
Epidural (morphine, fentanyl)
Intrathecal (morphine, fentanyl)

Opioids – pharmacokinetics

Absorption:

- **Depends on way of administration**
  - Opioids are absorbed through mucous membranes
  - Also, subcutaneous injection and it can also penetrate the spinal cord adequately after epidural and intrathecal administration
- **Low bioavailability after p.o. administration → ↑ first-pass effect = ↑ p.o. doses**
- **So → Alternative way of application (transdermal, buccal, sublingual) is preferred**

Distribution: (distribution = the movement of the drug between the blood and various tissues in the body)

- **High degree of plasma protein binding is characteristic for opioids (about 90%)**
- **The maximal concentration is reached in brain, liver, kidney**

Metabolism:

- Mostly, opioids undergo excessive **first-pass metabolism in the liver** before entering the systemic circulation
- **Opioids are metabolized by cytochrome P450 + subsequent conjugation with glucuronic acid**
- During their metabolism, they produce **active metabolites**
  - **Morphine-6-glucuronide – which increases ↑ analgesia**
  - **And morphine-3-glucuronide – increases neurotoxicity**
- **Specific types of opioids are the ester types of opioids**
  - Ester types of opioids are for example **heroine** and **fentanyl**
  - They have **short half-life** – because they are rapidly metabolized
    - They are hydrolyzed by **blood esterases** after their administration

The most common side effects of opioids:

- **Tolerance**
- **Dependence (physical, psychological)**
- **Abstinence syndrome**
- **Nausea, vomiting**
- **Constipation**
- **Urine retention**
- **Effects of histamine!** (Opioids induce histamine release)
- **Respiratory depression (High doses, combinations!)**

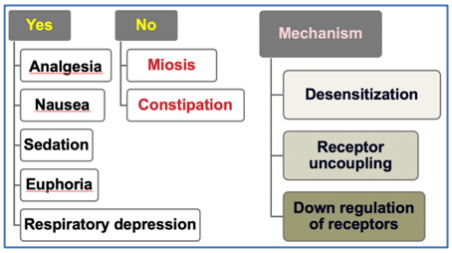
Side effect	Elimination of side effects of opioids
Nausea and nausea	Antiemetics: → Neuroleptics (prochlorperazine) → H_1 receptor antagonist (I. generation) → 5-HT_3 receptor antagonists – setrons → Scopolamine patch Prokinetics: metoclopramide ROTATION OF OPIOIDS
Pruritus	H_1 receptor antagonists (I. generation)
Constipation	Fiber diet, laxatives, metoclopramide, peripherally acting opioid antagonist (methylnaltrexone)
Sedation	ROTATION OF OPIOIDS, psychostimulants
Hyperalgesia	ROTATION OF OPIOIDS

- **Opioids cross the placenta and cross into maternal milk → contraindicated in pregnancy**
- **Fast penetration through blood brain barrier → contraindicated in children**

Elimination of side effects of opioids

- There are several ways of how to reduce these side effects
  - E.g., by **reducing the dose**, **changing one opioid drug for another** (**rotation**) or **change the way of administration**
- You can manage the nausea and vomiting with ***antiemetics***
- You can treat **pruritus** by using ***antagonist of H1 receptor***
- You can manage the **constipation** by ***laxatives***
  - → Methylnaltrexone **decreases opioid-induced constipation**
  - It is a peripherally acting (doesn't cross BBB) ***Mu receptor antagonist***
- Rotation of opioids
  - = The process of changing one opioid drug for another in order to improve pain control and reduce side effects
  - Changing one preparation to another opioid with the current dose reduction may achieve recovery of analgesic effect
  - Because individual opioids have different internal affinity for different opioid receptor subtypes, or different pharmacokinetics
- Hyperalgesia is the condition in which you experience an enhanced sensitivity to pain

Tolerance



- Tolerance is a process characterized by neuroadaptation which results in reduced drug effect
  - **Transient administration** of opioids leads to a phenomenon called "**acute tolerance**"
  - Whereas **sustained administration** leads to development of classic- or **chronic tolerance**
- This process of phosphorylation of receptors causes desensitization, receptor uncoupling and formation of complexes with arresting and downregulation of receptors
- Tolerance occurs in the case of ***analgesia***, ***nausea***, ***sedation***, ***euphoria***, ***respiratory depression***
- There is **no tolerance** in the case of **miosis** and **constipation**
  - For this reason, miosis is a good diagnostic factor for opioid dependence

Management of opioid dependence:

- Substitution therapy + psychotherapy…
- Aim:
  - To relieve opioid craving, suppress the abstinence syndrome, and block the euphoric effect associated with opioids
- Drugs:
  - Buprenorphine (+ naloxone → SUBOXONE, ZUBSOLV sbl. Tbl)
- Gradual ↓ of dose (min 6-12 months – years)

Opioid – principles of pain therapy:

- Analgesic administration at regular time-interval
- Patient with chronic pain → long-lasting analgesic + short acting with rapid onset for breakthrough pain
- Do not combine analgesics with similar chemical structure
- Do not combine opioid agonist with mixed agonist-antagonists → abstinence syndrome
- Termination of therapy → gradual ↓ in dose
- Pharmacological ↓ of opioid side effect
- Non-opioid analgesics have opioid-sparing effect
- Analgesics are ineffective in psychogenic pain
  - This pain has to be treated with a psychiatrist

2. Opioid analgesics – agonists of opioid receptors (20)

Intro = topic 1!!

= Pure agonists of opioid receptors

- **Strong analgesic effect:**
  - **§ Morphine, § Oxycodone, § Methadone, § Fentanyl, § Sufentanil**
- **Weak analgesic effects:**
  - **Codeine, § DH-codeine**

❖ Opium is obtained from the seed capsule of the opium poppy - ***Papaver somniferum***

❖ These substances are marked with § (she called it "paragraph" in lecture)

➢ There are particular regulations and legislations of prescription, storage and production of opioids

❖ Codeine is without this §

➢ The opium registration does not fully apply to codeine

➢ However, it must be stored in locked areas

Mechanism of action of pure agonists

❖ Opioids act on the **presynaptic** and **postsynaptic level** (opioids have pre- and post-synaptic activity)

- **1. Activation of pre-synaptic opioid receptors** (= *decrease in the release of excitatory NTs*)
  - **Closing of voltage-gated calcium channels** on the presynaptic nerve terminals **(→ ↓ Ca^{2+})**
    - ➢ = this leads to a **decrease the in release of excitatory neurotransmitters** such as **glutamate** and **substance P**
- **2. Post-synaptic level (**= *hyperpolarization* of the membrane)
  - **Opening of potassium channels**, causing an **efflux of potassium ions out of the cell → hyperpolarization**

❖ In summary, opioid mechanism is complex → mixed presynaptic and postsynaptic activity

➢ The result of opioid mechanism is:

- **Stabilization of the membrane, reduced activity of the cell membrane** (hyperpolarization) – post-synaptic
- And **reduced release of excitatory neurotransmitters** – pre-synaptic

Clinical use of opioid agonists

- **→ Pain therapy (acute, chronic, cancer pain)**
  - ➢ ***Opioids increase the pain threshold!***
  - ➢ Opioid analgesics are effective in ***nociceptive pain*** (**cancer pain** for example)
    - Opioids are **less suitable for visceral pain** → they are **absolutely ineffective in neuropathic pain**
      - For neuropathic pain, only **atypical** derivates of opioid analgesics can be used
- **→ Acute lung edema**
  - ➢ Intravenously administered morphine provides **relieve of dyspnea** from **pulmonary edema**
    - Most important in this term is the reduction of anxiety and fear
- **→ Reduced pain after Myocardial infarction**
- **→ Premedication before anesthesia**
  - ➢ Opioids are frequently used as premedication drugs before anesthesia
    - Because of their sedative, anxiolytic and analgesic properties
- **→ Cough – Codeine is very useful as a cough suppressant**
  - **Antitussive effect – agonist on μ_2 receptors (Codeine) → antitussive agent**
- **→ (Diarrhea – Loperamide, Diphenoxylate)** Opioid drugs also used as antidiarrheal drug (seen in GIT notes)

Opioid receptor agonists – Effects/side effects

- **After a dose of opioid agonist, the patient feels euphoria (PSYCHIC DEPENDENCE)!**
  - **A feeling or state of intense excitement and happiness (relieve from anxiety and fear)**
    - Euphoria may trigger the desire for repeated administration and lead to addiction
  - **Rare situation – dysphoria (emotional and mental discomfort, restlessness)**
    - ➢ Paradoxically, in some cases, after administration of pure opioid agonists, a condition of dysphoria associated with unpleasant symptoms may occur instead of euphoria
      - A person who experiences these rare effects, probably has **higher number of kappa receptors in the CNS**
- **Sedation – feeling of calmness, removal of tension, drowsiness and weak amnesia!!!**
  - **Combination with hypnotics, sedatives, alcohol**

- **Respiratory depression (OIRD) – Decrease sensitivity of pneumotaxic center to PCO2**
  - → The most dangerous side effect of opioids
  - Morphine-like opioids depress the respiration partially by direct effects – on the respiratory center
    - This is the **primary cause of death from opioid overdose is respiratory failure**
- **Dose dependent (hypnotics, alcohol, sedatives)**
  - → Risk of respiratory depression is further increased by combination with other CNS depressants (BNZ or barbiturates)
- **Opioids cause constriction of the pupils → Miosis**
  - **By acting on the pupillary constrictor + and by excitatory action on the parasympathetic nerve innervating the pupil**
  - Remember → Tolerance does not affect miosis caused by opioids = good diagnostic factor for opioid dependence
- **All clinically used Mu agonists cause some degree of nausea and vomiting**
  - **They cause this by direct stimulation of the chemoreceptor trigger zone in the medulla**
- **CVS**
  - **Bradycardia, hypotension...**
  - Morphine-like opioids produce peripheral vasodilation, reduce the peripheral resistance and cause bradycardia, hypotension
  - These effects are due to release of histamine from mastocytes
- **GIT (Opioid induced constipation)**
  - **Constipation (↓propulsive peristaltic waves in the colon)**
  - Constipation is a very typical effect of opioids
  - Opioid-induced constipation is mostly due to activation of the Mu receptors, which inhibit gastric emptying, reduce the mucosal secretion, increase fluid reabsorption, diminish peristatic waves in colon
  - Opioid-induced constipation is dose-dependent and is more common in long-term treatment
- **Biliary tract**
  - **Biliary spasm – CI: biliary colic**
  - Also, very important information – opioid agonists reduce the biliary and pancreatic secretion
    - Morphine induces spasm of the bile duct muscle
    - The bile duct sphincter contraction increases the pressure of gall bladder, and cause its rupture
  - So, opioid analgesics are ***not suitable for pain relive in biliary colic***
- **Uterus**
  - **Decrease tonus – delivery time prolongation**
- **Skin:**
  - **Release of histamine- redness, itching...**
  - *Opioid agonists release histamine from mastocytes* → pruritus is common
- **Immune System:**
  - **Immunosuppressive, increased susceptibility to infection and tumor spread**
  - Long-term administration of opioids has immunosuppressive effects – increases susceptibility to infections and cancer disease

Opioid agonist – addiction

- **Physical – Psychological**
- **Euphoria – Stimulation of dopamine release in nucleus accumbens**
- **Opioids – reduce inhibitory action of GABA in D mesolimbic pathways "reward system"**

- Opioids induce pleasant feeling of euphoria, due to release of dopamine in nucleus accumbens
- **Tolerance** and **adaptation** of **opioid receptors** is responsible for the development of both physical and psychological dependence
- This effect is due to inhibition of GABA activity in interneurons, which under normal physiological condition have inhibitory effect on the mesolimbic pathway
- Do not forget that when finishing opioid administration, doses should be gradually reduced to avoid withdrawal syndrome
  - Tapering the drug slowly may decrease the unpleasant withdrawal symptoms

Opioid withdrawal syndrome

- Opioid withdrawal syndrome occurs when a patient who has taken opioids for a long time, suddenly decreases the opioid dosage
- Common symptoms of withdrawal include lacrimation, sweating, anxiety, restlessness, muscle and joint ache, tremor, hallucination and other symptoms

Drug	Onset, Hours	Peak	Resolution, Days
Buprenorphine	4–48	96 h	14–21
Fentanyl (intravenous)	2–5	8–12 h	4–5
Heroin	6–12	24–72 h	7–10
Short-acting prescription opioids	6–12	24–72 h	7–10
Long-acting prescription opioids	12–36	2–5 days	10–14
Methadone	24–72	4–6 days	14–21

Side effect	Elimination of side effects of opioids
Nausea and nausea	Antiemetics: → Neuroleptics (prochlorperazine) → H_1 receptor antagonist (I. generation) → 5-HT_3 receptor antagonists – setrons → Scopolamine patch Prokinetics: metoclopramide ROTATION OF OPIOIDS
Pruritus	H_1 receptor antagonists (I. generation)
Constipation	Fiber diet, laxatives, metoclopramide, peripherally acting opioid antagonist (methylnaltrexone)
Sedation	ROTATION OF OPIOIDS, psychostimulants
Hyperalgesia	ROTATION OF OPIOIDS

The most common side effects of opioids:

- **Tolerance**
- **Dependence (physical, psychological)**
- **Abstinence syndrome**
- **Nausea, vomiting**
- **Constipation**
- **Urine retention**
- **Effects of histamine!**
- **Respiratory depression (High doses, combinations!)**

Elimination of side effects of opioids

- The aim of the pain management, especially in long-term sick patients, is to improve their quality of life
- Opioid therapy is associated with numerous side effects
- There are several ways of how to reduce these side effects
  - E.g., by **reducing the dose**, **changing one opioid drug for another** (**rotation**) or **change the way of administration**
- You can manage the nausea and vomiting with **antiemetics**
- You can treat **pruritus** by using **antagonist of H1 receptor**
- You can manage the **constipation** by laxatives
  - → Methylnaltrexone decreases opioid-induced constipation
  - It is a peripherally acting (doesn't cross BBB) Mu receptors antagonist
- Rotation of opioids
  - = The process of changing one opioid drug for another in order to improve pain control and reduce side effects
  - Changing one preparation to another opioid with the current dose reduction may achieve recovery of analgesic effect
  - Because individual opioids have different internal affinity for different opioid receptor subtypes, or different pharmacokinetics
- Hyperalgesia is the condition in which you experience an enhanced sensitivity to pain

Opioids:

§ Morphine

- **The "Gold standard" opioid agonist**
- **Used for estimation of equivalent dose of other opioids**
  - For example, during opioid switching (rotation)
- **Recommended for the treatment of strong/severe pain**
- It exists in many application forms:
  - Perorally as sustained releasing tablet
  - Also i.v., s.c., rectal
  - Intramuscular administration is **not** recommended → it is painful

Codeine

- **P.o.**
- **It has mild analgesic effect**
- **CYP2D6 metabolism (to morphine)**
- Do not forget the genetic polymorphism of cytochrome P40 that lead to the inability to convert codeine to morphine
  - And thus, making codeine ineffective
  - Or the opposite, other polymorphism can lead to enhanced metabolism
    - And thus, increase sensitivity to codeine effect
- **Analgesic combinations with paracetamol → "codamol"**

§ Oxycodone

- **P.o. slow-releasing forms (12 h)**
- **Oxycodone + paracetamol, ibuprofen**
- **Oxycodone + naloxone**

§ Methadone

- Methadone has historically been used in the **substitution therapy of opioid addiction**
  - Methadone is **lipophilic** and is accumulated in the body
    - → Which is why it **doesn't have as pronounced withdrawal syndromes as morphine**
  - In some countries, it is also used for the **treatment of resistant pain**
- The mechanism of action is:
  - It **inhibits serotonin reuptake** and **inhibition of NMDA receptors**
    - Which explains why it's **effective for neuropathic pain**

Short acing opioid – Analgesic

- **Sufentanil, Fentanyl**
- Opioids with short half-life and rapid onset of action predetermine these analgesics to treat acute pain
- They are used in anesthesiology
- The action of fentanyl and its congeners, sufentanil, alfentanil, are similar to other Mu receptor agonists
  - But they are destroyed in plasma by esterases (= they are short-acting)
- Fentanyl is approx. 100x more potent than morphine
  - And sufentanil is approx. 1000x more potent than morphine

Fentanyl

- **Fast onset of action (to 3 min), short effect (30 min)**
- **~~? Peroral~~ (↑ first-pass effects, low biological availability - 65%)**
- After peroral administration, fentanyl is destroyed in the liver – fentanyl has very low bioavailability
  - Which is why we prefer these alternative ways of administration
- **Administration:**
  - **Buccal, sublingual, intranasal (acute pain, breakthrough pain)**
  - Fentanyl formulations that permit rapid absorption of fentanyl through sublingual way, buccal mucosa
    - Fentanyl also exists as a, buccal film, buccal tablets, nasal spray for the **management of acute or breakthrough pain**
  - **Transdermal, epidural, i.v. (chronic pain)**
  - Fentanyl also exists in the form of **transdermal patches**
    - They provide **sustained release** of fentanyl for 48 hours or more
    - They are very good for the management of **chronic pain**

Sufentanil

- **↑ Lipophilic (7-10x more potent as fentanyl) → quick passage into CNS**
- Sufentanil is a very strong analgesic (1000x stronger than morphine)
- **Clinical use**
  - **Analgesia in anesthesiology**
  - **Treatment of breakthrough pain**
- **ZALVISO tbl. slg.**

- The intravenous form of sufentanil is used to promote analgesia, or as separate anesthetic
- It is suitable for longer and more painful performances, where potent analgesia is required to maintain cardiovascular stability of the patient
- Sufentanil is suitable for epidural administration during spinal anesthesia
  - An indication of epidural administration is suppressing post-operative pain after surgery, after caesarian section
- It can be used as additional analgesic to epidural administered local anesthetic bupivacaine during childbirth
- There also exists a new way of administration – sublingual tablets
  - For breakthrough pain
- Sufentanil has a very wide clinical use

3. Atypical opioid analgesics (9)

Intro – topic 1

Tramadol (↑ serotonin), Tapentadol (↑ serotonin + ↑ catecholamines)

❖ Atypical opioid agonists differ from the conventional opioids in that they have **serotoninergic** and **anti-adrenergic activity**

- **The Benefits of atypical opioids:**
  - **Lower occurrence of "opioid" side effects**
  - **Low dependence**
  - **Low tolerance**
  - **And very mild withdrawal syndrome**

Tramadol

- Tramadol is a **synthetic analog** with **weak Mu opioid receptor agonistic effect**
  - **= Agonist of opioid receptors**
- But tramadol also inhibits serotonin re-uptake → it has serotoninergic effect
  - **+ inhibits 5-HT reuptake = ↑ serotonin in synaptic cleft**
- Tramadol also influences other neurotransmitters
  - + mild antagonist on muscarinic and nicotinic receptors
  - And antagonistic effect on NDMA receptors
- But its **dominant effect is the serotoninergic activity**
- **Clinical use:**
  - Tramadol is recommended in the *treatment of mild-to-moderate pain*
  - **Acute, chronic pain**
  - Excellent analgesic effect is reached after the combination of tramadol with paracetamol
    - **+ Paracetamol** → It exists in fixed combination
- **Be careful when combining SSRIs and tramadol:**
  - ➢ **Combination with SSRI and other serotonin agonists → Serotonin syndrome**
  - – Because Tramadol has inhibitory effect on serotonin reuptake, tramadol should not be used in patients taking serotonin reuptake inhibitors → due to risk of serotonin syndrome

Tapentadol

- Tapentadol is similar to tramadol → **Agonist of Mu (μ) opioid receptors**
- But tapentadol has dual mechanism of action:
  - It has **serotoninergic** effect → **inhibits the reuptake of serotonin** = ↑ serotonin in synaptic cleft
  - But is **also inhibits the reuptake of catecholamines**
- **Clinical use:**
  - **Treatment of moderate to severe pain (acute following injury, surgery, etc.)**
    - Tapentadol is very useful for the management for *moderate-to-severe pain*
      - After surgery, after some injury, for **chronic musculoskeletal pain**
    - **Chronic musculoskeletal pain**
  - **Diabetic neuropathic pain**
    - Also, tapentadol is very effective in the management of neuropathic pain
      - **Tapentadol** = the *only type of opioid agonist that can be used for the suppression of neuropathic pain!*
- **!!! Combination with SSRI and MAO-I – serotonin syndrome or activation of sympaticus**
  - Combination with antidepressants (SSRI and MAO-I) can result in serotonin syndrome or adrenergic storm
    - Because of tapentadol's inhibition of reuptake of serotonin and catecholamines

4. Opioid analgesic: Agonists-antagonists (27)

Intro – topic 1

Mixed agonists-antagonists

- **Pentazocine**
  - **Agonist → kappa, antagonist → mu**
- **Buprenorphine**
  - **Agonists → mu, antagonist → kappa**

❖ Mixed agonists-antagonists are distinguished by their pharmacodynamic action on individual subtypes of opioid receptors
  ➢ For example, **pentazocine** acts as an **agonist on kappa** receptors and **an antagonist of Mu receptor**
  ➢ Or **vice versa for buprenorphine** (+Mu, -Kappa)

❖ The goal of the development of these drugs was to prepare substances with **lower opioid adverse effects**
  ➢ **Respiratory depression occurs less frequently after substances with agonist-antagonist effect**

❖ However, therapeutic doses of these substances have other complications and other benefits

Pentazocine

- **Kappa agonist (+ κ), Mu antagonist (- μ)**

Positives:

- **Good analgesic effect**
  - Kappa receptor → *spinal analgesia*
- **Decreased risk of dependence and respiratory depression**
  - Kappa receptors do not suppress respiratory center!!
  - Also, do not cause euphoria!!
  - Constipation is very mild compared to morphine

	μ	δ	K
Analgesia - Supraspinal - Spinal	 +++ ++	 - ++	 - ++
Respiratory depression	+++	++	-
Pupil constriction (miosis)	++	-	+
Reduced GI motility	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	+	-	+++
Physical dependence	+++	-	+

Negatives:

- **Higher doses – *sedative, dysphoric, psychomimetic (hallucination) effects***
  - Because it is kappa agonist
- **Ceiling effect (recommended dose 60 mg)**
  - Increased the dose does not increase analgesic effect, only increases side effects!!
- **!!! COMBINATION WITH PURE AGONIST – WITHDRAWAL SYNDROME**
  - When pentazocine (kappa agonist and Mu antagonist) is used in a patient already being treated with Mu receptor agonists (such as morphine) → it causes severe withdrawal syndrome
  - It is absolutely prohibited to combine pentazocine with pure agonists → Because you will induce withdrawal syndrome
- **Clinical use:**
  - Although the use of pentazocine in clinical practice is limited, it *may be suitable for reducing acute pain in parenteral form in some severe risk patients which are contraindicated for pure agonists*

Buprenorphine

- **Mu agonist (+ μ), kappa antagonist (- κ)**
- In contrast to pentazocine, buprenorphine is commonly used as opioid analgesic
- It is a semi-synthetic derivative → very high lipophilicity
- **Administration: sublingual, transdermal**
- **Clinical use:**
  - **Pain therapy (acute, chronic pain)**
  - **+ naloxone (SUBOXONE sublingual tbl.)**
    - **Substitution therapy for the treatment of opioid dependence (mild euphoria, withdrawal syndrome)**
    - **Buprenorphine causes very mild withdrawal syndrome!**

5. Symptoms and therapy of opioid analgesics poisoning (47)

Opioid intoxication

- **Symptoms:**
  - **Miosis**, **hypoventilation**, **coma**
- We have antidote for opioids:
  - Antagonists of opioid receptors → **Naloxone** i.m., i.v.
    - Duration of effect 2-4 hours – repeat dose

Naloxone inj., tbl., nasal spray

- **Naloxone is a competitive opioid receptor antagonist**
- **Single dose 0,2-2 mg i.v. ... every 2-3 min… maximal dose 10 mg – effect 1-3 hours**
  - You have to remember:
    - The dose of naloxone is titrated, we will start with low doses (approx. 0,2 mg) and then dose is gradually increased to 2 mg with repeated administration, maximal dose is 10 mg
- **Clinical use: Therapy (diagnosis) of intoxication with opioid analgesics**
  - Naloxone is commonly used to diagnose and manage respiratory depression related to opioid overdose
    - Or naloxone can be additionally used in a combination with opioid treatment to reduce the opioid related side effects
      - In low doses, naloxone is added to opioid analgesic trade products to reduce the side effects
- **Naloxone p.o., sbl. – reduction of opioid side effect**

❖ Naloxone should be administered with caution to patients who have received high doses of opioids or are physically dependent on opioids
  ➢ Because too high dose of naloxone abruptly discontinuities the effect of opioid agonists
    - So, it may cause acute withdrawal syndrome

The most common side effects of opioids:

- **Tolerance**
- **Dependence (physical, psychological)**
- **Abstinence syndrome**
- **Nausea, vomiting**
- **Constipation**
- **Urine retention**
- **Effects of histamine! → pruritus**
- **Respiratory depression (High doses, combinations!)**

Side effect	Elimination of side effects of opioids
Nausea and nausea	Antiemetics: → Neuroleptics (prochlorperazine) → H_1 receptor antagonist (I. generation) → 5-HT_3 receptor antagonists – setrons → Scopolamine patch Prokinetics: metoclopramide ROTATION OF OPIOIDS
Pruritus	H_1 receptor antagonists (I. generation)
Constipation	Fiber diet, laxatives, metoclopramide, peripherally acting opioid antagonist (methylnaltrexone)
Sedation	ROTATION OF OPIOIDS, psychostimulants
Hyperalgesia	ROTATION OF OPIOIDS

Elimination of side effects of opioids

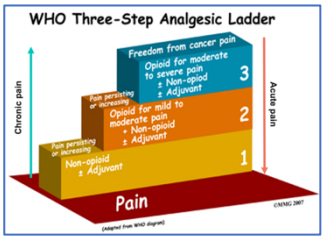
❖ There are several ways of how to reduce these side effects
  ➢ E.g., by **reducing the dose**, **changing one opioid drug for another** (**rotation**) or **change the way of administration**
❖ You can manage the nausea and vomiting with **antiemetics**
❖ You can treat **pruritus** by using **antagonist of H1 receptor**
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  ➢ Changing one preparation to another opioid with the current dose reduction may achieve recovery of analgesic effect
  ➢ Because individual opioids have different internal affinity for different opioid receptor subtypes, or different pharmacokinetics
❖ Hyperalgesia is the condition in which you experience an enhanced sensitivity to pain

NSAIDs – intro

WHO 3-step analgesic ladder:

1. **Non-opioids ± adjuvant (mild pain)**
2. **Opioids (mild to moderate pain)**
   ± Non-opioid
   ± Adjuvant
3. **Opioids (moderate to severe pain)**
   ± Non-opioid
   ± Adjuvant

- For chronic pain: (pain lasting for more than 3 months)
  - Start from step 1 and work your way up to step 3 according to severity
- For acute pain:
  - Start from step 3 and work your way down to step 1 as pain gets less severe



Categorization of non-opioid analgesics

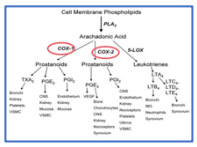
- **NSAID**
  - **Analgesics** + **Antipyretic** + **Significant anti-inflammatory effect**
  - NSAIDs inhibit the production of prostaglandins
    - Prostaglandins are important mediators of pain and inflammation
  - NSAIDs reach very good anti-inflammatory effect
- **Paracetamol**
  - **Analgesic** + **Antipyretic effect**
  - Paracetamol is not a member of the NSAIDs
  - Clinically used doses do not have anti-inflammatory effect
  - Their only therapeutic role is analgesia and antipyretic effect
- **Metamizol and other**
  - **Analgesic effect**
  - The other members are substances with dominant analgesic activity
    - Metamizole, propiconazole

NSAIDs:

- NSAID inhibit cyclooxygenases (COX-1 and COX-2), thereby reducing the production of prostaglandin, an important mediator of pain and inflammation
- NSAIDs possess very significant **antipyretic**, **analgesic** and **anti-inflammatory effects**

Metabolism of arachidonic acid

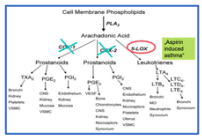
- Arachidonic acid is a fatty acid present in phospholipids of membranes of the cells
  - Arachidonic acid is metabolized to both pro-inflammatory and anti-inflammatory prostaglandins, thromboxane by the enzyme ***cyclooxygenase*** (***COX***)
  - And leukotriens by the enzyme ***lipoxygenase*** (***LOX***)
- The ***cyclooxygenase*** enzyme exists in 2 isoforms – COX 1 and COX 2
  - COX 1 and COX 2 have many very important roles in creating prostaglandins
    - The same prostaglandin may have a different (an even opposite) effect in different tissues
    - Prostaglandins play very important roles in regulation of both physiological and pathological processes (especially inflammation)
- The second pathway of arachidonic acid metabolism is by ***lipoxygenase***
- Long-term inhibition of cyclooxygenases by NSAIDs shift the metabolism of arachidonic acid to lipoxygenase pathway
  - Resulting in pro-inflammatory leukotriens being synthetized
  - They play a role in the pathomechanism of allergy and asthmatic complications
  - So, long-term administration of NSAIDs induce so-called "aspirin-induced asthma" or some other allergic complications



COX-1 Constitutive ↔ COX-2 inducible

- Prostaglandins are produced by oxygenation of arachidonic acid by cyclooxygenases (COX 1 and COX 2) to terminal prostaglandins

COX1:



- Is known as "**physiological**"
- It is responsible for the baseline levels of physiological functions of prostaglandins
- COX1 is expressed in most cells
- It controls **gastric function**, **perfusion of the kidneys**, **activity of thrombocytes**, **cardiovascular system**, **activity of endothelium**
- So, logically, inhibitors of COX 1 have wider pharmacodynamic activity in comparison with substances that block COX 2

COX 2:

- It is an **inducible enzyme** increased by tissue injury and other stimuli, such as bacterial lipopolysaccharides, inflammatory cytokines, interleukin 1, tumor necrosis factor α
- It is activated at injury sites
- Inhibition of COX 2 causes very good, very significant anti-inflammatory effect
  - Because an increase in COX 2 levels occurs in inflammatory processes, triggering increased synthesis of inflammatory prostaglandins

Categorization of NSAIDs: (they differ in the manner by which they interact with the COX enzyme)

- **COX non-selective**
  - Inhibits both COX 1 and COX 2
- **Preferential COX-2**
  - They have increased activity on COX 2 (increased anti-inflammatory effect)
  - But they are not completely selective (they are somewhere in the middle between non-selective and selective COX 2)
- **Selective COX-2**
  - COX 2 is the inflammatory isoform – so these substances have strong anti-inflammatory effect



NSAIDs – clinical use

- **Mild-moderate pain!**
  - **Acute and chronic pain** (particularly **musculoskeletal**, **inflammatory pain**)
  - **Postoperative pain**
  - **Headache**, **migraine** (pain of vascular origin)
  - (Pain arising from viscera = *not* well relieved by NSAIDs)
- **Anti-inflammatory** → primarily of musculoskeletal disorders
- **Rheumatoid arthritis**
- **Inflammatory arthritis**
  - ➢ We have to emphasize, NASIDs only provide symptomatic relieve form the pain and inflammation associated with these rheumatoid diseases → NSAIDs don't reduce the progress of pathological injuries of tissues
- **Dysmenorrhea**
  - Pain arising from the viscera is usually not relieved by NSAIDs – an exception to this is menstrual pain
  - Release of prostaglandins by endometrium during menstruation controls the endometrial shedding and contraction of uterus
    - Prostaglandins may cause severe cramps and other symptoms of primary dysmenorrhea
  - NSAIDs have very good effects in the treatment of dysmenorrhea
- **Fever** (**ASA**, **ibuprofen**)
- **Prophylaxis in thromboembolic diseases** e.g., **transient ischemic attack**, **unstable angina**, & **MI** (30-100 mg/day) **only ASA**
- **Kawasaki disease** (**ASA**) (Kawasaki disease is a disease in which blood vessels throughout the body become inflamed)
  - Kawasaki disease a specific indication for NSAIDs – especially ASA is used
- **Acute gout attack** (especially **indomethacin**)

Contraindications/Caution

- **Gastroduodenal ulcers** (all)
- **Renal diseases** (all)
- **Pregnancy** (all)
- **Bronchial asthma**, **allergy** (all)
- **Recent myocardial infarction**, **unstable angina**, **heart failure** (all, not ASA)
  - ASA is used as a prevention of some complications of these diseases
- **Children up to 12y** (only ASA) → Reye's disease
- **Acute hemorrhage** (all, especially ASA!)

NSAID drug interaction

- **ACE-I:**

❖ The function of ACE inhibitors is mediated by preventing the breakdown of bradykinin that stimulate the prostaglandin production
  - ➢ Thus, logically, NSAIDs may decrease the effectiveness of ACE-I, by blocking the production of vasodilatory prostaglandins
    - **Concurrent use results in a blunted antihypertensive effect**

- **Anticoagulants:**
  - NSIADs may ***increase the frequency or severity of bleeding***
- **Bisphosphonates, Corticosteroids:**
  - Concomitant use ***increases the risk gastric ulcer formation***
- **Do not combine 2 NSAID each other**
  - NSAIDs have "***ceiling effect***" – you will not increase the analgesic activity, only the occurrence of side effects

NSAID and pregnancy

- **NSAIDs should not be given during pregnancy**
- **NSAIDs cross the placenta**
- NSAIDs may cause embryo-fetal and neonatal adverse effects
- **Use in early pregnancy:**
  - Increases the risks of miscarriage and malformations
- **After 30 weeks:**
  - Increases the risk of premature closure of the fetal ductus arteriosus
- **Before delivery:**
  - Several hours before parturition, there is induction of myometrial COX 2 expression, which produces prostaglandin E2 and F2α – which markedly increase the contraction of myometrium
  - Thus, inhibition of these prostaglandins reduces the uterine contractility (prolongation of delivery)
- Also, the use of NSAIDs late in pregnancy may increase the risk of postpartum bleeding
- *You can see from all that that risk > benefits = NSAIDs are contraindicated in pregnancy*
- Fetal and neonatal adverse effects affecting the brain, kidney, lung, skeleton, gastrointestinal tract and cardiovascular
- Should be given in pregnancy only if the maternal benefits outweigh the potential fetal risks, at the lowest effective dose and for the shortest duration possible

6. Non-selective NSAiD (37)

- The prototype of non-selective COX inhibitors is acetylsalicylic acid (aspirin)
- According to mechanism of action, non-selective COX inhibitors are either reversible or irreversible
  - The only irreversible is aspirin – others are reversible inhibitors of COX

- **Irreversible inhibitor – ASA**
- **Reversible inhibitors – other derivates**

a) Analgesic effects of NSAID

- **Inhibition COX1, COX2**
  - **↓ prostaglandin synthesis** (+ other mediators)
    - Inhibition of eicosanoids, prostaglandins, thromboxane – represent an important aspect of the analgesic action
  - **↓ Activity of nociceptors**
  - **+ Multiple other mechanism**
- **NSAIDs are drug of choice in the treatment of acute or chronic conditions where pain, especially pain associated with inflammation are present**

b) Anti-inflammatory effect of NSAID

- **COX-2 inhibition**
  - **↓ inflammatory mediators (PG)**
- **O_2^- radicals production inhibition**
- **Inhibit the inflammatory-nitric oxide synthase (i-NOS) production**
- **Inhibition of lysosomal activity (PMNL)**
- **Synthesis of cytokines is inhibited**

- NSAIDs have their chief clinical application as anti-inflammatory agents in the treatment of musculoskeletal disorders
  - Such as rheumatoid arthritis, osteoarthritis
  - And other inflammatory conditions such as headache, migraine

c) Antipyretic effect of NSAID

- **Inhibition of COX-1 (COX-2)**
- **↓ thermoregulatory neurons activity in hypothalamus (↓ synthesis of PGE2 and IL-1)**

- The hypothalamus regulates the setpoint at which body temperature is maintained
  - This setpoint is elevated in fever
  - NSIADs promote its return to the normal setpoint
- **ASA** and **ibuprofen** are recommended to suppress fever response by inhibiting prostaglandin production or IL-1 synthesis
  - They are the drugs of choice for antipyretic effect

d) Antithrombotic effect of NSAID

- Acetylsalicylic acid (ASA)

- Small dose (30-100 mg /day) irreversibly inhibits thromboxane A2 synthesis in the platelets without affecting prostacyclin synthesis in the vascular endothelium.
- ASA (other NSAID) must be stopped one 3 days prior to surgery if potential bleeding complications are a concern.

- CVS lecture!
- Except for ASA, other non-selective NSAIDs have minimal anti-thrombotic function
  - From NSAIDs, only ASA is used therapeutically for anti-thrombotic functions

a) Acetylsalicylic acid (ASA, Aspirin)

- Irreversibly inhibits COX-1 + COX-2
- Blocks the synthesis of prostaglandins and thromboxane A2

❖ ASA is the **oldest derivate of NSAIDs** and it's the **prototype of non-selective NSAIDs**
❖ ASA has the unique property of acetylating COX 2 – which is not seen in other NSAIDs
  ➢ But of course, ASA blocks both COX 1 and COX 2

❖ Despite the introduction of many new NSAIDs, aspirin is still widely used analgesic, anti-pyretic and anti-inflammatory agent
❖ It is an over-the-counter drug

- **Prototype of NSAIDs**
- **Combinations**: (ANOPYRIN, ASPIRIN, ECOTRIN, GENPRIM, ACYLCOFFIN, ASPRO, ASAPHEN...)
  - **+ Caffeine**
    - Caffeine increases only the analgesic effect; caffeine increases the CNS activity if ASA and it's used in trade products recommended for the management of pain – we will not reduce fever with trade products containing caffeine
  - **+ (vasoconstrictor) phenylephrine**
    - In other trade products, ASA can be combined with vasoconstrictors – for example phenylephrine
    - These vasoconstrictors reduce mucus membrane edema
    - They are recommended in common cough associated with rhinitis
  - **+ Vitamin C**
    - This combination has no rational justification – only increases the price of the trade product

ASA – Pharmacokinetics

ASA = WEAK ACID

- **It is well absorbed from the stomach, better from the upper small intestine (pH!)**
  - Alkalization of the stomach reduces the absorption (because acids in alkalization = more polar = not well absorbed)
- **It is rapidly metabolized to acetic acid and salicylates**
  - Salicylate = active metabolite
  - Acetylsalicylic acid = a prodrug which is transformed into its active metabolite, salicylate, in the stomach and in the intestinal mucus membrane
- **90 % bound to plasma protein (albumin)**
  - = Interactions
- **Salicylates is conjugated with glucuronic acid and glycine**
- **Excreted by the kidney**
- **Alkalinization of the urine increases the rate of salicylates excretion**
  - **Very important** – this approach is used for the treatment of intoxication with ASA
  - Because ASA is a weak acid, it is ionized when exposed to basic environment (such as alkaline urine)
    - Ions are poorly reabsorbed from urine and are excreted more readily
    - Urine alkalization is the treatment regime that increases ASA elimination
    - We can alkalize urine by administering i.v. sodium bicarbonate – to increase the pH in urine to higher or equal to 7,5
  - This is called "ion trapping" it also works well for overdosing of other weak acids – such as phenobarbital and other barbiturates

ASA differences compared with other NSAIDs:

- Irreversible COX-inhibitor
  - The others are reversible
- It has long-term antithrombotic effect
- Reye´s syndrome
  - ! children up 12 years – recovering from viral diseases
  - A problem of ASA is the Reye's syndrome
  - Reye's syndrome is a rare but serious condition that causes swelling in the liver and brain
  - It most often affects children with viral infections – most commonly the flu and chicken pox
  - Symptoms can be confusion, seizures, loss of consciousness
  - It requires emergency treatment – early diagnosis and treatment of Reye's syndrome can save the child's life
  - **So, we should be cautious when giving aspirin to children with viral diseases**

Other non-selective NSAIDs – <u>reversible</u> inhibitors of COX

- Except for ASA, all the other non-selective NSAIDs are reversible inhibitors of COX
  - These are also weak acids
- We can divide them according to their half-life:
- **Short acting**: Half-life 2-6 hours (3-4x daily)
  - **Ibuprofen**
  - **Flurbiprofen**, **diclofenac**, **indomethacin**
- **Intermediate:** Half-life 10-14 hours (2x daily)
  - **Naproxen**
- **Long acting:** Half-life 24-70 hours (1x daily)
  - **Oxicams**
- **↓ antithrombotic, antipyretic**
- **Strong anti-inflammatory effect**
- **Used for anti-inflammatory effect for the treatment of rheumatoid disease**

❖ The NSAIDs derivates in the blue frame have higher anti-inflammatory action – higher activity on COX 2

- ➢ Therefore, they are not used to decrease fever or as anti-thrombotics
- ➢ They are **only used to inhibit pain and inflammation in rheumatoid complications** – muscle aches and other musculoskeletal inflammatory conditions

- Ibuprofen

- **"Modern aspirin" (pediatric use!)**
  - **Does not cause the Reye's syndrome!**
- **Comparison with other NSAIDs:**
  - Fewer side effects, such as gastrointestinal bleeding
  - At low doses, without antithrombotic activity
  - Ibuprofen might be a weaker anti-inflammatory than other NSAIDs (except for ASA)
  - Specific clinical application of ibuprofen:
    - **Used to close a patent ductus arteriosus in a premature baby**
      - Patent ductus arteriosus is a persistent opening between the pulmonary artery and the aorta
      - Ibuprofen is used to *close ductus arteriosus in premature babies*

- Indomethacin tbl., supp.

- Very frequently used NSAID
- Very strong analgesic effect and anti-inflammatory properties
- **Strong COX inhibition**, **10-40x higher analgesic effects as ASA**
  - But logically, we have to take into account the occurrence of side effects!
- Indomethacin is used for *postoperative pain*
- Also used for *closure of ductus arteriosus*

Risk for developing ulcers: indomethacin > diclofenac > ASA > ibuprofen

- Diclofenac p.o.

- Another very frequently used NSAID
- It has analgesic and anti-inflammatory effect
  - Its potency against COX 2 is greater than several other NSAIDs
- Diclofenac reduces intracellular concentration of free arachidonic acid in leukocytes
  - This activity improves the anti-inflammatory effect
- Local apl. forms: VERAL gel, **VOLTAREN** gel, transdermal patch, dental, eye solutions...
- ARTHTOTEC (+ misoprostol)
  - Diclofenac is also available in combination with misoprostol
  - Misoprostol is a synthetic prostaglandin E1 – it is a gastroprotective substance
  - This combination is recommended for risk patients with gastrointestinal ulcers or erosions – for gastroprotection

Oxicams

- Long acting

- The main advantage for oxicams is their long half-life
  - It permits 1x day dosing
- **Piroxicam**

Prevention of gastric side effects

- NSAID + gastroprotection:
- **Effervescent tablets**
  - For mild discomfort, effervescent tablets can be used
  - They contain small amounts of bicarbonate (so, they also reduce the absorption)
- **Misoprostol – CYTOTEC**
  - NSAIDs also exist in fixed combination of coadministration of misoprostol
  - = the best solution for patients at risk
- **PPI? (reduce absorption)**
  - Or they can be combined with PPIs → but they increase the pH of stomach = decrease the absorption of NSAIDs
- **"Pro-drug" systems**
- **Rheumatoid diseases – Preferential COX inhibitors for risk patients**

Side effects of non-selective COX inhibitors:

→ GIT side effects of NSAID

- Gastric damage is a typical side effect of NSAIDs
- It is related to the **Gastrointestinal COX 1 inhibition**
  - COX 1 controls the production of prostaglandins in epithelial cells
    - Cytoprotective prostaglandins – especially prostaglandins A2 and E2
      - These eicosanoids inhibit acid secretion by the stomach and enhance mucosal blood flow in the stomach and promote the secretion of cytoprotective mucus bicarbonate in the intestines
    - Logically, inhibition of these protective prostaglandins will have a negative impact of the gastrointestinal mucosal membrane
- The most symptoms associated with gastrointestinal toxicity of NSAIDs include:
  - Gastric discomfort, dyspepsia, gastric bleeding, gastric ulcer…
- Don't forget that NSAIDs should be used with caution in individuals with inflammatory bowel disease, Chron's disease, ulcerative colitis
- **Risk for developing ulcers**: **indomethacin > diclofenac > ASA > ibuprofen**
- Risk increases with duration, type and dose of treatment
- The risk of an ulcer is 10–15 times higher if NSAIDS and glucocorticoids are administered simultaneously!
  - Helicobacter pylori infection and heavy alcohol consumption also increase the risk of ulcers

→ Renal function impairment

- Prostaglandins control the perfusion of the kidneys
- So, another side effect of NSAIDs is **hypoperfusion of the kidneys** and **they reduce GFR**
- **Electrolyte and fluid abnormalities** (edema, hyperkalemia, hyponatremia)
- **Worsening of hypertension**
- In very rare cases, acute renal failure known as **Analgesic nephropathy**:
  - It is the result of prolonged NSAID use
  - And it results in tubulointerstitial nephritis and papillary necrosis (↑ creatinine/BUN ratio, slight ↑ K+)

→ Pseudo-allergic reaction

- Inhibition of prostaglandin with subsequent overproduction of proinflammatory leukotrienes:

- A shift in leukotriene metabolism (COX → LOX) increases the risk of hypersensitive reactions
  - Certain individuals display hypersensitivity after NSAIDs administration
- Symptoms include:
  - Urticaria and angioedema
  - Bronchial asthma
  - **Aspirin-exacerbated respiratory disease** (AERD)
- These symptoms occur in approx. 20% of patients which asthma or some other allergic conditions
  - But they only occur in 1% of healthy individuals
- **Treatment of NSAID hypersensitivity is similar to that of other severe hypersensitivity reactions!**
  - Support of vital organ function, administration of epinephrine
  - Aspirin-induced asthma can be managed with inhibition of leukotriens
    - We can use zileuton as inhibitor of LOX, or we can use leukotriene receptor antagonists

Other side effects

- **Salicylism:**
  - Large doses of NSIADs for long time therapy can cause CNS symptoms – called salicylism
  - It starts with a strong Headache, tinnitus, hearing difficulty, blurring of vision (= these are good typical factors of NSAID intoxication – if they are present, it is necessary to stop the therapy and control the risk of intoxication)
    - Other symptoms are GIT upset, irritability & hyperventilation
- **Hypoprothrombinemia** and bleeding tendency
  - Very rare – occurs especially in the case of ASA
  - As ASA competes with vitamin K, → so decreasing prothrombin synthesis
  - Only high doses! (Rare – especially ASA)
- **ASA – Reye's syndrome:**
  - In children with viral infection ASA may cause liver injury and encephalopathy (CI children till age of 12 y)

7. Preferential and selective NSAiD (64)

Categorization of NSAIDs: (they differ in the manner by which they interact with the COX enzyme)

- **COX non-selective**
  - Inhibits both COX 1 and COX 2
- **Preferential COX-2**
  - They have increased activity on COX 2 (increased anti-inflammatory effect)
  - But they are not completely selective (they are somewhere in the middle between non-selective and selective COX 2)
- **Selective COX-2**
  - COX 2 is the inflammatory isoform – so these substances have strong anti-inflammatory effect

Preferential COX-2 inhibitors

- **Nabumetone**
- **Nimesulide**
- **Meloxicam**

- Preferential COX-2 inhibitors are the **most commonly prescribed NSAIDs for rheumatoid inflammatory conditions** (rheumatoid arthritis, osteoarthritis, musculoskeletal syndrome, lower back pain and other musculoskeletal inflammatory complications
- Preferential COX-2 inhibitors have a very good balance between anti-inflammatory effect and occurrence of side effects
- **Benefit:**
  - **↑ anti-inflammatory, ↓ SE (GIT...)**
    - They are substances with increased anti-inflammatory effect and reduced negative effects of GIT
- **Indications:**
  - Treatment of inflammatory diseases – rheumatoid arthritis, osteoarthritis, musculoskeletal syndrome (low back pain) ...

Selective COX-2 inhibitors

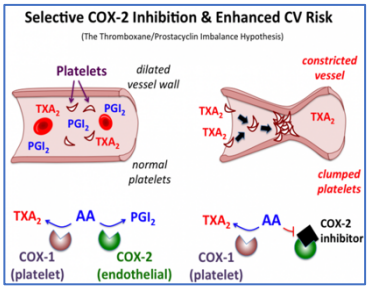
- COXIBS (celecoxib, etoricoxib)

- Selective COX-2 inhibitors are known as "coxibs" – due to their suffix (celecoxib, etoricoxib)
- They reduce the activity of COX 2
  - COX 2 produces the inflammatory type of prostaglandins
  - These prostaglandins play an important role in regulation of inflammation during some rheumatoid compilations, together with TNα, IL-1, IL-6, IL-8 and other cytokines
- Inhibition of the activity of prostaglandins by COX 2 inhibitors reach very good anti-inflammatory effect

Selective COX 2 inhibitors

Indication and doses			
Substance	Osteoarthritis	Rheumatoid arthritis	Postoperative pain
Etoricoxib	30-60 mg/day (**no more than 7 days**)	90 mg/day (**no more than 7 days**)	90 mg/day (**no more than 3 days**)
Celecoxib	200 mg mg/day (**no more than 7 days**)	200 mg mg/day (**no more than 7 days**)	
lumiracoxib	Stopped registration – hepatic toxicity		
Valdecoxib	Stopped registration – CVS toxicity		
Rofecoxib			
Parecoxib			

- Despite the good anti-inflammatory effect of COX 2 inhibitors, they have some problems
- Several COX 2 inhibitors have been introduced into clinical use
  - However, the registration of these active substances has been stopped due to occurrence of adverse reactions
  - COX 2 inhibitors cause a significant increase of heart attacks, strokes and have hepatic toxicity
    - Lumiracoxib, valdecoxib, Rofecoxib and parecoxib where removed from the marked because of these concerns
- Only celecoxib and etoricoxib have limited use in clinical practice
  - They can only be administered in the case of severe osteoarthritis or rheumatoid arthritis which don't respond to other medication
  - They can be administered for no more than 7 days for osteoarthritis and rheumatoid arthritis
    - And no more than 3 days for post-operative pain
  - → Because the risk of complications is very serious



COX-2

What is the problem with the selective COX 2 inhibitors?

- There is a significant increase in cardiovascular risk
  - So many pharmaceutical companies have withdrawn some COX 2 inhibitors from the market
- Because new data shows that COX 2 is an inducible inflammatory isoform of the COX enzyme
  - However, it plays an important role in the regulation of many physiological processes:

- Regulation:

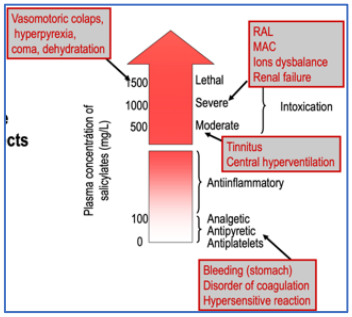
- **Inflammation**
- **Ovulation**
- **Mental functions**
- **Kidney, liver**
- **CVS** (especially endothelial activity)
- **Tumor angiogenesis**

- So, inhibition of COX 2 in the endothelium and in thrombocytes increases the pool of arachidonic acid
  - And logically, this arachidonic acid has to be metabolized – and thus, it is metabolized by alternative ways:
    - By thromboxane synthase into thromboxane A2
      - Which increases the activity of thrombocytes – stimulates the activity of endothelial smooth muscle!!!

Selective COX-2 inhibitors

- **Effect**
  - COX 2 inhibitors have very good analgesic and anti-inflammatory
- **Advantages in comparison to nonselective NSAIDs**
  - Minimal gastrointestinal side effects (= good)
- **Side effects**
  - *Increased risk of heart attack and stroke*
  - *Renal side effects in at-risk patients*
  - *Deterioration of chronic renal failure*
  - *Worsening of hypertension*

- **Contraindications:**
  - **Chronic heart failure** (especially the more serious sates: NYHA II-IV)
  - **Recent myocardial infarction**
  - **Serious hypertension**, **angina pectoris**
  - **Cerebrovascular** and **peripheral vascular disease**

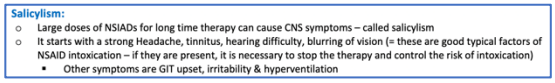


8. Symptoms and therapy of NSAiD poisoning (63)

NSAID poisoning

- Poisoning of NSAIDs is very frequent
  - NSIADs are over the counter drugs, → home medications and are very frequently used
- **Aspirin – dose dependent effects**
  - The effects of aspirin are dose dependent
  - Very low levels of aspirin (30-100 mg/day) are used for *anti-platelet indications*
  - Higher doses (1 g) are used for *analgesic or antipyretic indications*
  - Higher doses are used for anti-inflammatory indications
  - And doses above that can cause the typical features of ASA intoxication

Symptoms:



- The symptoms start with:
  - *Restlessness*, *tremors*, *convulsion*, *vomiting*, *dehydration*
- And the continue with **salicylism** (= CNS effects)
  - Tinnitus, hearing difficulty (**tinnitus)**, blurring of vision, hypotension
- Then *hyperventilation* → respiratory alkalosis, → leading to metabolic acidosis, hyperpyrexia and coma

- Treatment:

- **Alkalization of urine**
  - **Solution of bicarbonate (NaHCO3) by i.v. – corrects metabolic acidosis and alkalinization of urine (= enhanced excretion)**
  - The antidote for NSAID poisoning is a solution of ***bicarbonate*** administered intravenously
  - It corrects the metabolic acidosis
  - And also, it enhances the excretion of NSAIDs by the kidney
    - **By alkalization → ionization of NSAIDs (weak acids) → reduce the reabsorption form urine → increase the excretion**
    - **= Ion trapping**
- ***Activated charcoal*** 1g/kg p.o. (till 1hour only) prevents absorption.
  - Activated binds to the surface of many molecules (many toxins) and many drugs
- Anticonvulsants e.g., i.v. diazepam – in case of convulsions
- Cold fomentation and ice bags – in case of hyperpyrexia
- Correct dehydration by i.v. fluids (5% dextrose)
- Correct hypoprothrombinemia (rare) by i.v. vitamin K
- Hemodialysis may be needed
  - Only in very serious states of NSAIDs poisoning

9. Analgesic - antipyretic drugs (52)

- Non-opioid analgesics are divided into: NSAIDs and antipyretics
- The prototype of antipyretics is ***paracetamol***
  - It is an effective alternative to NSAIDs
  - It has **analgesic** and **antipyretic** effects
    - However, its ***anti-inflammatory effect is only achieved in doses which are hepatotoxic***
  - Thus, paracetamol is ***not*** a member of the NSAIDs (it is not anti-inflammatory)
    - Only analgesic and anti-pyretic

Paracetamol (acetaminophen, APAP)

- **Analgesic and antipyretic**
- **No anti-inflammatory activity**
- **Weak inhibitor of peripheral** but **strong inhibitor of central COX** (in the brain)
- Also, it modulates serotoninergic (5-HT) receptors
  - The mechanism of action is not fully known…
- Alternative to ASA and ibuprofen as **analgesic** or **antipyretic**
  - Useful for pregnant women (which are contraindicated for NSAIDs) and children

- Paracetamol is an over-the-counter drug
- **Combinations:**
  - **+ caffeine**
    - The combination with caffeine increases the analgesic effects
  - **+ guaifenesin**
    - The combination with guaifenesin is recommended for treatment of tense cluster headache
  - **+ oxycodone, tramadol, codeine (codamol)**
    - Paracetamol is also combined with opioids – it has opioid-sparing effect
    - For example, paracetamol + codeine = codamol
  - + (vasoconstrictor) phenylephrine, pseudoephedrine
    - This combination reduces the nasal mucus membrane edema
  - **+ vitamin C**
    - Like in the case with NSIADs – this only increases the price of the trade product

Clinical uses of paracetamol

Paracetamol is a suitable substitute to aspirin or ibuprofen for analgesic and antipyretic use
→ Benefit:

- It is recommended for patients with:
  - A) **Peptic ulcer**
  - B) **Prolonged bleeding time**
  - C) **Children**
  - D) **Pregnancy** (risk-benefit ratio for the women and fetus has to be evaluated)

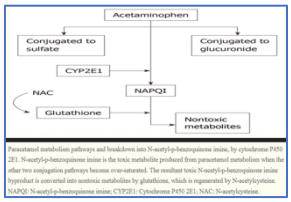
Adverse effects of paracetamol

- **Paracetamol is usually well tolerated at recommended therapeutical doses**
- **1) Occasionally:**
  - A) Skin rash
  - B) Allergic reactions
- **2) In acute overdose**
  - A) Hepatic necrosis (Dose-dependent)
  - The most serious and acute adverse effect of paracetamol is overdosage
    - The results can be fatal hepatic necrosis + renal tubular necrosis and hypoglycemic coma may also occur as a consequence of hepatic failure

Paracetamol – pharmacokinetics

- Paracetamol is a weak base
- It is metabolized in the liver
  - Low doses – are metabolized by glucuronic acid conjugation
  - High doses – are metabolized by cytochrome P450 → hydroxylation + glutathione participation
    - For this mechanism, the glutathione participation is necessary
    - Glutathione is a donor of sulfhydryl group
      - Sulfhydryl (SH) deficiency causes toxic hepatocyte necrosis
- !! liver disease, combination with alcohol, malnutrition, alcoholism!!

Paracetamol metabolism



Paracetamol metabolism pathways and breakdown into N-acetyl-p-benzoquinone imine, by cytochrome P450 2E1. N-acetyl-p-benzoquinone imine is the toxic metabolite produced from paracetamol metabolism when the other two conjugation pathways become over-saturated. The resultant toxic N-acetyl-p-benzoquinone imine byproduct is converted into nontoxic metabolites by glutathione, which is regenerated by N-acetylcysteine.
NAPQI: N-acetyl-p-benzoquinone imine; CYP2E1: Cytochrome P450 2E1; NAC: N-acetylcysteine.

- ❖ Paracetamol (acetaminophen) in lower doses conjugated to sulfate and glucuronic acid
- ❖ In higher doses, the conjugation is saturated, so higher doses have to be metabolized through another metabolic pathway – through cytochrome P40 2E1 and hydroxylation
  - ➢ The toxic metabolite NAPQI is formed
- ❖ In the overdose of paracetamol, accumulation of this toxic metabolites produces oxidative hepatocyte injury, liver cell necrosis
- ❖ Other factors that increase the risk of intoxication are:
  - ➢ Depletion of intracellular glutathione
    - It causes hepatocytes to be highly susceptible to oxidative stress and apoptosis
  - ➢ Deficiency of glutathione can be potentiated by the combination with alcohol, malnutrition, viral infection can reduce the activity of conjugation reaction
  - ➢ Very high doses of paracetamol saturate the conjugation
- ❖ These factors increase the probability of paracetamol intoxication

Paracetamol – intoxication

- ❖ This type of intoxication is relatively frequent
- ❖ It is very dangerous – because it's silent

- Symptoms of Intoxication:

1. 0-24 h – nausea vomiting, headache
   - During the first 24 hours, the symptoms are non-specific (nausea or headache), or the patient can be asymptomatic
2. 24 -72 h – disturbances – acid-base, electrolytes, liver functions (AST, ALT)
   - Then, intoxication continues with electrolyte disbalance, reduced function of the liver enzymes
3. 72-96 h – liver failure (Acute kidney failure in approx. 50% of patients with acute hepatic failure).
   - The intoxication continues with liver failure, acute kidney failure
4. 5 days – death from liver failure
   - Then after 5 days – death from liver failure can be caused by untreated intoxication of paracetamol

→ If acute liver failure doesn't develop, patients typically begin to recover within 2 weeks after ingestion of paracetamol

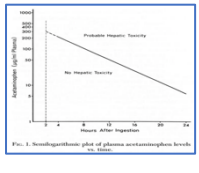
Treatment of paracetamol intoxication

- The drug of choice – Antidote:
  - Is peroral or intravenous administration of **<u>N-acetylcysteine</u>** (NAC) 50 - 200 mg/kg
    - N-acetylcysteine is a donor of sulfhydryl group
- Activated charcoal administered < 4 hours after ingestion
  - You can use activated charcoal to inhibit the absorption of paracetamol
  - Activated charcoal binds to the surface of paracetamol – but also to the N-acetylcysteine
    - In the case you use activated charcoal administration, you have to you N-acetylcysteine intravenously
- Measure acetaminophen (APAP) levels 4 hours after ingestion (or immediately, if ingestion occurred > 4 hours prior to presentation)
- Treatment of liver failure
- Liver transplant in severe cases

Rumack-Matthew nomogram

- ❖ To evaluate the risk of hepatic toxicity after administration of paracetamol, nomograms are used in clinical practice to quickly determine the risk of paracetamol poisoning
- ❖ Nomogram uses the plasma levels of paracetamol and time after injection to predict the severity of liver injury

Sever liver damage occurs in 90% of patients with paracetamol concentration in plasma greater than 300 µg/ml at 4 hours after administration of paracetamol



12. Antimicrobial agents

1. **General principles and side effects of ATB therapy (46)**
2. **Antibiotics for local application (15)**
3. **Natural (classic) PNC (19)**
4. **Broad spectrum PNC (40)**
5. **Cephalosporin ATB (13)**
6. **Tetracyclines (21)**
7. **Aminoglycosides (60)**
8. **Lincosamide ATB (5)**
9. **Macrolide ATB (28)**
10. **Sulphonamides (31)**
11. **Quinolones (23)**
12. **Antituberculotics (10)**
13. **Antimycotics (7)**
14. **Antihelmintics (35)**
15. **Antiviral chemotherapy (32)**
16. **Antimalarial drugs (34)**

1. General principles and side effects of ATB therapy (46)

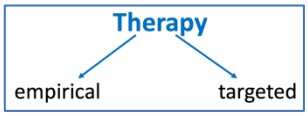
Antibiotics =

- Medicines that help stop infections caused by bacteria
- Killing the bacteria or keeping them from replicating

The earliest therapy
- Therapy has to be started as early as possible
- Earlier start = lower number of bacteria = much more effective treatment

Uses of antibiotics

a) Therapy:



❖ Generally, we use antibiotics for therapy of some infectious diseases
- ➢ Therapy can be either:
- ➢ **Empirical:**
  - Therapy, *without knowing exactly what pathogen is causing the disease*
  - → Use **broad-spectrum ATBs** (e.g., ampicillin + amoxicillin)
  - May lead to dismicrobia → superinfection
- ➢ **Targeted:**
  - *When we know what the pathogen is*
  - → Use **narrow-spectrum ATBs** (they have fewer side effects)

b) Prophylaxis:
- ➢ Especially surgical prophylaxis
- ➢ Most often we use the 1st generation of cephalosporins
  - **Cefazolin = drug of choice for surgical prophylaxis!**

ATBs according to mechanism of action:

A. Cell wall synthesis inhibitors: (beta-lactams)
- ❖ **1. Penicillins**
  - ➢ **Basic/natural penicillins**
  - ➢ **Anti-staphylococcal (penicillinase resistant) penicillins**
  - ➢ **Broad-spectrum penicillins (aminopenicillins)**
  - ➢ **Anti-pseudomonal penicillins**
- ❖ **2. Cephalosporins**
  - ➢ 5 generations – based on different spectrum of activity
- ❖ **3. Carbapenems**
- ❖ **4. Monobactams**
- ❖ **Other inhibitors of cell wall synthesis:**
  - ➢ Vancomycin
  - ➢ Bacitracin

B. DNA and RNA synthesis inhibitors
- ❖ **DNA synthesis inhibitors:**
  - ➢ ***Fluoroquinolones***
- ❖ **RNA synthesis inhibitors:**
  - ➢ Rifampin (TBC)

C. Ribosomal inhibitors (Protein synthesis inhibitors)
- ❖ **30S subunit**
  - ➢ ***Aminoglycosides***
  - ➢ ***Tetracyclines***
- ❖ **50S subunit**
  - ➢ ***Macrolides***
  - ➢ ***Lincosamides***

D. Inhibitors of Metabolic Pathways
- Acting as antimetabolites
- ❖ ***Sulphonamides***

Bactericidal	Bacteriostatic
Inhibitors of cell wall synthesis: → Beta-lactams Penicillins, Cephalosporins, Monobactams, Carbapenems → Bacitracin → Vancomycin	**Protein synthesis inhibitors:** → Tetracyclines → Macrolides → Chloramphenicol → Lincosamides
Inhibitors of DNA synthesis: → Fluoroquinolones	**Inhibitors of metabolic pathways:** → Sulphonamides
Inhibitors of RNA synthesis: → Rifampicin	
Protein synthesis inhibitors: → Aminoglycosides	

ATB Classification – type of effect

❖ Based on the effect on bacterial cells, we divide ATBSs to **bactericidal** and **bacteriostatic**

- Bactericidal

❖ **Bactericidal** → lead to **death of microbes**

❖ Bactericidal ATBs influence the **cell wall** (*Beta-lactams*), **DNA** (*Fluoroquinolones*) and **RNA** (*Rifampicin*)

- Bacteriostatic

❖ **Bacteriostatic** → **stop the growth of bacteria**, then the patient's immune system will remove the bacteria from the body

❖ Bacteriostatic ATBs are **anti-metabolites** or **protein synthesis inhibitors**
- ➢ Aminoglycoside is an exception – they are protein synthesis inhibitors, but aminoglycosides block not only the elongation of newly created peptides – but also its initiation = **bactericidal effect**
- ➢ Whereas the bacteriostatic ATBs only block the elongation

Features of antibiotics (things to keep in mind when choosing ATB)

- **1. Spectrum of activity of the ATB (broad vs. narrow spectrum)**
- **2. Effectiveness against resistant organism**
  - Bacteria are able to produce different pathogens
    - For example, β-lactamase, is a special enzyme which degrades of β-lactam rings of antibiotics
  - So, even if the bacteria are in the spectrum of activity of this antibiotic – there can be **resistance**
- **3. Route of administration**
  - For example, *aminoglycosides are **not** absorbed after peroral administration*
    - = Aminoglycoside should never be administered perorally when we want systemic effects
    - If we want local effects in the intestine, then after peroral administration, they will be effective
- **4. Combinations of ATBs**
  - Broadens their spectrum of effectivity
  - It's beneficial to combine ATBs which are effective on growing + effective on non-growing bacteria
  - It is good to **combine aminoglycosides** (non-replicating) **with penicillins** (replicating)
    - Because this combination blocks both **non-replicating** and **replicating** (growing) bacteria
- **5. Duration dependent vs concentration dependent effect:**

  → **Duration dependent effect:**
  - The effectiveness of some antibiotics depends on how long time the concentration of antibiotic in plasma is higher than the ***minimum inhibitory concentration*** (MIC)
    - MIC = the concentration leading to killing or inhibiting the growth of some bacteria
  - = More frequent dosing

  → **Concentration dependent effect:**
  - For other ATBs, their effect depends on the ***peak concentration*** (the maximum concentration – Cmax)
    - **Aminoglycosides** + **fluoroquinolones** (only ones!)
  - = Large dose 1x daily

  → **Post-antibiotic effect:**
  - = When suppression of bacterial growth is still present even after the concentration of ATB in plasma is not higher than minimal inhibitory concentration (MIC)
    - Can be due to ATB stays inside cells (fluoroquinolones)
    - Also typical for aminoglycosides
- **6. Interrelated pharmacokinetic parameters**
  - Absorption, distribution, interactions at the level of metabolism etc.
  - For example, tetracyclines have high affinity to Calcium (generally bivalent cations, Ca^{2+}, Mg^{2}), if diet contains high concentration of calcium, then tetracyclines will be connected to calcium and it will lead to generation of chelates → the absorption of tetracyclines will be dramatically reduced
    - So, coadministration of tetracyclines and products containing milk should be prevented
- **7. Safety, tolerability and Toxicity**
  - We should know typical side effects which are to be expected for different group of antibiotics
    - For example, penicillins are famous for their risk of allergy
  - **Contraindicated in pregnancy**: Aminoglycosides, tetracyclines and fluoroquinolones
  - **Contraindicated in children:** Tetracyclines and fluoroquinolones and

Duration of ATB treatment

Generally, the duration of treatment can be:

- **One-shot** – (**single dose**)
  - E.g., **uncomplicated gonorrhea** can be treated with a single dose of ceftriaxone (cephalosporin ATB)
- **5-7, 7-10 days**
  - Common infection (airways)
- **Long-lasting**
  - TBC, sepsis, endocarditis...

Different sources of toxicity:

- **Neurotoxic** Sulphonamides, anti-tuberculotics...
- **Nephrotoxic** Aminoglycosides, amfoterB...
- **Hepatotoxic** rifampicin, ketoconazole...
- **Hemotoxic** chloramphenicol, sulphonamides...
- **Ototoxic** Aminoglycosides
- **GIT-toxic** Tetracyclines, sulphonamides, erythromycin...
- **CNS-toxic** Anti-tuberculotics, polymyxin...

ATB – Adverse effects

Allergic

- The ***most common adverse effects are allergic reactions***, they can be either:
  - **Local**
  - Or **systemic**
- Many ATBs have high risk of allergies, for example:
  - **Penicillins**, **cephalosporins**, **sulphonamides**, **nitrofurantoin**, **vancomycin**...
- **Immediate**: (2 min-2 h) → Anaphylactic shock, angioneurotic edema, asthma attack, urticaria
- **Accelerated**: (2-24 h) → Urticaria, pruritus, respiratory problems
- **Delayed**: (24h- 26 days) → Fever, urticaria, pain and edema of joints, organic lesions, hemolytic anemia...

Biological adverse effects:

1. Resistance

- Generally, resistance is not an adverse effect – it is the problem of effectiveness of ATB is reduces
- We solve this problem by changing the ATB to a group which is more effective
- **= Relative** or **complete lack of effect of antimicrobial against previously susceptible microbe**
- Resistance is associated with an increase in MIC

There are many mechanisms of resistance:

- a. **Enzymatic destruction of drug**
  - *Bacteria can start producing antibiotic degrading enzymes*, resulting in inactivation of antibiotics
  - e.g., β lactam antibiotics can be inactivated by the enzyme **β lactamase**
- b. **Alteration of drug's target site**
  - Penicillin-binding protein (PBP) is an example of drug's target site
    - Bacteria may start to produce a different target site which will not be able to bind to antibiotics
  - *PBP alteration is typical for **MRSA*** - Methicillin-resistant Staphylococcus aureus *(staphylococci which are resistant to anti-staphylococcal penicillins)*
- c. **Prevention of penetration of drug**
  - Gram negative bacteria have porins on their surface
    - If these porins are not able to allow the antibiotics to go in, it creates resistance
    - (→ the penetration through porins is inhibited)
  - → *Typical for **fluoroquinolone** resistance*
- d. **Rapid ejection/efflux of the drug**
  - If we suddenly have an overexpression of efflux pumps – you will not be able to reach sufficient concentration inside the cells
  - As soon as the antibiotic enters the cell, almost immediately it can be removed by the efflux pumps
    - → *Typical for **tetracyclines**, **macrolides** and **aminoglycosides***
- e. **Alteration of metabolic pathway**
  - The enzyme will not be inhibited, but the cell will start to produce different enzymatic pathway which will lead to the production of the final product
  - → *Typical for when we are using **sulphonamides***

Factors increasing the risk of resistance

- **A. Exposure to sub-optimal levels of antimicrobial**
  - This is why it is so important to follow the recommendations and time interval
- **B. Exposure to microbes carrying resistance genes**
  - They can be transferred in different ways

2. Dismicrobia

- Means that you will impair the normal (physiological) bacterial flora
- Dismicrobias and superinfections can be complications when we use **broad-spectrum antibiotics**

3. Superinfection

- Superinfection may lead to such a level of dismicrobia that even bacteria (or fungi) which are normally suppressed by normal bacterial flora starts to overgrow
- There can be a fungal superinfection – you suppress normal bacterial flora with broad spectrum antibiotics – and suddenly we develop candidiasis
- Or there can be a superinfection with a bacterial strain, which is resistant to the ATB used
  - An example of this can be superinfection with clostridium difficile

2. Antibiotics for local application (15)

Intro – TOPIC 1
Use:

- **Prophylaxis:**
  - May be useful in preventing infections in clean wounds,
- **Therapy:**
  - In early treatment of infected dermatoses and wounds
  - In reducing colonization of the nares by staphylococci
  - And in management of acne vulgaris.
- ***Neomycin*** and ***bacitracin*** are the most commonly used.

a. Aminoglycosides

- Aminoglycosides are protein synthesis inhibitors which inhibit the ribosomal 30S subunit
  - They inhibit both initiation and elongation of protein synthesis = bactericidal effect
- Spectrum of effect:
  - In order to have effects, aminoglycosides need to enter the bacteria, which they are not very good at
    - Gram positive bacteria have thicker wall than gram negative = aminoglycosides cannot penetrate gram+ bacteria
    - The also require an oxygen dependent cotransporter in the cell membrane to be transported into the cell = they have no effect on anaerobic bacteria
  - = aminoglycosides can only target gram negative aerobic bacteria
- **Aminoglycosides are not absorbed from GIT** → Whenever we administer aminoglycosides **orally** – it is just for **GIT decontamination** = **local effect**
  - Only for *intestinal infection*
  - Only parenteral administration – i.m., i.v. → will lead to systemic effect
- **Topical** administration in the form of cremes, gels or drops
- Topical administration can be used in children

→ 1. Neomycin

- Neomycin is an aminoglycoside
- All aminoglycosides must be administered parenterally except for Neomycin which is ***associated with severe nephrotoxicity*** with systemic use and is therefore ***only limited to topical application of skin infections or p.o. (***Neomycin is often administered before colorectal surgeries, to reduce infections after surgery)
- Adverse effects:
  - Contact dermatitis is a common reaction to topically applied Neomycin

→ 2. Gentamicin

- Aminoglycoside ATB, ointment or cream. Water soluble and excreted in urine

b. Bacitracin

- = an antibiotic which ***inhibits bacterial cell wall synthesis***
- Active against G+ and G-
- Its use is restricted to topical application ***due to its potential for nephrotoxicity with systemic use***.
- Used for variety of ***localized skin*** and ***eye infections*** (ophthalmic solution), and for the ***prevention of wound infections.***
- Adverse effects:
  - Contact dermatitis reports of anaphylaxis and immunologic allergic contact urticaria.
- It is poorly absorbed through skin → systemic toxicity is rare

Examples of other reasons to use local ATB:

Musculoskeletal infections:

- The appropriate use of antimicrobial agents has decreased morbidity and mortality from orthopedic-related infections. Although systemic antibiotic use has been used for many years, new methods of local antibiotic delivery may result in increased antibiotic levels, decreased toxicity, and greater efficacy.
- The basis for using local antibiotic delivery systems in the treatment of bone and soft tissue infection is either to supplement or to replace the use of systemic antibiotics.
- **Indications**: Prophylaxis in total hip arthroplasty, periprosthetic hip infection, infected knee prosthesis, osteomyelitis
- **Gentamicin, Vancomycin Cefazolin, Ciprofloxacin, Tobramycin, Cefuroxime, Teicoplanin**

Periodontal disease or tooth extraction:

- While systemic antibiotics have a very limited use in treating typical periodontal disease, there has been much interest in local antibiotic delivery.
- If an antibiotic can be delivered directly to the pocket, without the patient having to take systemic doses, there are far fewer side effects, and fewer chances of resistant bacteria forming. In addition, with direct local delivery, the concentration of the antibiotic at the diseased site can be 100 times greater than taking the medication orally.
- The antibiotic is delivered with a syringe in single unit doses.

Arestin

- To sterilize intestine in intestinal infections

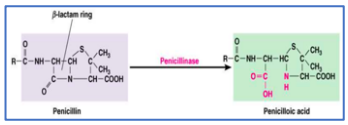
3. Natural (classic) PNC (19)

- **Penicillins**
- **Cephalosporins** and Cephamycins
- **Monobactams**
- **Carbapenems**

Inhibitors of cell wall synthesis > β lactams > Penicillins

- Beta-lactam antibiotics

– These 4 groups have a **beta-lactam ring** in their structure
– And all of them **inhibit** with the **synthesis of the cell wall** →***Bactericidal***



β-lactamase (penicillinase)

❖ ***β-lactamase*** breaks the beta-lactam ring of beta-lactams
  ➢ If bacteria start producing this degrading enzyme → **resistance**
❖ To solve this:
  ➢ We either have to combine these antibiotics with **beta-lactamase inhibitor** "-bactams"
    ▪ = Inhibitors of beta-lactamase and broaden the spectrum of beta-lactam ATBs and prevent development of resistance to beta-lactam ATBs
  ➢ Or we can switch *completely different group of antibiotics* which have different mechanism of action

Mechanism of action of beta-lactams

- Beta-lactams inhibit the enzyme ***transpeptidase*** (= ***penicillin-binding protein*** – **PBP**) → inhibits the synthesis of peptidoglycan → leads to autolysis (destruction) of the bacteria
  - Modification of PBP can also cause resistance
- Penicillins are **only effective against rapidly growing organisms** that synthesize peptidoglycan

Mechanism of PNCs action
- They bind to penicillin binding protein (PBP)
- Inhibit transpeptidase
- Interfere with cross linkage
- Inhibit synthesis of peptidoglycan
- Which leads to autolysis (destruction) of bacteria

- **Bactericidal activity** only during the growth of bacteria and synthetization of cell wall
  - Due to their effect (impaired cell wall synthesis) → they are bactericidal agents
- Penicillin is **concentration-dependent** (must be over MIC)

- Penicillins

Penicillin sub-class	Leading examples	Main activity against
Natural penicillins	**Penicillin G, penicillin V**	**Aerobic Gram-positive cocci** (incl. pneumococci and enterococci), **Neisseria** spp. and some **anaerobes**
Penicillinase-resistant	**Methicillin, oxacillin, cloxacillin**	**Penicillinase-producing strains of Staphylococcus aureus**
Aminopenicillins (extended spectrum)	**Ampicillin, amoxicillin**	**Broad spectrum of Gram-positive** and **Gram-negative pathogens**, but **not** Pseudomonas
Anti-pseudomonal (extended spectrum)	**Ticarcillin, piperacillin**	**Increased Gram-negative spectrum**, including **Pseudomonas**

Classification of penicillins:

Penicillins - adverse effects

- The major adverse effect of penicillins is **hypersensitivity**

→ **Hypersensitivity** – cross-sensitization, cross-reactivity
→ **Minimal direct toxicity** (but if present it may be:)

- **Pain & inflammation at injection site**
- **Gastrointestinal disturbances** (up to pseudomembranous colitis)
  - Broad spectrum (amoxicillin and ampicillin) may lead to pseudomembranous colitis
- **Secondary infections** (candidiasis)

Penicillins – Principal features

	Advantages and uses	Disadvantages
Natural penicillins	• Inexpensive	• Narrow spectrum • Resistance

Natural/basic penicillins:

Penicillin G:

"**Acid labile** drug" **means** a drug that is easily destroyed in **acidic** environment.

- **i.v. administration**
  - Because it is **acid-labile** → has to be administered intravenously (i.m.) (**there are no other ways to administer it**)
- Due to short half-life, it should be administered in 4-6 doses per day
- Can be given in higher concentration → increased antibacterial activity
- Used against **more serious infections** than penicillin V
  - Streptococci, meningococci, enterococci, pneumococci, staphylococci, treponema pallidum, clostridium sp., actinomyces
- Has more chance of developing severe side effects than penicillin V
  - E.g., joint pain, anaphylaxis, hemolytic anemia
- Drugs → ***Benzylpenicillin*** (i.v.), ***Benzathine*** (i.m.), ***Procaine*** (i.m.)

Penicillin V:

- **P.o. administration** (acid-stable = survives acidic environment)
  - However, poor bioavailability
- Administered every 6 h (4x/day)
- Used against minor infection (e.g., tonsillitis, pharyngitis, skin infection caused by streptococcus pyrogens)
- Drugs → ***Phenoxymethylpenicillin, penamecillin***

Smá summary um pencillin til að skilja betur:

1 Natural penicillin
- Er Narrow spectrum og notað þegar þú ert viss um hvaða bacteria er til staðar

2 Penicillinase-Resistant:
- Staphylococci er með hátt resistance á móti pencillin, þannig ef það er grunur um staphylococci er notað þessi lyf sem eru minna resistant!
- T.d. cloxacillin (Starklox) er mjög vinsælt lyf → notaði þetta þegar eg fekk lymphangitis sem mjög liklega vegna staphylococci

3 Broad spectrum:
- Lyf þegar þú ert ekki viss um bacteriuna, og oft notað til að byrja lyfjagjöfina
- Færð einstakling á spitalann og hann er með sýkingu og þú hendir honum á augmentin strax (Mjög vinnsælt lyf)

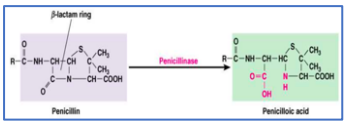
4. Broad spectrum PNC (40)

- **Penicillins**
- **Cephalosporins** and Cephamycins
- **Monobactams**
- **Carbapenems**

Inhibitors of cell wall synthesis > β lactams > Penicillins

- Beta-lactam antibiotics

– These 4 groups have a **beta-lactam ring** in their structure
– And all of them **inhibit** with the **synthesis of the cell wall**



β-lactamase (penicillinase)

❖ ***β-lactamase*** breaks the beta-lactam ring and forms penicilloic acid (inactive metabolite)
  ➢ If bacteria start producing this degrading enzyme → **resistance**
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a. **Extended-spectrum penicillins – aminopenicillins**

- The major representatives are:
  - **Ampicillin – i.v.**
  - And **amoxicillin – p.o.** ***(→Augmentin!)***
- **Penetration through the gram-negative outer membrane** = broader spectrum
  - The benefit of them is that they can go through the outer membrane of gram negative
    - And when they are inside, they can act on this ***transpeptidase*** reaction
- They may be inactivated by many beta-lactamases which are released to this periplasmatic area
  - That's why they are very often combined with **beta-lactamase inhibitors**
    - E.g., **Augmentin** → amoxicillin + clavulanic acid (β-lactamase inhibitor)
- Dosing: → they are usually given in doses of around 250-500 mg
  - Ampicillin = Every 6 hours in case of ampicillin
  - Amoxicillin = Every 8 or 12 hours
- **Indications:**
  - **UTI**, **sinusitis**, **otitis**, lower respiratory tract infections,
    - They are also broad in the terms of that they are **effective in many diseases**

b. **Extended-spectrum penicillins – antipseudomonadal**

- **Ticarcillin** – p.o. (6 g divided in 4-6 doses) - **UTI**
- **Piperacillin** (3-4g divided in 4-6 doses), mezlocillin, azlocillin – active against selected G-bacilli (Klebsiella pneumoniae, Pseudomonas aeruginosa) – **UTI**
- Indication → **Treat pseudomonal infection in hospitals** (pseudomonal is a type of bacteria)
- Often combined with B-lactamase inhibitors
  - That's why the only available form is intravenous administration
- Often used in combination with **beta-lactamase inhibitors**

5. Cephalosporin ATB (13)

- **Penicillins**
- **Cephalosporins** and Cephamycins
- **Monobactams**
- **Carbapenems**

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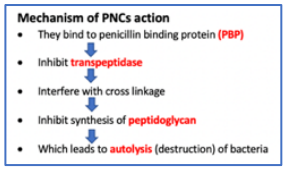
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Cephalosporins (widely used)

5 generations of cephalosporins

- Even though we have the 5th generation, doesn't mean that we don't use the 1st and 2nd generations
- Generations differ in their **spectrum of activity** (and in their route of administration and side effects etc.)

- Cephalosporins are generally considered **broad-spectrum** ATBs
  - The 3rd and 4th generations have broader spectrum
  - The 1st generation has a relatively narrow spectrum
- Also, resistance to β-lactamase increases with generations (1st – least resistance, 4th generation – best resistance)
- 1st generations → against G+, little or no effect against G-
- 2nd generation → Mainly against G-, less against G+
- 3rd generation → Good against both G+ and G-
- 4th generation → Good against G- and better than 3rd generation against G+

Pharmacokinetics

- **1st, 2nd and 3rd generations of cephalosporins are both available parenterally and orally**
- **4th and 5th generations are only available parenterally (only i.v.)**
  - The target by developing these later generations was to develop potent antibiotics while not losing time and energy having to think about the absorption and bioavailability
    - This is why we administer 4th and 5th generations parenterally
- Most cephalosporins **do not** penetrate cells or the CNS
  - **Except for 3rd generation, which penetrate into CNS**
    - 3rd generation cephalosporins belong to crucial drugs used for therapy of **bacterial meningitis**
- Mostly excreted unchanged by the kidneys
  - Most of them do not influence live metabolism – they are excreted by kidneys
    - This is why they are effective also in urinary tract infections

Cephalosporin	URTIs – upper airways	LRTIs – Lower airways	SSTIs – Skin, soft tissues	UTIs – Urinary	STDs – Sex. Dis.
1st generation	✓	✓	✓	✓	–
2nd generation	✓	✓	✓	✓	✓
3rd generation	✓	✓	✓	✓	✓
4th generation	–	✓	✓	✓	–

Therapeutic uses

- **Upper respiratory tract infections** and **otitis media**
- **Septicemia** caused by **G-** (Pseudomonas)
  - Especially 3rd and 4th generations
- **Urinary tract infections**
  - Because they are mostly eliminated via urine in unchanged form
- **Bacterial meningitis** – N. meningitidis (also streptococcal infections)
  - 3rd generation – because they penetrate into CNS (remember this)
- **Gonococcal infections**
  - A ***single dose of ceftriaxone*** may lead to healing of gonococcal infection
- **Prophylaxis in surgery**
  - Gynecological, urological, orthopedic procedures, etc.
  - Especially 1st generation cephalosporins are used in prophylaxis in surgery
    - **Cefazolin = drug of choice for surgical prophylaxis!**

1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation
• **Both p.o. + parenterally** • Relatively **narrow spectrum** • Mainly and more effective against **G+ cocci** - Str. Pneumonia, str. Pyrogens, st. aureus, st. epidermidis - Except enterococci + MRSA • Very limited effect against **G-** • Weak resistant against β-lactamase of gram- • Resistant against penicillinase (don't have to be combined with β-lactam inhibitors • Often used in **surgical prophylaxis** **Drugs:** • ***Cephalexin*** • ***Cefadroxil*** • ***Cefazolin*** **Effective against G+, limited effect against G-**	• **Both p.o. + parenterally** • **Immediate spectrum** • Mainly and more effective against **G- bacteria** • Modest activity against **G+** • Higher resistance against B-lactamase of G- • Resistant against staphylococcal penicillinase • Used for acute ORL, resp. disorders **Drugs:** • ***Cefuroxime*** (p.o., inj.) • *Cefprozil* (p.o.) • *Cefoxitin* (inj) (cephamycin → anaerobic bacteria!)	• **Both p.o. + parenterally** • **Broad spectrum** • Does penetrate into CNS • **Enhanced G- activity** • Enhanced resistance against β-lactamases • Different from 1+2 Gen: - Lower activity against **staphylococcus** + good activity against **streptococcus** • Antipseudomonal activity: - *Ceftazidime, Cefoperazone* **Drugs:** • Inj.: - *Ceftriaxone, Cefotaxime, Ceftazidime, cefoperazone, ceftizoxime* • P.o. (for more severe inf.): - *Cefixime*	• **Only parenterally** • Enhanced **G-** and **G+** activity • Active against **P. aeruginosa** • Resistance against B-lactamases • Higher affinity to PBP • ONLY for **severe** infections • Different from 3rd Gen: - It has increased effectiveness against **G+** bacteria **Drugs:** • *Cefepime* (inj)	• **Only parenterally (i.v.)** • Higher affinity to PBP • Reserve ATBs for **MRSA**, **PRSP**, **pseudomonas**, **enterococci** • **Used for nosocomial infections by polyresistant strains** **Drugs:** • *Ceftaroline* • *Ceftolozane/Tazobactam*

- ❖ So, we started from gram positives (1st) generation – and slowly we changed the ratio towards gram negative
  - ➢ However, the activity against streptococci is still relatively good for the 3rd generation
- ❖ In the 4th generation – the effectiveness for gram-negative bacteria is as good as in 3rd generation, but the 4th generation has also increased effectiveness against gram-positive bacteria

Adverse effects of cephalosporins

- Generally, the adverse effects are similar to penicillins
- **Hypersensitivity reactions** – most common
- **5-10% cross-sensitivity with PNC allergic patients**
  - So, we have to be on alert in case the patient has a history of penicillin allergy
  - In case of cross-sensitivity, we call it **allergy to β-lactams**
- **1-2% hypersensitivity reactions in non-PNC allergic patients**
- **Nephrotoxicity - especially cefradine (not used often nowadays)**
- **Thrombophlebitis (i.v.)**
- **Superinfections (candidiasis, colitis)**
  - Dismicrobias and superinfections can be complications when we use broad-spectrum antibiotics
    - They can lead to either fungal infections (candidiasis) or overgrow of some pathogens (pseudomembranous colitis)
- **Diarrhea** - oral cephalosporins
  - Due to dismicrobia in GIT – the normal microbial flora is influenced and leads to problems
- **Cefamandole**, **ceftazidime**, **cefoperazone** → these agents inhibit liver enzymes and may cause:
  - **A) bleeding disorders**
    - If these agents are taken together with anticoagulants – leads to bleeding because the other drugs will be more active due to pharmacokinetic interactions at the level of biotransformation
  - **B) flushing, tachycardia**
  - **C) vomiting with alcohol**
    - These agents inhibit liver enzymes – except for cyp450, they may also inhibit aldehyde dehydrogenase
    - So, they may have so-called ***disulfiram effects*** → used to treat alcohol dependence
      - Gastrointestinal discomfort is produced after ingestion of alcohol by inhibiting aldehyde dehydrogenase = aversive treatment

Cephamycin:

- A group of drugs which are affective against **anaerobic bacteria** (this is important to remember)
- Why is it important to remember?
  - When we use surgical prophylaxis, and we expect a contamination with anaerobic bacteria, it is not enough to use cefazolin (1st generation, first-line)
    - In this case we have to combine cefazolin with some agent which is effective against anaerobic bacteria
    - Or we can choose a Cephamycin, which already has combined action against both aerobic and anaerobic bacteria!
- Drugs:
  - *Cefoxitin* (2nd generation cephalosporin), *Cefotetan, Cefmetazole, Flomocef*

6. Tetracyclines (21)

Intro – Protein synthesis/Ribosomal inhibitors:

- Antibiotics affecting ribosomal subunits are divided into 2 big categories
  - **1. Those affecting the <u>50S</u> subunit**
    - **Chloramphenicol**
    - **Macrolides**
    - **Lincosamides**

    } **<u>Bacteriostatic</u>** → inhibiting elongation of amino acids
  - **2. Those affecting the <u>30S</u> subunit**
    - Further divided into 2 groups:
    - a. **Tetracyclines** (thirty starts with T – T-T)
      - Tetracyclines bind to the 30S subunit and they block the binding of tRNA → and inhibit protein synthesis
      - They block the elongation → **<u>bacteriostatic</u>** effects
    - b. **Aminoglycosides** (A = first in alphabet)
      - In contrast to tetracyclines, they block the elongation, but they also block the initiation
      - They result in the production of faulty proteins, which are later on incorporated into the bacterial cell wall which becomes ineffective
      - This means that aminoglycosides have **<u>bactericidal</u>** effects

Tetracyclines

- Tetracycline is a protein synthesis inhibitor – reversibly inhibits the 30S subunit (t for thirty)
  - They prevent **elongation** of amino acid chains = bacteriostatic
- **Natural**:
  - **Tetracycline**
    - Natural tetracycline is short-acting, has to be administered every 8 hours – 4x per day
- **Semi-synthetic**:
  - **Doxycycline**
  - **Tigecycline**

  } These 2 are long-acting tetracyclines
    - Semi-synthetic doxycycline and tigecycline are long-acting – administered 1x per day

Pharmacokinetics

- <u>Absorption</u> is affected by:

- **food**:
  - **Divalent cations** (**<u>Ca2+</u>**, **<u>Mg2+</u>**, Fe2+, Bi2+ - **chelates**), ***dairy products*** and ***antacids***

- Absorption of tetracyclines is influenced by divalent cations (X^{2+}) – **especially calcium and magnesium**
  - Some food contains a lot of calcium – like milk (dairy products)
    - So, 2-3 hours after administration of tetracyclines, patient should not ingest dairy products
      - If diet contains high concentration of calcium, then tetracyclines will be connected to calcium and it will lead to generation of **chelates** – and the absorption will be dramatically reduced

- <u>Distribution</u> of tetracyclines is very good

- Penetration into cells = we can use them for **atypical bacteria**
- Distribute widely to tissues, body fluids
- Bile (except cerebrospinal fluid) - bind and damage growing **bone** and **teeth**
- Cross **placental** barrier
- Excreted in **milk**

- <u>Elimination</u> mainly via liver and kidney

- Some of TTC have **enterohepatic** circulation
  - Tetracyclines are partly reabsorbed when eliminated by bile – this prolongs their duration of action

Clinical Uses

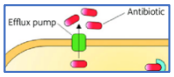
- They have **broad-spectrum** effect:
  - **G+**, **G-**, **anaerobes**, **atypical bacteria** (Chlamydiae, Mycoplasma), Rickettsiae and some protozoa
- Drug of choice:
  - In **Mycoplasma pneumoniae**
  - And also, for **syphilis** therapy – Spirochetes (treponema pallidum)
- General use in:
  - **Respiratory**, **urinary tract**, **biliary infection**, **tularemia**, **brucellosis**, **shigellosis**, **acne vulgaris**....
- They are also used often after extraction of teeth – to prevent creation of some focus
  - Because they are **also active against anaerobic bacteria**
- In combination – ulcer disease caused by Helicobacter pylori
  - In case we have a patient, who is allergic to penicillin (cannot take ampicillin) → we can use tetracyclines as an alternative in combination therapy to treat Heliobacter pylori infection

Adverse Effects

- **Gastrointestinal irritation**
  - Nausea, vomiting and diarrhea
  - Intestinal flora – superinfection
    - Logically, because they are broad-spectrum ATBs
- **Bony structures and teeth**
  - Teeth discoloration
  - Bone growth inhibition
- **Contraindication in young children to 12 years** and **during pregnancy** – teratogenic

❖ Unfortunately, tetracyclines are quite toxic – we should prevent their use in children and in pregnancy
- So, they are teratogenic

Mechanisms of Resistance



❖ The most important factor of resistance for tetracyclines is **increased production of efflux pumps**
- Increase in efflux pumps leads to fast removal of tetracycline from cytoplasm, so tetracycline won't have time to influence the metabolism of these bacterial cells
  - As TTCs are absorbed into the cytoplasm of bacteria – it is immediately ejected from the cell
- (You won't reach sufficient concentration of TTC for them to inhibit the 30S ribosomal subunit)

Synthetic tetracyclines: (longer half-life)

Doxycycline p.o.

❖ Available in different medicinal forms – we prefer peroral forms, **tablets** or **capsules** (also available in injections and suspension)
- ***Give with meals to decrease GIT upset***
  - But not with dairy – because even though it doesn't create the chelates as much as natural tetracycline – still some may be created
- It is important to take it with water to **avoid esophageal irritation**, **ulceration**

Tigecycline i.v.

- **Very broad spectrum**
  - G+, G- bacteria, anaerobes, MRSA
  - But it has no activity against Pseudomonas, Proteus
- A benefit of tigecycline is **less resistance**
  - Because it is **not affected by specific efflux pump**
- By slow i.v. infusion
- It is mostly used for the treatment of skin, soft tissue, intra-abdominal infections

7. Aminoglycosides (60)

Intro – Protein synthesis/Ribosomal inhibitors:

- Antibiotics affecting ribosomal subunits are divided into 2 big categories
  - **1. Those affecting the 50S subunit**
    - **Chloramphenicol**
    - **Macrolides**
    - **Lincosamides**

    } **Bacteriostatic** → inhibiting elongation of amino acids
  - **2. Those affecting the 30S subunit**
    - Further divided into 2 groups:
    - a. **Tetracyclines** (thirty starts with T – T-T)
      - Tetracyclines bind to the 30S subunit and they block the binding of tRNA → and inhibit protein synthesis
      - They block the elongation → **bacteriostatic** effects
    - b. **Aminoglycosides** (A = first in alphabet)
      - In contrast to tetracyclines, they **block the elongation**, but they also block the **initiation**
      - They result in the production of faulty proteins, which are later on incorporated into the bacterial cell wall which becomes ineffective
      - This means that aminoglycosides have **bactericidal** effects

Aminoglycosides

- = **Concentration dependent**!!!!!!
  - Their effect depends on the ***peak concentration*** (the maximum concentration – Cmax)
- **From the drugs inhibiting protein synthesis, aminoglycosides are the only ones which are bactericidal**
  - The others are all bacteriostatic

Pharmacokinetics

- Absorption → Poor oral absorption

- **Aminoglycosides are not absorbed from GIT** → Whenever we administer aminoglycosides **orally** – it is just for **GIT decontamination** = **local effect**
  - Only for intestinal infection
- Only parenteral administration – i.m., i.v. → will lead to systemic effect
- Topical – skin, eye, airways
- Topical administration can be used in children
  - In contrast, parenteral administration is usually contraindicated for children and especially in pregnancy (teratogenicity)

- Distribution

- Minimally protein bound (10%)
  - Do not penetrate into the CNS, eye, milk
  - May cross the placenta

- Elimination

- Strong tissue binding at the injection site
  - Elimination T1/2 from tissues - much longer than from plasma
- Aminoglycosides are famous for their ***post-antibiotic effect*** (2-8hrs)
  - So, even though plasma concentration is below MIC, the effect is still present, because it stays in tissues
- Not metabolized
- 90 % eliminated by kidney
  - = if there is reduced clearance of creatinine → recalculate the dosing in order to prevent its toxicity
- Because they are eliminated by kidneys – they are quite effective in therapy of UTIs

It is good to **combine aminoglycosides with penicillins**

- Because this combination blocks both **non-replicating** and **replicating** (growing) bacteria

Antibacterial Spectrum

- **Most bacterial species are sensitive**
- **Intracellular** concentration-dependent up on oxygen transport system in the cell membrane – absent in anaerobes
- Only clinically useful against organisms growing in **aerobic** conditions
- They are also effective in **aerobic G negatives**:
  - Pseudomonas, Proteus, Klebsiella, Serratia, E. coli, Mycobacteria

- Important: Aminoglycosides require oxygen
  - Without oxygen, they would not be effective
  - This means that they can only be used in aerobic conditions (not useful for anaerobic bacteria)
- For anaerobic bacteria → chloramphenicol, tetracyclines and Cephamycins
  - But not aminoglycosides…

Adverse Effects

- Dangerous factors:
- **Using continuously more than 5 days**
  - Continual exposure to aminoglycosides should be prevented → leads to increased risk of toxicity
    - Especially, **oto**-, **nephro**- and **neurotoxicity**
- **High dose**
  - Higher dose = increased risk of toxicity
- **Elderly and children**
- **Renal insufficiency**
  - Because aminoglycosides are mainly excreted by kidneys
- Concurrent use with loop diuretics or other nephrotoxic drugs

Concentration dependence – Dose related!!!!

- The effects and adverse effects are dependent on **concentration** of aminoglycosides (not on the time interval)
- Compared to other ATBs, there is a huge difference between the effectiveness
  - In aminoglycosides (and fluoroquinolones), the effect depends on the concentration we reach
    - – it should be 10-12x higher than minimum inhibitory concentration (MIC)
  - Whereas the effect of other ATBs depends on the duration (exposure time)
    - – for how long time each day, we are over the MIC
  - That's why, whenever we use systemic administration of aminoglycosides, we use them **1x daily** (not like with penicillin G for example – every 6 hours)
    - Because we only want to reach as high concentration as possible
      - (Time over MIC is not a factor)
- For effect, it is important to increase the concentration
  - But if there is a problem with elimination (impairment of kidneys, or immature elimination mechanisms in children), then the duration of toxic exposure is much longer
  - This leads to increased toxicity – but not increased effects

Typical side effects of aminoglycosides:

- **Ototoxicity** – leading to cochlear and vestibular impairment
  - Irreversible damage
  - Auditory - tinnitus, hearing loss
  - Vestibular - vertigo, ataxia, loss of balance – audiometric testing for early detection
- **Nephrotoxicity**
  - Leading to further retention of aminoglycosides in kidney up to necrosis
    - And thus, increasing the toxicity
- **Neurotoxicity**
  - Paresis – influences the end plates
- **Allergic reaction** – after local administration
  - But not as often as in penicillins

Aminoglycosides – classification		
-mycin (Streptomyces Spp.)		**-micin (Micromonospora Actinomycetes)**
• ***Streptomycin*** (inj) - Used in TBC - For Tularemia, brucellosis, plaque - G- bacillary infection of UT • ***Spectinomycin*** (inj) - Used in single dose for Neisseria gonorrhea - Especially for women w. hypersensitivity to PNC + cephalosporin (B-lactam allergic patients)	• ***Neomycin*** (locally) • ***Kanamycin*** (locally) • ***Amikacin*** (inj) • ***Tobramycin*** (locally) - More active against Pseudomonas Aeruginosa - Less Ototoxic + nephrotoxic	• ***Gentamicin*** (inj, locally) - Wide range of activity: ○ Serratia, Staph aureus - Combination w. PNCs → in bacterial endocarditis - Pseudomonas (effective w. *gentamicin*, *carbenicillin* or *ticarcillin*) - Initial treatment of bacteremia

Spectinomycin

- Spectinomycin belongs to the aminoglycosides
  - But due to its **low toxicity**, sometimes it is categorized outside of them
- Aminocyclitol – similar to AG
- Interaction with 30S – inhibition of protein synthesis
- Used as one **single dose** for **treatment of gonorrhea** caused by **penicillinase-producing Neisseria gonorrhea**
  - Or in patients allergic to PNC
- **Adverse effects** – hypersensitive reactions
  - After this single-dose gonorrhea treatment, we almost never observe oto-, nephro- and neurotoxicity
  - Only problem is that there can be hypersensitive reactions

TANGS do NOT Kill anaerobes

- **T** = Tobramycin
- **A** = Amikacin
- **N** = Neomycin
- **G** = Gentamycin
- **S** = Spectinomycin
- do
- **N** = Nephrotoxic/neurotoxic
- **O** = Ototoxic
- **T** = Teratogenic
- Kill anaerobes

8. Lincosamide ATB (5)

Intro – Protein synthesis/Ribosomal inhibitors:

- Antibiotics affecting ribosomal subunits are divided into 2 big categories
  - **1. Those affecting the 50S subunit (50S)**
    - **Chloramphenicol**
    - **Macrolides**
    - **Lincosamides**

    } **Bacteriostatic** → inhibiting elongation of amino acids
  - **2. Those affecting the 30S subunit (30S)**
    - Further divided into 2 groups:
    - a. ***Tetracyclines*** (thirty starts with T – T-T)
      - Tetracyclines bind to the 30S subunit, and they block the binding of tRNA → and inhibit protein synthesis
      - They block the elongation → **bacteriostatic** effects
    - b. ***Aminoglycosides*** (A = first in alphabet)
      - In contrast to tetracyclines, they **block the elongation**, but they also block the **initiation**
      - They result in the production of faulty proteins, which are later on incorporated into the bacterial cell wall which becomes ineffective
      - This means that aminoglycosides have bactericidal effects

Lincosamide – Drugs:

1 ***Lincomycin***
2 ***Clindamycin*** → most commonly used member
3 ***Pirlimycin***

Lincosamide – General:

Mechanism of action:

- Bacteriostatic mechanism, same mechanism as macrolides → bind **50S** subunit → inhibiting elongation of protein synthesis

Pharmacokinetics:

- Approx. 90% of p.o. are absorbed and peak occurs within 2-4 h
- i.m. result in strong absorption with peak occurring in 1-2 h
- 90% bound to plasma proteins
- ***Clindamycin*** is generally more stable and rapidly absorbed than ***lincomycin***
- Broad distribution in several tissues (except CSF)
- They accumulate in highest concentration in kidney + lungs
- ***Clindamycin*** accumulates in macrophages, inflammation → high penetration into tissues
  - Clindamycin can be given perorally, parenterally or as a topical cream
  - It is mainly used to treat anaerobic bacterial infections of the lungs and mouth → in other words, above the diaphragm
  - The cream form can also be given to treat acne

Clinical use:

- **They are used against G+ bacteria (unable to pass through porins of G- bacteria)**
- Often used for patients allergic to PNCs
- Common for skin infection
- Other possible indication → dental + abdominal infection, abscess, Pelvic inflammatory disease, anaerobic infection
- *Clindamycin* → said to be effective in treatment of acne, toxic shock syndrome and malaria

Side effects:

- Common side effects:
  - Mainly GIT disturbances (ranging from diarrhea to lethal ***pseudomembranous colitis***)

9. Macrolide ATB (28)

Intro – Protein synthesis/Ribosomal inhibitors:

❖ Antibiotics affecting ribosomal subunits are divided into 2 big categories
- ➢ **1. Those affecting the 50S subunit (50S)**
  - **Chloramphenicol**
  - **Macrolides**
  - **Lincosamides**

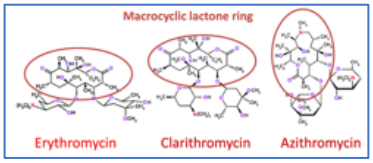
  } **Bacteriostatic** → inhibiting elongation of amino acids
- ➢ **2. Those affecting the 30S subunit (30S)**
  - Further divided into 2 groups:
    - a. Tetracyclines (thirty starts with T – T-T)
      - ♦ Tetracyclines bind to the 30S subunit, and they block the binding of tRNA → and inhibit protein synthesis
      - ♦ They block the elongation → **bacteriostatic** effects
    - b. **Aminoglycosides** (A = first in alphabet)
      - ♦ In contrast to tetracyclines, they **block the elongation**, but they also block the **initiation**
      - ♦ They result in the production of faulty proteins, which are later on incorporated into the bacterial cell wall which becomes ineffective
      - ♦ This means that aminoglycosides have **bactericidal** effects

Macrolides

- Macrolides are protein synthesis inhibitors – affecting the 50S subunit
  - Blocking elongation of amino acid side chain = **bacteriostatic**
- **Macrolides have time-dependent activity**
  - So, not like in aminoglycosides (which are concentration-dependent)
  - This is the reason why it is so important for erythromycin for example to be taken every 6 hours
    - ➢ To keep the rate of dosing
- Extra-, **intracellular** activity
- **Post-antibiotic effect** (3 – 7 hours)
  - Longest **post-antibiotic effect** is present in **azithromycin** – which is why we can use it every 24 hours

Erythromycin, **clarithromycin** and **azithromycin** are 3 mostly used macrolides

❖ They have a special macrocyclic lactone ring (= common characteristic for all of them)
- ➢ Which means they all have common problems regarding resistance



Macrolides – Drugs:		
Erythromycin (1952)	***Clarithromycin*** (1980)	***Azithromycin*** (1980)
• **Naturally occurring macrolide** • Disadvantages: - **Low bioavailability** (poor absorption) - **Acid lability** - **Narrow spectrum** - **Poor GI intolerance** - **Short elimination half-life** **Indication:** • Major indication is **substitute of PNC** in Penicillin allergic or resistant patient • **Pertussis**, **diphtheriae** • **Atypical infection** (legionella, mycoplasma pneumonia) • **H. pylori infection** in combination therapy **Dosing** → every 6 h	• Structural derivative → **broader spectrum activity** • **High interaction potential** like *erythromycin* but **better absorbed** - Good pharmacokinetics - Its **toxicity is lower** + **time interval is prolonged** **Indication:** • Very good activity on G+ and especially L. pneumophila, Ch. Pneumoniae • H. pylori infection • ***Drug of choice for atypical bacteria***	• Strongest activity against Hemophilus, M. pneumoniae, Neisseria, H. pylori, Campylobacter • Good effect on atypical mycobacteria • More effective on G- • Does NOT inhibit CYP450 → Fewer interactions than eryth. and clarith. • Longest Post-antibiotic effect - → Thus, can be used 1x day • 3 days therapy is usually enough **Indication:** • Mainly in respiratory infection

Currently, macrolides are drugs of choice in therapy of infections caused by atypical bacteria!
- ➢ ***→clarithromycin***
- ➢ Remember this!

Advantages of the newer macrolides
- **Advantage**
- **Broader spectrum**
- **Higher activity (G-)**
- **Improved tolerability**
- **Less toxicity**
  - Less toxic than aminoglycosides
  - They don't influence kidneys and the vestibulocochlear system as much
  - If the cause toxicity, it is hepatic toxicity
- **Improved PK properties**
  - Orally effective
  - Well absorbed = Better bioavailability
  - Better tissue penetration
  - High blood concentration
  - Prolonged half-lives (newer agents)
    - Erythromycin = every 6 hours, clarithromycin = every 12 hours, Azithromycin = every 24 hours

Pharmacokinetics

- Absorption

Erythromycin

- The absorption of erythromycin is **very weak** – because it is **acid labile** (destroyed in stomach)
  - ➢ Administered in *enteric coating*
  - The bioavailability is less than 40%
  - This is the reason why it has to be taken every 6 hours
- This is why we prefer clarithromycin and azithromycin

Clarithromycin

- **Acid stable** and well absorbed regardless of presence of food

Azithromycin

- **Acid stable** – food can decrease absorption of capsules

- Distribution

- Distribution is generally very good
- Extensive tissue and cellular distribution
- **Clarithromycin** and **azithromycin** → extensive penetration
- Into body fluids (except brain, CSF)
  - Into prostatic fluids, also
- Special ability – to accumulate in the macrophages (= **atypical bacteria**!!)
  - Inflammation – ↑ penetration into tissue

- Metabolism

- Macrolides are metabolized especially in the liver
- **Erythromycin** and **clarithromycin** have high interaction potential
  - Because they **inhibit cytochrome P-450** → Drug interactions!!!!!
- Erythromycin and clarithromycin inhibit the metabolism of drugs which are also metabolized by CYP450
  - So, the concentration of these drugs in the body will be increased in the body = stronger effect
    - ➢ (Theophylline, anticoagulants, astemizole, carbamazepine, statins, antiarrhythmic drugs I. class)
- **Azithromycin has much better profile regarding interactions**

- Excretion

- Excreted in bile in the active form + Partially reabsorbed (enterohepatic circulation)

Macrolide – Spectrum:	
1. **G- Aerobes:** • H. influenzae (not *erythromycin*), M. catarrhalis, Neisseria sp. • Do NOT have activity against any Enterobacteriaceae 2. **G+ Aerobes:** • Methicillin-susceptible staphylococcus aureus • Streptococcus pneumonia (resistance) • Group and viridians streptococci • Bacillus sp., Corynebacterium sp. 3. **Anaerobes:** • Activity against upper airway anaerobes	4. **Atypical Bacteria** (excellent activity): • Currently macrolides are drug of choice against atypical bacteria inf • Legionella pneumophila, chlamydia sp., mycoplasma sp., ureaplasma urealyticum. 5. **Other bacteria:** • Mycobacterium avium (non-TBC mycobacterium), treponema pallidum, campylobacter, borrelia, Bordetella, brucella, pasteurella

Adverse Effects (Generally, side effects are not so frequent for macrolides)

- Macrolides mostly lead to **gastrointestinal** and **liver impairment**
  - Nausea, vomiting, diarrhea, dyspepsia
  - Erythromycin, less with new agents
- Cholestatic **hepatitis** – rare > 1 to 2 weeks of erythromycin estolate
- Thrombophlebitis – i.v. Erythromycin and Azithromycin
- **Other** → Ototoxicity, QTc prolongation, Allergy, **Drug interactions** (especially erythromycin and clarithromycin)

Macrolides can be used in children and in pregnancy
- Fluoroquinolones and tetracyclines are contraindicated in children and pregnancy
- This is why macrolides are used so often

10. Sulphonamides (31)

Sulfonamides – General:

- **Inhibitors of metabolic pathways**

Mechanism of action:

- Folic acid is synthesized from **PABA**, and sulfonamides are **synthetic analogs of PABA**
  - Because of their structural similarity, they **compete for bacterial enzyme** → inhibit folic acid synthesis
- Sulphonamides inhibit the first step of folic acid synthesis → inhibit the formation of dihydrofolic acid
- = **Folate antagonists**:
  - **Folic acid** is **essential for synthesis of RNA + DNA** and other compounds necessary for cellular growth
  - Inhibition of folate synthesis → inhibit growth of bacteria = **bacteriostatic**

Spectrum of effect:

- Sulphonamides are broad spectrum → both gram+ and gram-, as well as nocardia (similar to TBC)

Pharmacokinetics:

- **Absorption:**
  - P.o. → well absorbed (except ***sulfasalazine*** → thus used for chronic inflammatory bowel disease)
  - i.v. sulfonamides are usually reserved for patients who are unable to take p.o.
  - They are usually not used topically (but some are used for burns associated sepsis – ***silver sulfadiazine***)
- **Distribution:**
  - Distribute well throughout the body, into body fluids and ***well into CSF*** → can be
  - Can pass through placental barrier
- **Metabolism:**
  - Metabolized in liver
- **Excretion:**
  - Eliminated by kidney

Mechanism of resistance:

- Only organisms which synthesize their folate de novo are sensitive to sulfonamides
  - Thus, if patient's diet is high in folic acid → resistance
- Also, increased efflux pumps

Side effects:

1 **Crystalluria:**
  - Nephrotoxicity may develop as result of crystalluria

2 **Hypersensitivity:**
  - Such as rashes, angioedema, Stevens-Johnson syndrome (rather common)
  - Occurs in long term administration

3 **Hematopoietic disturbances:**
  - Hemolytic anemia is encountered in patients w. glucose-6-phosphate dehydrogenase deficiency

4 **Kernicterus:**
  - In newborns, sulfa drugs displace bilirubin from albumin → bilirubin into CNS

Contraindication:

- Newborns, infants, pregnancy

Sulfonamides – Classification:					
Antibacterial drugs:	**Anti-diabetic:**	**Diuretics**	**Anticonvulsants**	**Dermatologic drugs:**	**Other**
• ***Sulfadiazine***	• *Tolbutamine*	• *Indapamide*	• *Acetazolamide*	• *Silver Sulfadiazine*	• *Sotalol*
• ***Sulfasalazine***	• *Glipizine*	• *Metipramide*			
• ***Sulfamethoxazole***		• *Furosemide*			

❖ Bactericidal action is found in:
  ➢ Cell wall synthesis inhibitors
  ➢ Inhibitors of nucleic acid synthesis
  ➢ Also, aminoglycosides (protein synthesis inhibitors)
    ▪ (→ because they change the proteins necessary for cell wall synthesis)

11. Quinolones (23)

❖ Quinolones are inhibitors of DNA synthesis → **bactericidal** drugs
❖ They have a broad spectrum
❖ **Concentration dependent** (PEAK)
  ➢ Their effect depends on the ***peak concentration*** (the maximum concentration – Cmax)
    ▪ **Aminoglycosides** + **fluoroquinolones** (only ones!)
  ➢ = Large dose 1x daily
❖ They have **post-antibiotic effect** (1-2 h) → because they penetrate cells
❖ Contain 4 generation of drugs

Classification

Quinolones – (non-fluorinated) → 1st generation

- The first generation is **obsolete**, we don't use it anymore
- The first generation did not contain fluorine in the molecule
  – Their **bioavailability and distribution are poor**
- **Their spectrum is very narrow**
- **Low antimicrobial activity**
- They were eliminated quite fast and unchanged by urine
  – This was their benefit – the reason why they were used for UTIs

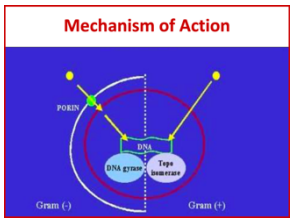
Fluoroquinolones → (2nd, 3rd, 4th generation)

- By adding fluorine to quinolones increases their effect and enhances their pharmacokinetics
- **Higher antimicrobial activity** and **bactericidal effects**
  – Able to penetrate cells, so it can go into cells (e.g., macrophages)
- **↑ gyrase affinity** (enzyme involved in replication of DNA)
- They can reach **intracellular** pathogens, too
  – So, even **atypical bacteria** are affected
  – They reason why they have **long post-antibiotic effect**
  – Because they penetrate into cells
    ➢ Even the concentration in plasma is decreased – they are still present in the area where they need to work
- **Broader spectrum**

Quinolones – Generations:

Generation:	Drug names:	Spectrum:
1st	• *Nalidixic acid*	• G- • Not pseudomonas sp.
2nd	• ***Norfloxacin*** • ***Ciprofloxacin*** • ***Ofloxacin***	• G- (pseudomonas species) • G+ (S. aureus) • Some atypical bacterias
3rd	• ***Levofloxacin*** • ***Moxifloxacin*** • ***Pefloxacin***	• Same as 2nd generation - But with extended G+ and atypical bacterial
4th	• ***Gemifloxacin***	• Same as 3rd generation - With broad anaerobic activity

- Fluroquinolones have better pharmacokinetics
  – So, they also have systemic effect – can be used for sepsis
  – They are also used for respiratory infections and diarrhea
  – 3rd and 4th generation can be used for tuberculosis as 3rd-line treatment
- Remember that most of them are available in peroral from – because they have very good bioavailability after peroral administration
- Their intravenous forms are reserved for severe systemic infections
  – Especially in sepsis



Mechanism of action

- ❖ Fluoroquinolones block both enzymes, gyrases (topoisomerase II) as well as topoisomerase IV
  - ➢ Result is that the replication process will be inhibited
  - ➢ By inhibiting topoisomerase 4 and DNA gyrase, the replication process will be blocked

- **1. Inhibition of bacterial DNA Gyrase (Topoisomerase II)**
- **2. Inhibition of bacterial Topoisomerase IV**
  - – **They prevent bacterial DNA from unwinding and duplicating**
  - – **Inhibiting DNA synthesis, replication (to RNA) and transcription** → Rapid cell death

Resistance of fluoroquinolones

In gram negatives

- ❖ As for gram negatives, fluoroquinolones must cross the cell wall in the bacteria, so, porins are necessary
  - ➢ The resistance of **gram negatives** is mostly based on **unavailability of these porins**
  - ➢ (Changed molecule)

In gram negatives and positives

- ❖ Associated with **increased production of efflux pumps**

Pharmacokinetics

- Absorption

- – Significantly decreased absorption↓ with Al+, Mg+, Ca+, Fe+, Zn+
  - ➢ Chelate formation like in tetracyclines
  - ➢ Prevent foods and drugs containing cations – also antacids (they contain these cations!)
- Longer half-life in newer agent - 1 x or 2 x daily

- Distribution

- ➢ Highest concentration in (con > serum):
  - ▪ Prostate, stool, bile, lung, neutrophils, macrophages, kidneys!
- ➢ Lower concentration in (con < serum):
  - ▪ Prostatic tissue fluid, bone, CSF

- Elimination

- Eliminated by kidneys – !! renal function = ***They are good for UTIs***

- Drug interactions

- Fluoroquinolones inhibit cytochrome 450 (like macrolides)
  - – So. Drugs metabolized by cytochrome 450 will have longer half-life
  - – Warfarin, ranitidine, cyclosporine, caffeine, opioids, rifampicin, glibenclamide

Therapeutic Use

• ***Urinary tract infection***	• Bone, joint Infections (G-)
• ***Skin, Soft Tissue Infections***	• Infectious diarrhea – (traveler's diarrhea)
• ***Urethral, Cervical gonococcal infections***	• Typhoid fever, salmonellosis, shigellosis
• ***Prostatitis***	• Nosocomial pneumonia, cystic fibrosis
• ***Sexual, Chlamydia, gonococcal infections***	• Acute sinusitis, otitis

Quinolones - adverse effects

• **1. GIT** → Nausea, vomiting	• **6. Photosensitivity** - (Similar to TTC)
• **2. CNS** → Headache, dizziness, confusion, insomnia, seizure (rare)	**7. Liver function**
• **3. Cardiovascular** → Torsades de pointes (rare) - arrhythmias	• **8. Blood glucose disturbances in DM patients**
• **4. Musculoskeletal** – Rupture of tendon (rare) arthro-pathogenic effect – This is why most of them are **contraindicated in children**	• **9. Dismicrobia** • - Enterocolitis
• **5. Neurologic** → Polyneuropathy (rare)	• **10. Resistance**

→ Fluoroquinolones are contraindicated in pregnancy due to risk of teratogenicity

12. Antituberculotics (10)

- Tuberculosis is an infectious disease caused by one of several mycobacterial species
  - ***Mycobacterium tuberculosis, M. africanum, M. bovis, M. canetti***
- The cell wall of mycobacteria is thicker compared to other gram+ or gram- bacteria
  - The cell wall of mycobacteria, contains mycolic acid → this where they get their name from
  - The mycolic acid is one of the main targets of the many antituberculotic drugs
- Tuberculosis usually affects the lungs (pulmonary form), but can also affect other organs (extrapulmonary form)
- 90% of tuberculosis infections are latent (= no symptoms), but 10% of latent infections progress to active disease
  - Classic symptoms of TBS are fever, night sweats, persistent cough, bloody phlegm, chest pain…
- Tuberculosis is the deadliest infection worldwide
  - In the last year it was covid-19 – but it is expected that tuberculosis will regain its position at #1

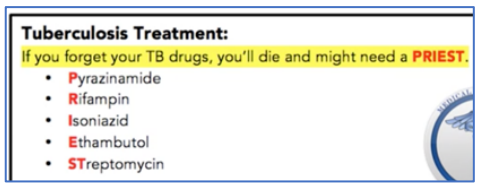
General principles of pharmacological treatment of tuberculosis

- The goal of the treatment is to cure the patient and prevent the development of resistance and transmission to other people
- **General principles of drug treatment of pulmonary TB:**
  - Single drug treatment is associated with higher relapse rate
    - So, usually a **combination of 4 antiTBC drugs** are used
  - In case of failing regimen: change of drug combination – **NEVER ADD SINGLE DRUG**
    - (it's better to change the combination of antiTBC)
- The treatment regimen, in case of tuberculosis caused by strains susceptible to antituberculotics, can be divided into 2 main phases:
  - The 1st phase is called **initial phase**
    - Here the patient is taking the combination of 1st line antiTBCs – ***rifampicin***, ***isoniazid***, ***pyrazinamide*** and ***ethambutol*** for 2 months
    - The goal of this phase is rapid reduction of number of bacilli and also reduction of developing of resistance
  - The 2nd phase is called **continuation phase**
    - Here the patient is taking isoniazid and rifampicin daily, or twice weekly for 4 more months
    - The goal of this phase is to stop the replication of residual mycobacteria
- The duration of treatment regimen for TBC susceptible to antiTBCs is 6 months
- And duration of treatment regimen for multidrug-resistant TB and extensive-resistant TB is 2 years

Resistance

- What is alarming is the increasing number of resistant forms of tuberculosis
- Normal TBC infection – susceptible to all 1st- and 2nd-line antiTBC drugs (curation rate = 90%)
- We recognize **3 main forms** of resistant TBC:
  - **Multi-drug-resistant** TBC (MDR-TB)
    - Here the mycobacterial strain is resistant to the 1st line isoniazid and rifampicin
    - The curation rate is 50%
  - **Extensively drug-resistant** TBC (XDR-TB)
    - Here the mycobacterial strain is resistant to the 1st line isoniazid, rifampicin and to 2nd line fluoroquinolones and injectable drugs (e.g., amikacin or kanamycin)
    - The curation rate is only 10%
  - And the recently reported **total drug-resistant** TBC (TDR-TB)
    - These mycobacterial strains are resistant to all available 1st-line and 2nd line antiTBC drugs
    - Including the new generation drugs

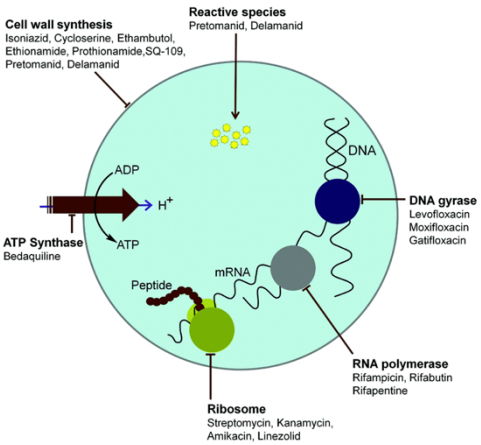
Antituberculotic drugs



- Antituberculotics are divided into 2 groups:
- **1st line antituberculotics**
  - **Isoniazid** (H) (***Bactericidal activity***) **(S)**
  - **Rifampicin** (R) (***Bactericidal activity***) **(S)**
  - **Ethambutol** (E) (***Bacteriostatic activity***)
  - **Pyrazinamide** (***Bactericidal activity***) **(S)**
    - They also have **sterilization effect** – it means that these drugs effectively kill also the bacterial persisters
    - The persisters are mycobacterium tuberculosis cells exhibiting resistance
- **Streptomycin**
  - *Streptomycin is somewhere between 1st and 2nd line antiTBCs
- **2nd line antituberculotics**
  - These drugs are usually in the treatment of drug-resistant tuberculosis, or are given to patients in case of intolerance of 1st line antituberculotics
  - **Fluoroquinolones** (levofloxacin, moxifloxacin)
  - **Injectable aminoglycosides** (kanamycin, capreomycin, amikacin)
  - **Cycloserine**
  - **Ethionamide**
- **New generation drugs**:
  - **Delamanid** and **Bedaquiline**
  - These 2 drugs are reserved only for the treatment of multidrug-resistant TB (MDR-TB) and extensive drug-resistant TB (XDR-TB)
  - Mycobacterium tuberculosis strains resistant to these drugs have also been documented
    - Bacteria resistant to these drugs are **total drug-resistant**
    - Therefore, it is still necessary to search for new antiTBC drugs

Overview of antituberculotics and their mechanism of action

- **Cell wall synthesis is affected by:**
  - Isoniazid
  - Ethambutol
  - Ethionamide
  - Cycloserine
  - Delamanid
- **Synthesis of nucleic acids is affected by:**
  - Fluoroquinolones (block DNA gyrase)
  - Rifampicin (block RNA polymerase)
- **Protein synthesis is affected by:**
  - Aminoglycosides (Amikacin, Kanamycin, Capreomycin)
  - Streptomycin
- **ATP synthesis inhibition:**
  - Bedaquiline



13. Antimycotics (7)

- Antimycotics or *antifungals* are used to treat fungal infections.
- Classification of mycosis:
  - Mycosis can be ***superficial***, like on the skin or hair
    - Treatment: local or systemic antimycotics
  - It can also develop into ***systemic*** infections (especially in immunodeficient patients)
    - Treatment: aggressive therapy by systemic antimycotics (Amphotericin B is 1st line!)
- Antifungals are either:
  - Fungistatic → meaning that they inhibit fungal growth
  - Fungicidal → meaning that they kill the fungi
- The cell wall of fungi is different compared to, gram+, gram- and mycobacteria
  - The cell wall of fungi, contains ***beta glucans*** and their cytoplasmic membrane contains ***ergosterol***
  - These 2 components are the main targets of many antimycotics

Antifungal drugs

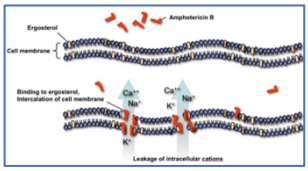
- Ergosterol inhibitors:

1. Polyenes

- **Mechanism of action:**
  - Directly bind to ***ergosterols*** in cytoplasmic membrane of fungi
    - After the binding to ergosterol, it creates pores in the membrane, through which intracellular cations are leaked from the fungi cell to the environment = fungicidal action

a. Amphotericin B

- ***Most effective***, ***widest spectrum of activity*** and ***lowest incidence of resistance***
- Indication: **The first-line treatment for severe systemic mycoses**
  - Effective against candidosis, aspergillosis and cryptococcus
- **Adverse effects: Acute** (nausea, vomiting, fever), **Chronic** (Nephrotoxicity)
- Administered i.v.



Local polyene antifungals:

b. Nystatin

- Local polyene antibiotic with fungistatic and fungicidal action
- ***ONLY administered topically***, too toxic for parenteral administration
- Nystatin is indicated for the treatment of superficial candida infections
  - Including diaper rash, esophageal candidosis and vaginal yeast infections

2. Azoles

- **Mechanism of action:**
  - Inhibition of ergosterol synthesis by blocking the ***14-α-demethylase*** enzyme
    - This enzyme is crucial for the synthesis of ergosterols – its function is to convert lanosterol to ergosterol in the synthetic pathway of ergosterol
  - However, they also inhibit human cytochrome P450 enzymes
    - → Due to this, azoles are mainly used topically (to treat superficial mycoses)
- Azoles are divided into:
  - The older imidazoles
    - ***Ketoconazole***, ***clotrimazole***, ***miconazole***
  - And newer group of Triazoles
    - ***Itraconazole***, ***fluconazole***, ***voriconazole***
  - The only difference between these 2 groups is that imidazoles contain an imidazole ring, while triazoles contain triazoles rings

Classification of azoles antifungals (IMIDAZOLES remember of COMET-K):
Clotrimazole
Oxiconazole
Miconazole
Econazole
Tioconazole
Ketoconazole

Classification of azoles antifungals (TRIAZOLES remember of FIT VIP):
Fluconazole
Itraconazole
Terconazole
Voriconazole
Isavuconazole
Posaconazole

Local azoles

- Azole creams are used to treat ***dermatomycoses*** → a red, itchy, scaly, circular rash on the feet and hands
- Azoles can also be used to treat ***tinea versicolor*** (hypo- or hyperpigmentation in patches of skin)
- Topical azoles are also used to treat ***yeast infections*** → such as oral or vaginal candidiasis
- Side effects:
  - Topical use of azoles is generally considered to be safe, since absorption through skin in minimal
  - Most common side effect is skin irritation

Systemic azoles

- Certain azoles can be taken perorally or through i.v. for treatment of systemic mycosis
  - Or orally/vaginally for candidiasis
- But due to their inhibitory effect on cytochrome P450, they are usually 2nd or 3rd line therapy after other medications (→ amphotericin B = 1st line!)
- The azole with the narrowest spectrum of activity is ***ketoconazole*** → only used for candidiasis
- ***Fluconazole*** is effective against candida species as well as cryptococcus neoformans
  - = given as prophylaxis medication for prevention of cryptococcal meningitis in people with AIDS
- Wider spectrum azoles like ***itraconazole*** and ***voriconazole*** can also treat previous fungi but they are also effective against histoplasma and coccidiosis species
- Broadest spectrum azole → ***isavuconazole*** can be used to prevent a variety of fungal in the immunocompromised
- Side effects:
  - Hepatoxicity + inhibition of CYP450 (accumulation of drugs like warfarin and phenytoin)
  - Ketoconazole also inhibits synthesis of androgens → gynecomastia + infertility

3. Allylamines

- Allylamines are lipophilic, keratinophilic and chemically synthesized
- **Mechanism of action**
  - Inhibition of ***squalene epoxidase*** (an enzyme necessary for synthesis of ergosterol)

Terbinafine, Naftifine

- Effective against ***dermatophytes***, for example Microsporum, trichophyton and Epidermophyton species
- **Pharmacokinetics:**
  - Topically administration, (terbinafine is also give perorally for systemic absorption)

B-glucan synthase inhibitors:

Echinocandins

- Fungal cell wall is made up of different carbohydrates, for example beta-glucans
  - Beta glucans are made by the enzyme ***beta-1,3-glucan synthase***
  - This enzyme is not found in human cells = good target for antifungal medications
- Echinocandins are drugs which inhibit ***beta-1,3-glucan synthase***
  - Destroys fungal wall → fungicidal action
- Echinocandins are only available i.v., since they are not absorbed through GI tract
- Drugs: ***Anidulafungin***, ***micafungin*** and ***Caspofungin***
  - They are only effective against fungal species that have ***beta-1,3-glucan synthase***
  - But if they have this enzyme, it's extremely rare for fungi to have resistance for these medications
  - Due to this, echinocandins are often used to treat fungal infections which are resistant to the more common antifungal medications – like amphotericin B and the azoles
- Indications:
  - Candidiasis:
    - Mucocutaneous candidiasis, which affect skin, nails and oral mucosa
    - Disseminated candidiasis, when the infection spreads to organs
  - Invasive aspergillosis

Antimetabolites (inhibitor of RNA and DNA)

Flucytosine

- Flucytosine is a systemic antifungal drug with a narrow spectrum of action
- It is the only representative of antimetabolites
- **Mechanism of action:**
  - Inhibition of nuclei acids synthesis
    - It is actively transported into the cell and subsequently deaminated to its active substance, which then inhibits the synthesis of RNA and DNA
- **Never used as monotherapy!**
  - Due to rapid development of resistance
  - Flucytosine is used in combination therapy with amphotericin B in patients with cryptococcal meningitis
  - Also, it is used in combination therapy with itraconazole, mainly in patients with chromoblastomycosis
- **Side effects:**
  - Granulocytopenia, vomiting

Mitotic inhibitor

Griseofulvin

- **Mechanism of action:**
  - A drug which binds to tubulin and interferes with microtubule function
    - Thus, **inhibiting mitosis**
- **Pharmacokinetics:**
  - Perorally
  - Accumulation in the new formed skin
- **Adverse effects:**
  - Allergies, hepatitis
  - Drug interactions with warfarin, phenobarbital
- **Antimicrobial spectrum:**
  - Their antimicrobial spectrum is narrow
    - Only for dermatophytes (Epidermophyton, Trichophyton)
  - It is ineffective against candida species and aspergillus species
  - Also, it is not used in the treatment of systemic mycoses

14. Antihelmintics (35)

Anti-Helminthics – General:

- *Group of drugs that* treat infections caused by parasitic worms (helminths)
  - They do this by either stunning or killing them, without causing significant damage to the host.
- Sometimes called **Vermifuges** (those that stun) or **Vermicides** (those that kill)
- Pills containing antihelmintics are used in mass deworming campaigns of school-aged children in many developing countries
- Almost 350 species of helminths have been found in humans
  - Humans usually become infected by eating raw or incompletely cooked fish or meat containing larvae

3 major group of helminths which infect human are:

1. Cestodes (tapeworm):

- Can grow to huge lengths (up to 7 meters)
- species: Taenia solium (pork), Taenia saginata (beef)
  - transmitted via undercooked pork and beef
- They live in the intestine and where they grow and lay eggs
- They are usually asymptomatic but can cause:
  - GI symptoms, cysticercosis: if newly hatch worms burrow into different parts of the body, like eyes → can cause blindness and also brain → can lead to seizures and death

2. Trematodes (liver fluke):

- They are obtained by fish
- Goes into intestinal wall → to the liver + bile duct (where they grow and feed on bile)
- Symptoms:
  - Liver + pulmonary + intestinal + blood infections

3. Nematodes (roundworm):

- Mostly obtained by oral ingesting of nematode eggs → hatch in the small intestine and cause GIT symptoms → Bore through the gut into the blood stream → travel to the lung + up the trachea and are coughed → than they are swallowed again → mature into adult form in the intestine
  - There they will lead to infection (severe infection can lead to obstruction of intestine)

<table>
<tr><th colspan="4">Anthelmintics – Drugs:</th></tr>
<tr><th colspan="2">Benzimidazoles</th><th colspan="2">Pyrantel pamoate</th></tr>
<tr>
<td>Mechanism of action:
• Inhibit formation of microtubules which forms the cytoskeleton in the worms
Indication:
• Broad spectrum agents
• 1st line therapy for neurocysticercosis
Drugs:
• Albendazole. mebendazole</td>
<td>Side effects:
• Usually rare
• GIT disturbances, nausea + vomiting, liver toxicity
Contraindication:
• Mebendazole
- Pregnancy or child (<2 y.o.)</td>
<td>Mechanism of action
• Stimulates Nm receptors → uncontrollable muscle contractions → This causes the worm to lose grip on intestinal wall → pass out of the system → paralysis + expulsion of worms
Indications:
• Not absorbed → only affect roundworms in the GI tract</td>
<td>Side effect:
• Usually mild
• Nausea + vomiting, headache, rashes</td>
</tr>
<tr><th colspan="2">Ivermectin:</th><th colspan="2">Praziquantel</th></tr>
<tr>
<td>Mechanism of action:
• Paralysis parasite by:
- Stimulate GABA NTs → ↑ Cl^- → cell hyperpolarization → paralysis of worms</td>
<td>Side effects:
• Fever, GIT disturbances, allergy</td>
<td>Mechanism of action:
• It disrupts Ca permeability in the parasite → influx of ions → fast + prolonged contraction → paralysis → death of worm
Indications:
• 1st line therapy for most tapeworms + flukes</td>
<td>Side effects:
• Minimal
• Poor coordination, GIT disturbances, allergy
<u>Safe for pregnant woman</u></td>
</tr>
</table>

15. Antiviral chemotherapy (32)

Intro – Viruses:

- = ***Obligate intracellular parasite***
- Consist of nucleic acid core (DNA or RNA) in protein coat (Capsid)
- Some of them have lipoprotein envelope (not cell wall or membrane)
- They use host metabolic enzymes + host ribosome for protein synthesis

Antiviral activities – Ways to fight viral infection:

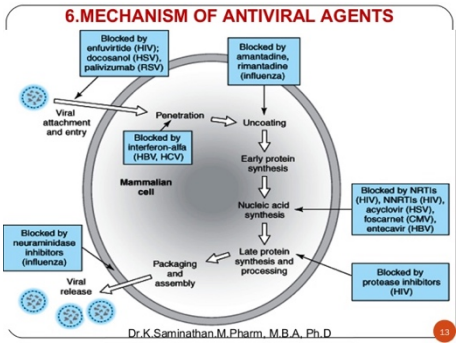
1 **Immune system**
- Competent immune system is the best response to viral infections
  - Immune cells are able to effectively suppress viral replication
- This is the reason why the most sensitive patients are the immunocompromised (cancer patients…)

2 **Interferons**
- From all mediators produced by the immune cells, interferons play a key role and are standardly utilized in the treatment of viral disorders
  - They can be endogenous or synthetic analogs

3 **Vaccines (prophylaxis)**
- Most antiviral vaccines work by inducing antibodies against specific glycoproteins, which are located on the surface of enveloped viruses – or against capsid proteins of non-enveloped viruses

4 **Antiviral drugs - Chemotherapy**

Replication of viruses – process:



1 **Attachment** of the virus to receptors on the host cell surface
2 **Entry** of the virus through the host cell membrane into cytoplasm
3 **Uncoating** of viral nucleic acid
4 Then, the process of **replication** is initiated:
- A. Synthesis of **early regulatory proteins**
- B. New viral **RNA or DNA**,
- C. synthesis of **late structural proteins**

5 **Assembly** (maturation) of viral particles
6 Lastly, newly synthesized functional viral particles are **released** from the cell

Antiviral drugs – Classification according to mechanism of action

→ We can classify anti-viral agent according to by how they interfere with the life cycle of the virus

1. **Inhibitors of fusion** or **release of virus from a host cell**
   - *Amantadine*, *rimantadine*
2. **Analogues of nucleosides and nucleotides (purines and pyrimidines)**
   - Their main role is to act as false precursor
   - ***Against → Herpes, CMV, HIV, RSV***
3. **Non-nucleoside inhibitors of reverse transcriptase (RT)**
   - ***Against → HIV***
4. **Direct inhibitors of DNA polymerase and reverse transcriptase (RT)**
   - Foscarnet
5. **Inhibitors of protease**
   - Proteases are groups of enzymes which are strongly associated with the process of maturation (assemble of viral particles into the newly synthesized, functional virus)
   - ***Against → HIV, HCV***
6. **Interferon alpha**
   - Hepatitis B and C, herpes

Groups 1, 2 and 3 all target the key enzyme which is responsible for the correct synthesis of viral nucleic acid

- Because viruses are intracellular parasites, existing inside the cell, antiviral against can potentially kill the host cell
  - So, treatment by antiviral agents is associated with relatively wide spectrum of side effects
- Good antiviral agent = agent which easily penetrates inside cells and has good absorption and distribution
  - Exception are agents from group 1 (interfering with fusion and release of virus from host cell)
    - These agents are regarded as the safest → they have the least number of side effects
    - Due their mechanism being outside of the host cell

Antiviral drugs – Clinical classification of drugs:

1 **Drugs against Herpes viruses**
- HSV, VZV → ***acyclovir, valacyclovir***
- CMV → ***ganciclovir, valganciclovir, Foscarnet cidofovir***

2 **Drugs against influenza viruses:**
- *Amantadine, rimantadine, oseltamivir, zanamivir*

3 **Drugs against Hepatitis B and C viruses:**
- HVC → *Adefovir dipivoxil, entecavir, lamivudine, telbivudine, tenofovir, INF alpha*
- HVB → *ribavirin, INF alpha, Boceprevir, Telaprevir*

4 **Antiretroviral drugs:**
- NRTI, NNRTI, PI, Entry/fusion inhibitors, integrase inhibitors

1. Drugs Against Herpes viruses

Herpes simplex (HSV), Varicella zoster (VZV):

A. *Acyclovir:*
- First drug for herpes

Mechanism of action:
- ↓ thymidine kinase → ⊖ DNA polymerase
- Competitive inhibition of deoxy-GTP for viral DNA polymerase

Pharmacokinetics:
- Oral, iv, topically
- Oral bioavailability =15-20% → ↓ w. increasing dose
- Unaffected by food
- Bioavailability ↑ 3-5x (about 70%) following administration
- Distributed widely in body fluids including CSF
- Percutaneous absorption in low

Indication:
- Acute herpes simplex infection, Genital herpes, systemic acyclovir prophylaxis…

Side effect:
- Topical → mucosal irritation + transient burning to genital lesions
- Oral → nausea + diarrhea + rash + headache + renal insufficiency, neurotoxicity
- I.v. → Renal insufficiency, CNS side effects

B. *Valacyclovir:*
- Derivative of *acyclovir* → prodrug
- Rapid conversion after oral adm (enzymes in liver + intestine)

Clinical use:
- Genital herpes, herpes zoster

Side effects:
- Thrombotic microangiopathy!

Cytomegaloviruses (CMV):

A. *Ganciclovir:* (i.v.)
- First dug for CMV
- Same mode of action as *acyclovir*
- Effective against **all herpes viruses** → with **additional CMV**!

Side effect:
- Myelosuppression, CNS toxicity

B. *Valganciclovir*:
- Derivative of *ganciclovir* (enzymes in liver + intestine)
- rapid conversion after oral adm → *ganciclovir*

Side effect:
- Myelosuppression

C. *Foscarnet* (i.v.):
- DNA chain inhibitor of phosphorylation
- Used to treat resistant HSV + *ganciclovir* resistant viruses
- Highly nephrotoxic

D. *Cidofovir* (i.v):
- Direct blocker of viral polymerase → ⊖ DNA replication
- Broad range of virus activity
- Used in CMV retinitis in HIV patients

2. Drugs Influenza viruses

Neuraminidase inhibitors (influenza A + B):

General:
- Interfere w. release of influenza virus from infected to new host cell
- Competitively inhibits neuraminidase activity → interfere w. virion adherence on the host cell surface
- Effective against **influenza A + B**

A. *Oseltamivir* (p.o.):
- Prodrug (activated by liver enzymes)
- Widely distributed
- Side effect → abdominal pain, headache, fatigue, rashes
- There has been ↑ resistance to *oseltamivir*

B. *Zanamivir* (inh.):
- 10-20% reaches lungs, rest stays in oropharynx
- Side effect → cough, bronchospasm, ↓ pulmonary function

M2 ion channel inhibitors (influenza A):

General:
- **Block M2 ion channels** if virus → ⊖ **uncoating** of viral RNA within host cells → **prevent replication**
- Activity against → **Influenza A** only
- There has been ↑ resistance against these drugs

Drugs:
- *Amantadine + Rimantadine*

3. Drugs against Hepatitis viruses		
HCV:	**HBV**	**Both:**
• Aim is to kill the virus • Patient will be negative 6 months after treatment ***Ribavirin***: • First choice HCV drug • ⊖ RNA dependent RNA polymerase • Combined w. INF alpha for treatment • Side effects → depression, fatigue, rashes…	• Long-term suppression of virus replication • Produces slow progression cirrhotic changes + prevent complications **Drugs:** • *Adefovir, Tenvofir* - Causes premature termination of DNA transcription • *Entecavir, Lamivudine, Telbivudine* - ⊖ Reverse transcriptase	• Improvement of histological structure + ↓ risk of hepatocellular cancer + ↓ cirrhotic changes • Delay the need of liver transplantation **Drug:** • *Interferon alpha*

- Vaccines are available against. → HBV + HAV

3. Drug against Hepatitis viruses – *Interferon alpha*

❖ Endogenous cytokine with complex antiviral, immunomodulatory and antiproliferative activity
  ➢ ⊖ viral protein synthesis
  ➢ ⊕ breakdown of viral RNA
  ➢ Bind to membrane receptors intracellularly
    ▪ ⊖ viral penetration and uncoating
❖ Parenteral administration (s.c.)
❖ Indication → Monotherapy in Acute HCV + chronic active HBV
  ➢ Used as combination treatment in chronic HCV
❖ Side effect → flu-like syndrome, autoantibodies…
❖ Contraindication → hepatic failure, autoimmune disease, history of arrythmia

RT = Reverse transcriptase

4. Antiretroviral drugs:

❖ They have different mechanism of action, usually used in combination

4. Antiretroviral drugs:				
NRTI	**NNRTI**	**Protease inhibitors**	**Entry inhibitors**	**Integrase inhibitors:**
• *Nucleoside RT inhibitors* **Mechanism of action:** • Competitive blocker of nucleoside binding to RT → termination of DNA chain → ⊖ RNA to DNA transcription **Side effect:** • Neurotoxicity, myelosuppression **Drugs:** • *Lamivudine, Abacavir …*	• *Non-nucleotide RT inhibitors* **Mechanism of action:** • Noncompetitive inhibitor of RT • So, it binds directly to RT → same result as NRTI **Side effect:** • Neurologic symptoms, hepatotoxicity, allergy **Drugs:** • *Nevirapine, delaviridine…*	**Mechanism of action:** • ⊖ viral HIV-1 protease → ⊖ functional mRNA → production of immature virions **Side effect:** • Hyperbilirubinemia, nephrolithiasis **Drugs:** • *Atazanavir, Saquinavir …*	**Mechanism of action:** • Competitive bind to viral gp41 protein → ⊖ fusion with the host cell **Side effect:** • Hypersensitivity reaction **Drugs:** • *Enfuvirtide, Maraviroc*	**Mechanism of action:** • ⊖ viral integrase → block viral DNA integration into host DNA → ⊖ viral replication **Side effect:** • ↑ creatine kinase **Drugs:** • *Raltegravir*

SARS-CoV-2????? (lecture 10 neðst)

16. Antimalarial drugs (34)

Intro – Malaria:

- Malaria is an infection than can be caused by plasmodium species (e.g., p. falciparum, p. vivax)
- Plasmodium is a single cell parasite which are spread by mosquitos

Pathophysiology:

- Once the plasmodium gets into the blood stream via mosquito bite, it infects liver cells and red blood cells, which causes a variety of symptoms
- At the time when the plasmodium gets into the blood via mosquito bite, it is in a stage of development – called ***sporozoite***

Hepatic phase

- Mosquito injects ***sporozoite*** into the blood stream → they travel into the liver and invade hepatocytes where they start to replicate
  - By p. falciparum, they will mature into ***merozoites*** (kill the hepatocyte)
  - In contrast, p. vivax sporozoites enter into a dormant hepatic phase where they are called ***hypnozoites*** (they can remain in this dormant phase for months to years until they wake up and mature into merozoites

Erythrocytic phase

- ***Merozoites*** are then released into blood stream where they go into erythrocytes
  - Once inside, plasmodium feeds on hemoglobin → it uses globin to fuel their growth
    - However, the *heme is toxic to them* (so it is converted to hemozoin)
  - Then they replicate in the erythrocyte which causes the erythrocyte to burst and all the merozoites go back into the blood stream
- Then they can either enter new erythrocytes or convert into **gametocytes** (stay in the erythrocytes) which can be picked up by mosquito
- Gametocytes will fuse to form **zygote** in mosquito → zygote will grow and, in the end, release many **sporozoites** → repeated circle

Symptoms:

- Usually appear 7-9 days after being affected
- ***High fever*** (most common)
- ***Hemolytic anemia***
  - Because red blood cells are destroyed when merozoites are released
  - ***Hemolytic anemia*** causes → fatigue, headache, jaundice

Antimalaria drug – Side effects:

- Hemolytic anemia, CNS disturbances, GIT disturbances

Clinical features:

- Tremor, fever (40-41°C), ↑ HR, sweating

Antimalarial drugs:	
Quinoline derivatives	***Primaquine***

Chloroquine + mefloquine
• They work by entering the plasmodium and inhibit the conversion of heme to hemozoin
  ➢ Heme is toxic to plasmodium → leads to their death
• Chloroquine is one of the most commonly used antimalarial medication
• It is effective against all species of plasmodium
  ➢ However, its widespread use has cause plasmodium falciparum to develop resistance against it via efflux pumps
  ➢ In this case, mefloquine is used
	• Drug that is different from ***chloroquine*** in that it has less effect against **sporozoites** in blood but much better effect against **hypnozoites** + **Gametocytes**
	• Usually always given long with ***chloroquine***

13. Drug poisoning

1. **General principles of drug poisoning treatment (16)**
2. **Treatment of drug poisoning - decontamination (30)**
3. **Treatment of drug poisoning - Elimination (11)**

1. General principles of drug poisoning treatment (16)

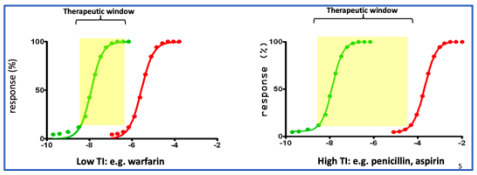
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- We can also classify intoxication:

According to route of administration	According to circumstances
• Inhalation • Peroral • Percutaneous • Parenteral	• Accidental • Accompanied by a drug abuse • Suicidal • Iatrogenic

Therapeutic index

- = The ratio between the dose **producing unwanted** (**toxic**) effects and the dose leading to **desired** (**therapeutic**) effects:
  - **= LD_{50}/ED_{50}** (LD = lethal dose, ED = effective dose)



Approach to the poisoned patient

- Any attempts to identify the poison **should not delay care**
- Initial management of the poisoned patient begins with the **ABCD**
  - **A** – **Airway**
  - **B** – **Breathing**
  - **C** – **Circulation**
  - **D** – **Disability**
    - → **AVPU** (= simplified form of GCS)
      - A = Awake, V = responsive to verbal stimulation, P = response to pain stimulation, U = unresponsive
    - → **Glasgow Coma Scale**
      - Eye opening response, verbal stimulation and motor response – 15 points = best response
  - **DEFG** (**Don't Ever Forget the Glucose**) – check the glucose level (hypoglycemic coma)

SAMPLE history
Signs and symptoms
Allergies
Medication
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Last oral intake
Events leading up to present illness / injury

- Once these are stable:
  - Begin considering how to minimize the poison's bioavailability
  - Check the history of the patient
  - Check physical signs (vital signs)
- **Clinical assessment and therapy – should proceed in simultaneously**

Goals of treatment

- To **decrease** the **poison absorption**
  - → If toxin is still present on skin or eye – remove it
  - → **Induce vomiting** (if patient is conscious)
  - → Perform **gastric lavage** (possible if patient is unconscious)
  - → Use of **activated charcoal**
  - → Perform **whole bowel irrigation**
- To **increase** the **poison elimination**
  - → Forced diuresis (furosemide + mannitol + K+ supplementation)
  - → Modulation of pH of urine
    - (Use sodium bicarbonate in order to increase pH → elimination of weak acids)
    - (Use ammonium chloride in order to decrease pH → elimination of weak bases)
  - → Extracorporeal removal of poison (hemodialysis or hemoperfusion)
- To **neutralize the poison** (by using specific antidotes)

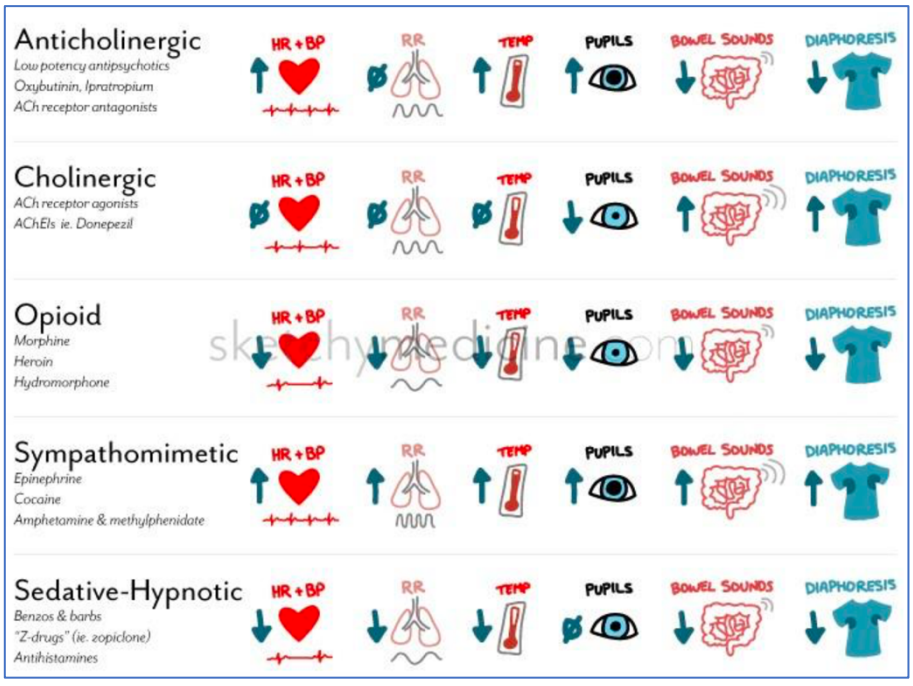
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Anticholinergics	Physostigmine	Digoxin Beta-blockers	Digibind Glucagon	Amanita phalloides	Sylmarine, Penicillin G
Inhibitors of ACHE	Atropine, pralidoxime	Heparin	Protamine, sulphate	Heavy metals	Chelators
Methemoglobin	Methylene blue	Methanol Ethylene glycol	Ethanol, fomepizole	Dabigatran	Idarucizumab
Cyanides	Hydroxocobalamin	Paracetamol	N-acetylcysteine	Rivaroxaban	Andexanet

Toxidrome (Toxicologic Syndrome) (extra info)

- It is defined as constellation of signs and symptoms associated with a specific group of toxins

We have 5 typical toxidromes

- **Anticholinergic toxidrome:**
  - Typical for antipsychotics, oxybutynin, ipratropium or antagonists of AcH receptors
  - We can observe ↑ heart rate, frequency of breathing is not affected, temperature is increased, pupils → mydriasis (dilation), contractility of GIT is decreased, and we can also observe decreased diaphoresis
- **Cholinergic toxidrome:**
  - Typical for agonists of AcH receptors and inhibitors of ACHE
  - Heart rate, frequency of breathing and temperate are not affected, why have miosis (constriction) and contractility of GIT + diaphoresis is increased
- **Opioid toxidrome:**
  - Typical for opioids, heroin, fentanyl and so on…
  - All factors are decreased (HR, resp. freq., temperature, very strong miosis, bowel sounds and diaphoresis)
- **Sympathomimetic toxidrome:**
  - Typical for epinephrine, cocaine and amphetamine
  - In contrast to opioids, all these factors are increased ((HR, resp. freq., temperature, mydriasis, bowel sounds and diaphoresis)
- **Sedative-hypnotic toxidrome:**
  - Typical for BNZs, barbs, anti-histaminics…
  - Decrease in all organs (except for pupils – no effect)



2. Treatment of drug poisoning - decontamination (30)

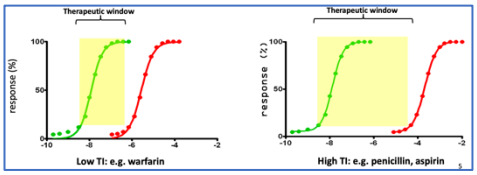
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Goals of treatment

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Cyanides	Hydroxocobalamin	Paracetamol	N-acetylcysteine	Rivaroxaban	Andexanet

To <u>decrease</u> poison absorption (How can we decrease absorption?)

a. We should **remove the toxin from surface skin or eye**

b. We can **induce vomiting/emesis** (gastric decontamination)

- **Vomiting**
  - Vomiting can be stimulated by mechanical irritation – at root of tongue
  - We can use salt water
  - Using emetics (???) (Apomorphine, emetine or syrup/solution of ipecac)
    - Using emetics is questionable and not recommended
- Inducing vomiting response is **only possible to perform in conscious patients**

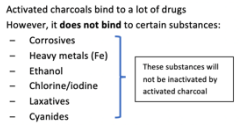
c. We can perform **gastric lavage**

- In contrast to vomiting, we can perform orogastric lavage in **unconscious patients**
- **Left lateral position delays spontaneous absorption of toxins**
- Fluid of choice: **warm water** or **saline** (200-300 ml)
  - We infuse warm water or saline and then aspirate it (repeated)
- In the last dose: **<u>activated charcoal</u>** (Carbo medicinalis, Carbo adsorbens)
- For intoxication with acids – we can neutralize acids with **MgO** (magnesium oxide)
- For intoxication with alkali – we can neutralize bases with **citric acid** (**5%**)

- **Indications** – if the drug was used:
  - Less than 1 hour on empty stomach
  - Less than 2 hours on filled stomach
  - More than 2 hours if GIT motility is slowed (typical for parasympatholytics and opioids)
- **Contraindication**
  - Intoxication with concentrated acids and bases
  - And where there is a danger of perforation
- **Complications**
  - Aspiration pneumonia
  - Administration of drug into the trachea
  - Damage of mucosa

d. We can use **<u>activated charcoal administration</u>**

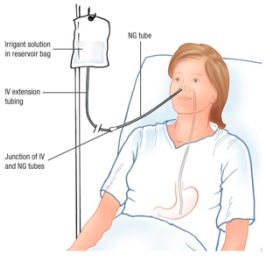
- = a **<u>universal antidote</u>**, it has a very large surface area (3000 m^2/g), and it can adsorb toxins from GIT
- Safe for adults, also for children
- Doses: Adults: **1g/kg**, 25-100g orally – Infants: 1g/kg/dose or 25-50 g orally
  - Dose may be repeated after 4-6 hours – especially for drugs with enterohepatic cycle
- Using activated charcoal should be **<u>avoided in paracetamol intoxication</u>**!
  - Because activated charcoal binds to the antidote for paracetamol intoxication, N-acetylcysteine
  - (So, don't use activated charcoal when using N-acetylcysteine)



e. We can try to **dilute toxins** – with milk/other drinks for corrosives

f. We perform **whole bowel irrigation**

- We use a solution of polyethylene-glycol (a.k.a. macrogol)
- Indications for bowel irrigation:
  - Intoxication with metals (As, Pb, Hg, Fe, Li…)
  - And for drugs in extended-release + slow-release drug forms
- Contraindications: Diarrhea, GIT bleeding/obstruction, <u>!! electrolytes</u>
- Complications – cramps and rectal irritation
- Procedure: We secure nasogastric tube to the stomach and apply a solution of macrogol



g. And finally, **endoscopic or surgical removal of non-absorbed poison**

3. Treatment of drug poisoning - Elimination (11)

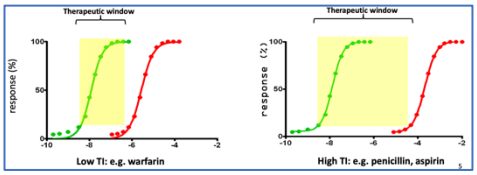
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To <u>increase</u> elimination

- How can we increase elimination? – In case the toxins have already been absorbed

- **Forced diuresis**
- We can manipulate with the pH of urine (**Alkalization/acidification of urine**)
- Finally, we can use some **extracorporeal removal of poison**
  - (Peritoneal dialysis, hemodialysis/hemoperfusion)

a. Forced diuresis

- For forced diuresis, we use **FUROSEMID** + **MANITOL** + **supplementation of K+** (all i.v.)
  - (Furosemide causes hypokalemia)
- **Contraindications:**
  - **Renal** and **CVS diseases**, and also **electrolytes disbalance**

b. pH of urine modulation

↑ Alkalization of urine (increasing pH of urine)

- We do this for **treatment of intoxication with weak acids**:
  - TCAs, phenobarbital, chlorpropamide, salicylates (aspirin)
- We use **sodium bicarbonate** (NaHCO3) – 50-100 mmol (4,2-8,4 mg) in 250-500 ml of NaCl (c = 0,45%)
  - → and we increase the pH of urine to about 7-8
- !! Hypokalemia may result

↓ Acidification or urine (decreasing pH of urine)

- Which **enhances elimination of weak bases**, e.g., amphetamines, phenytoin
- We use **ammonium chloride** (NH_4Cl) – 4g dose repeated after 2 hours
  - → and we decrease the pH of urine to about 5,5-6,5
- The disadvantage of this procedure is the risk of metabolic acidosis, encephalopathy (ammonia)

c. Extracorporeal removal of poison

- **Indications:**
  - When we have worse clinical outcome despite the conservative therapy
  - Or when we have lethal plasma concentration of poison
  - And in patients with acute renal and liver failure

We have 2 possibilities:

→ HEMODIALYSIS

- **<u>Intoxication with drugs of:</u>**
  - Low volume of distribution
  - Low protein binding
  - Low molecular weight (MW <500)
  - Water soluble
  - Diffusion of solutes across a semi-permeable membrane down a concentration gradient

→ HEMOPERFUSION

- **<u>Intoxication with:</u>**
  - High-molecular toxins
  - Toxins with strong bond to charcoal or used carrier
  - Blood is passed through a cartridge containing charcoal or other carrier (ion exchange resins)