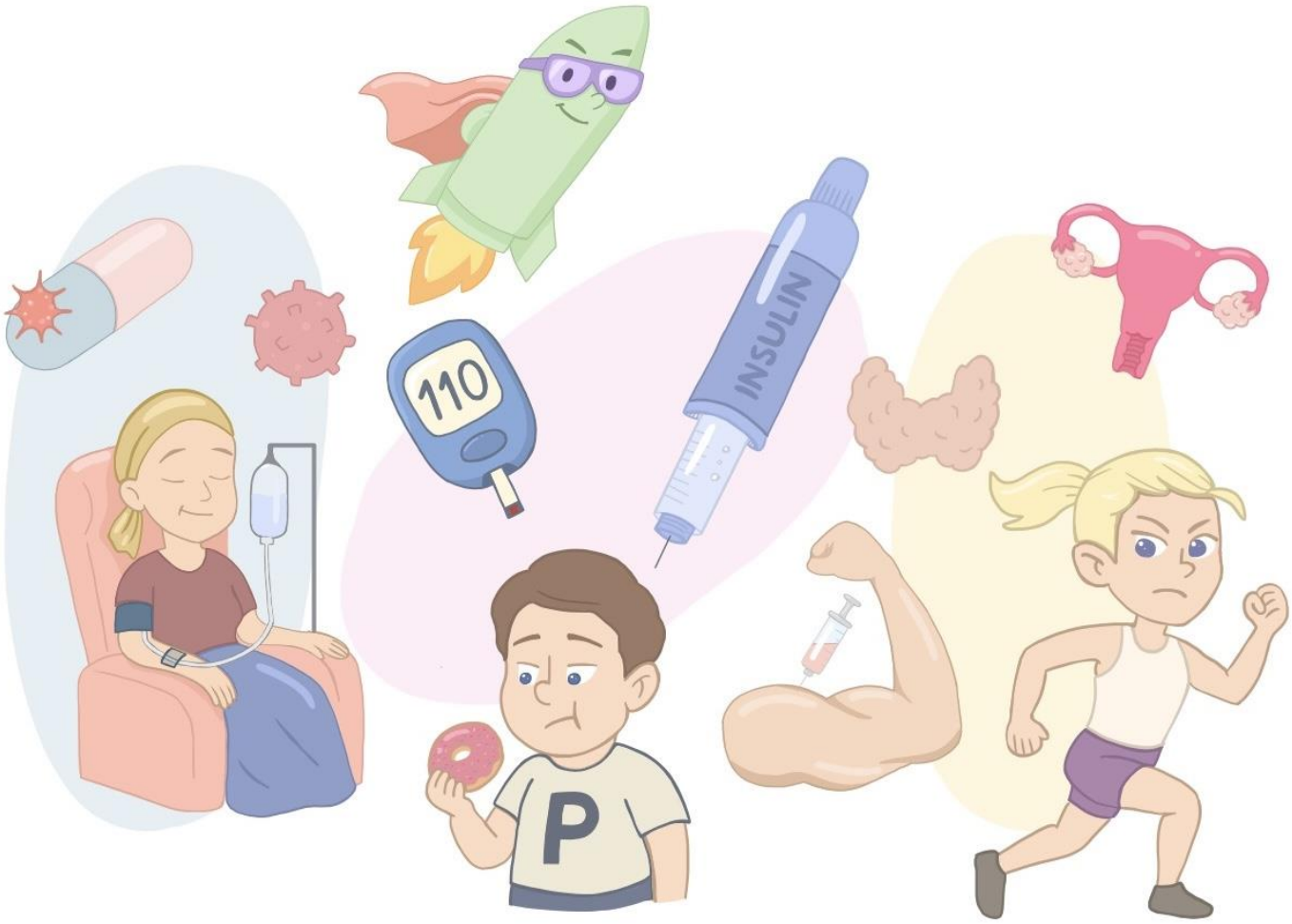

Pharmacology Exam 4

Camilla Håbjørg • Agnes Magnusdotter Eriksson

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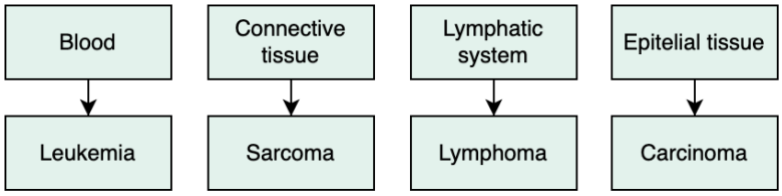
Section 1 – Anticancer and Immunomodulating Drugs

1.1 – General

- Cancer occurs when DNA mutations in stem cells disrupts key regulatory systems, leading to uncontrolled cell proliferation**.**
- Key regulatory systems include regulators of apoptosis, tumor suppressor genes and proto-oncogenes
- Cancers are named based on cell or tissue of origin



- Malignant lesions are the physical manifestations of areas that contain cancerous cells, and the term malignancy is commonly used to describe cancer.

	Benign lesions	**Malignant lesions (cancer)**
Cause	Local overgrowth of normal cells	DNA mutations that cause uncontrolled growth of abnormal cells
Growth	Slow	Rapid
Local invasion	No invasion of surrounding tissues	Invade and destroy surrounding tissues
Metastasis	Will *never* metastasize	Will metastasize

1.1.1 – Chemotherapy

- Chemotherapy are chemical substances that kill rapidly dividing cells
- Main goal is to halter DNA synthesis and cell division in cancer cells, eventually causing apoptosis

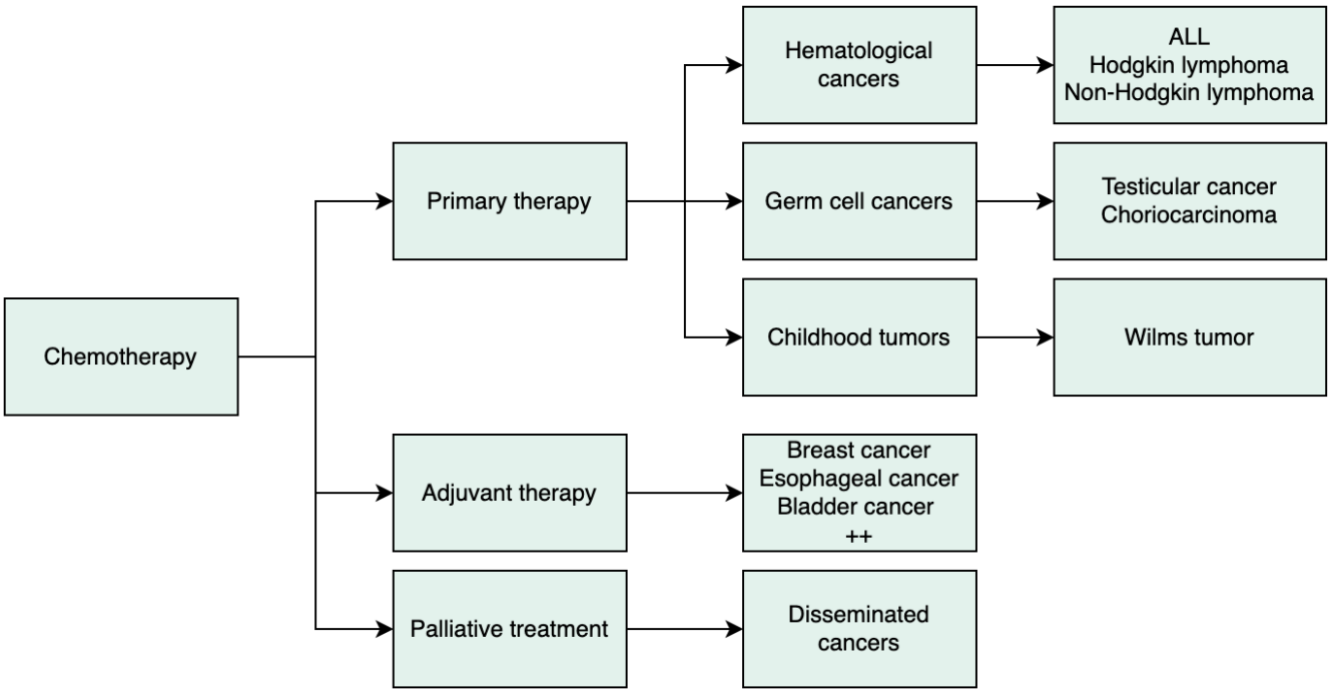
I. Cell-cycle

- Anticancer drugs can be separated in cell-cycle specific and nonspecific agents

	Cell-cycle specific agents	**Cell-cycle nonspecific agents**
Definition	Act on specific phases in the cell cycle	Act throughout the cell cycle, including G_0 which is the resting stage
Target	Rapidly proliferating cells	Dividing and resting cells
Clinical Indications	Rapidly dividing tumors	Tumors with mixed or slow growth
Toxicities	More acute onset	Delayed onset and longer duration
Examples	Methotrexate Vincristine	Cyclophosphamide Doxorubicin

II. Indications

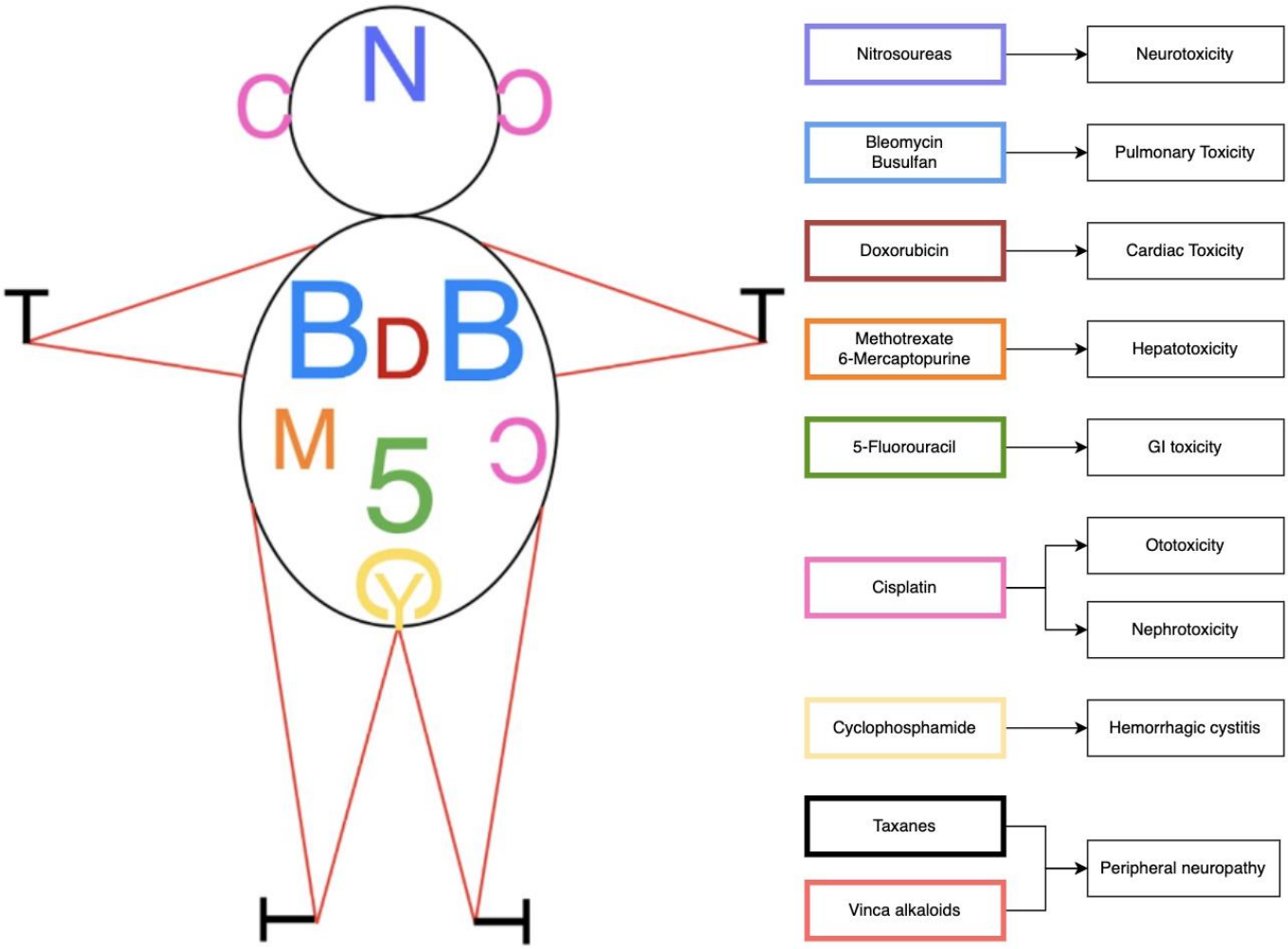
- Most cancer cells are rapidly proliferating cells, making them more susceptible to drugs that alter cell division and DNA
- The first-line treatment for localized cancer is usually surgery and/or radiotherapy, often combined with chemotherapy before or after to enhance patient outcomes.
- The standard approach for many cancers is a combination therapy, usually with both a cell cycle specific and nonspecific drug
- Combination chemotherapy targets multiple phases of the cell cycle, which increases treatment efficacy and reduces the risk of drug resistance.



- Adjuvant therapy is given *after* primary therapy to destroy residual cancer cells and reduce the risk of recurrence
- Neoadjuvant therapy is given *before* primary therapy to shrink the tumor, increasing the likelihood of complete removal

III. Toxicities

- Is a result of haltered cell division in healthy tissues that normally proliferate rapidly
    1. Intestinal epithelium → Diarrhea
    2. Bone Marrow → Myelosuppression
    3. Hair follicles → Alopecia
- A general overview of toxicities can be remembered by the "CHEMO-MAN"



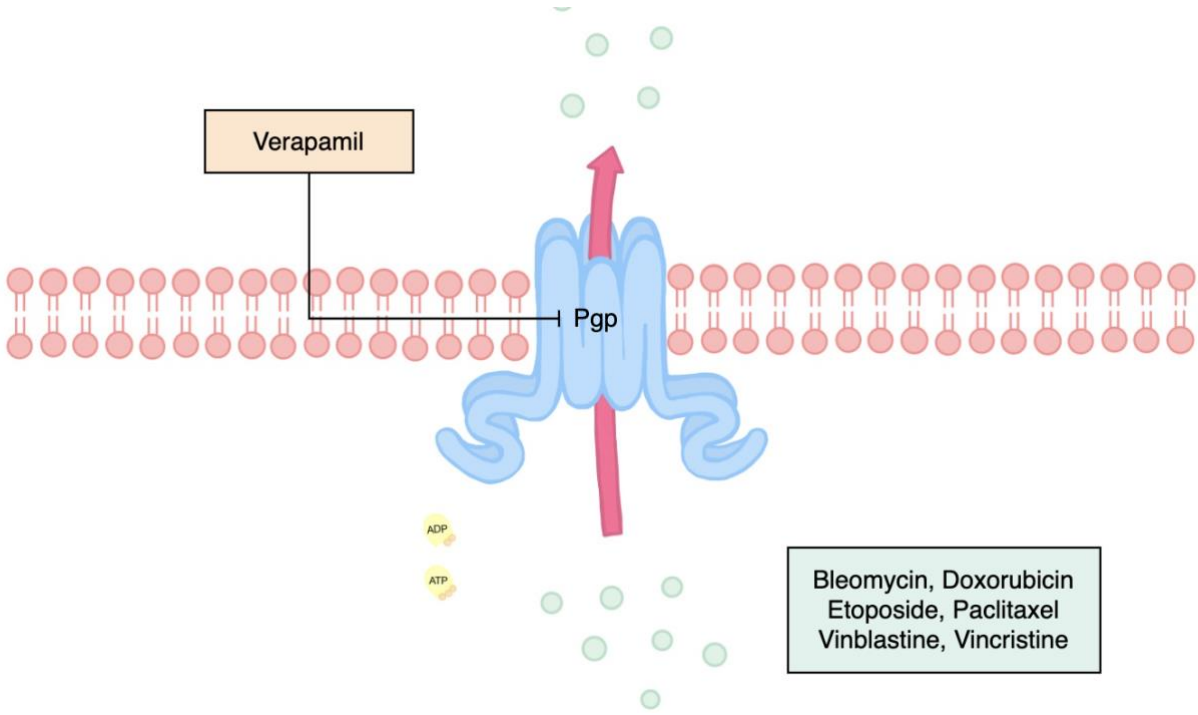
IV. Limitations

- Tumor cell resistance, which is the method that tumor cells use to decrease the effect of chemotherapy
    1. Drug efflux pumps, which pumps the chemotherapeutic drug out of the cell
    2. Decreased affinity or overexpression of target enzymes
    3. Decreased drug activation or increased drug inactivation
    4. Combination therapy decreases the risk of tumor resistance
- Production of host toxicity
    1. Nonspecific inhibition of cell division in normal tissues
- Inability to suppress metastasis

CLINICAL CORRELATION

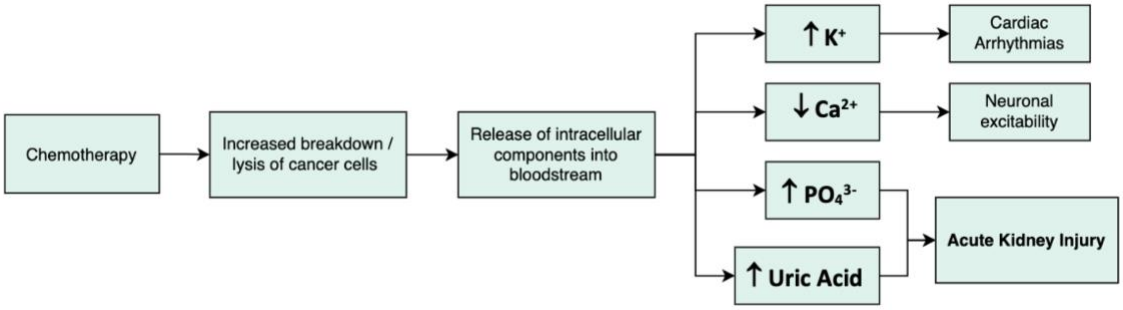
Verapamil

- P-glycoprotein is a drug efflux pump that uses ATP to export chemotherapeutic drugs out of the cell
- Verapamil is a calcium channel blocker that also inhibits the Pgp efflux pump, thereby increasing the intracellular concentration of certain chemotherapeutic drugs and potentially enhancing their effectiveness.



CLINICAL CORRELATION

Tumor Lysis Syndrome



Most commonly found after initiating chemotherapy in hematological cancer

Allopurinol is a Xanthine Oxidase inhibitor
→ Given to patients undergoing chemotherapy to inhibit the synthesis of uric acid due to the increased purine catabolism

Mercaptopurine and **Azathioprine** is metabolized by xanthine oxidase
→ Patients who take allopurinol have to reduce doses of Mercaptopurine/ Azathioprine by at least 50%

CLINICAL CORRELATION

Olanzapine
= An atypical antipsychotic

Commonly used as an antiemetic in cancer patients
Causes increased appetite and weight gain

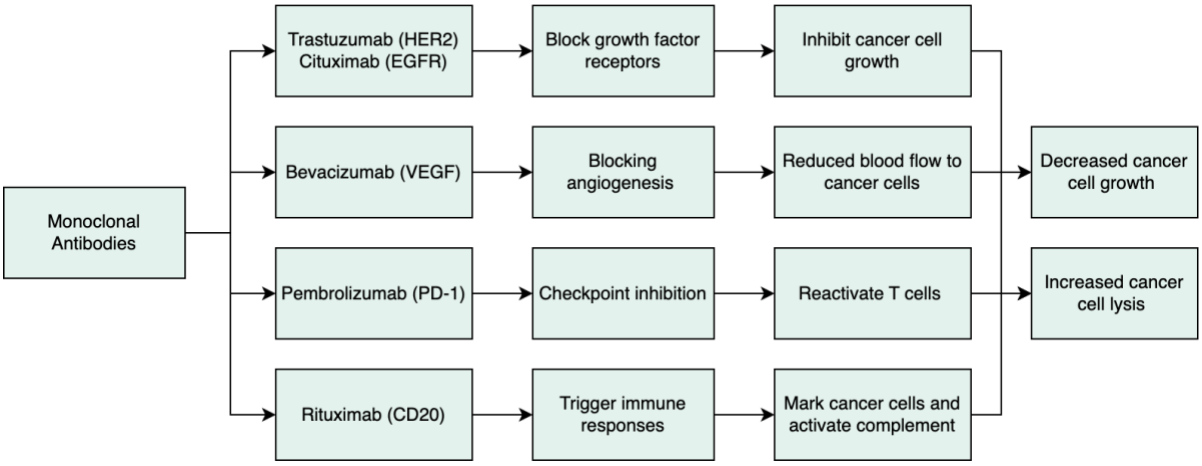
Will additionally reduce anxiety

1.1.2 – Cancer immunotherapy drugs

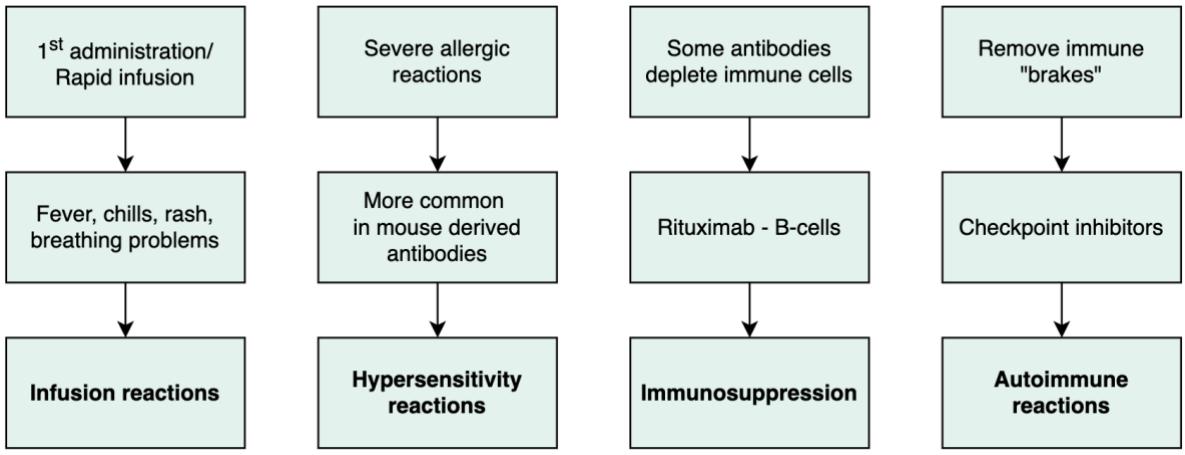
- The main purpose of cancer immunotherapy drugs is to stimulate the body´s own immune system to recognize and attack cancer cells.

I. Monoclonal Antibodies

- Monoclonal Antibodies are lab-made proteins that bind to specific antigens on cancer cells or immune cells
- They have to be given intravenously, because they are proteins which would be broken down by the GI tract if taken orally

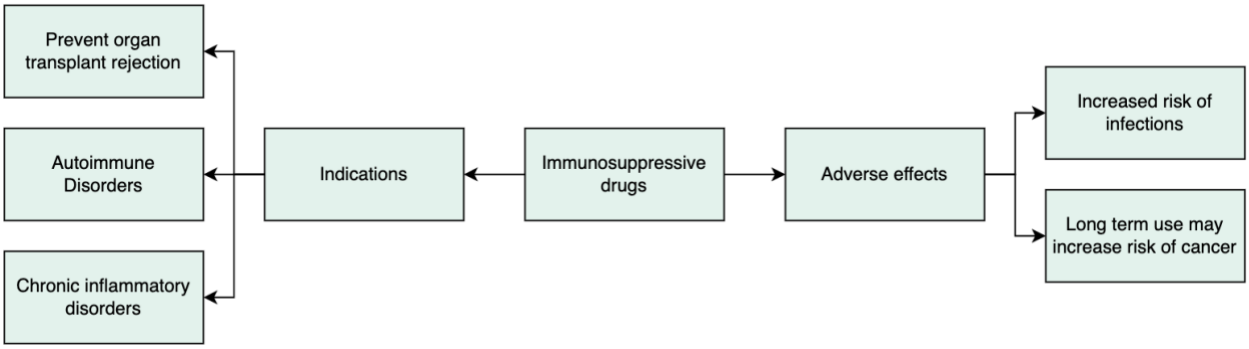


- Indications for monoclonal antibodies include cancer, autoimmune disorders, and some viral infections.
- Toxicities are less common than traditional chemotherapy because it normally does not attack healthy cells, but when they occur, it usually includes the immune system



II. Immunosuppressant Drugs

- Immunosuppressive drugs weaken the immune system to prevent it from attacking transplanted organs or overreacting against healthy cells



1.1.3 – Difference between Chemotherapy and Cancer Immunotherapy

	Chemotherapy	Cancer Immunotherapy
Mechanism of Action	Kill rapidly proliferating cells	Stimulate or enhance the body's immune system to recognize and destroy cancer cells more effectively
Specificity	Low – will kill both cancer cells and healthy cells	High – will mainly target cancer cells and immune checkpoints
Toxicities	Hair loss Diarrhea Myelosuppression	Autoimmune inflammation
Onset of Action	Rapid	Slower

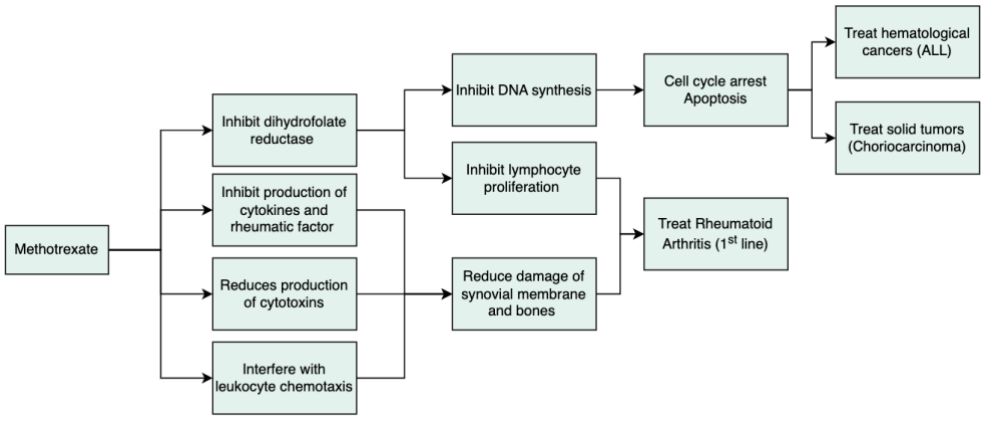
Chemotherapy is the big bomb that kills everything, while immunotherapy is the guided missile that only hits the target

1.2 – DNA Synthesis Inhibitors

- DNA Synthesis Inhibitors are analogs that inhibit enzymes required for DNA synthesis and further proliferation of cells.
- Cancer cells are rapidly proliferating cells, which makes them more susceptible to drugs that alter the DNA synthesis.

1.2.1 – Methotrexate

- Methotrexate blocks cell growth in cancer cells by inhibiting dihydrofolate reductase, but also has some additional mechanisms to target other conditions like rheumatoid arthritis.



- May be given intrathecally to prevent meningeal metastasis during chemotherapy for ALL.
- Activated folic acid can be administered together with methotrexate to reduce myelosuppression, without impairing drug efficacy.
- Methotrexate also interferes with cell growth that is crucial for the development of a fetus. Therefore, it is contraindicated in pregnancy and can be used as an abortifacient

1.2.2 – Mercaptopurine

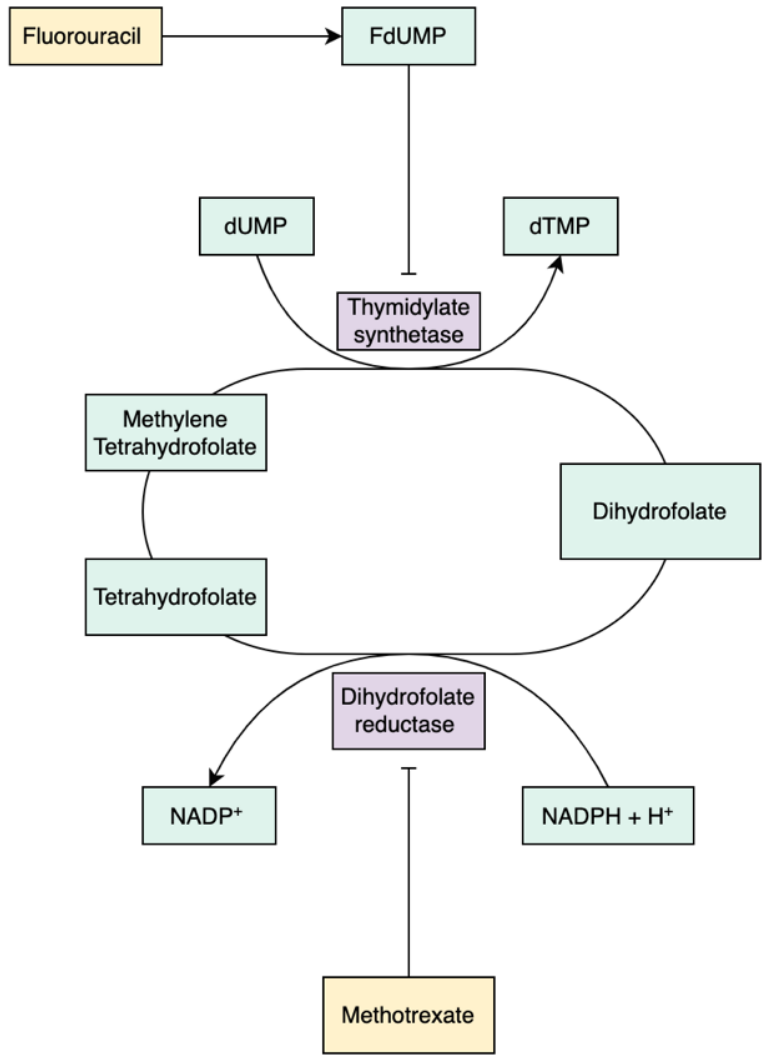
- Inhibit several steps in the biosynthesis of purine bases and purine recycling pathways
- Mercaptopurine is converted to its active form by hypoxanthine-guanine phosphoribosyltransferase (HGPRT), however, cancer cells can acquire resistance by deleting this enzyme.
- Metabolized by Xanthine Oxidase
- Indicated in acute lymphatic leukemia in remission together with methotrexate and in the management of Crohn's disease.

1.2.3 – Fluorouracil

- Fluorouracil blocks cell growth by inhibiting thymidylate synthetase. Thymidylate is an enzyme required to make thymidine, which is an essential building block in DNA.
- Administered IV due to severe toxicity to GI tract
- Indicated in solid tumors, especially breast, colorectal, and gastric carcinoma.

	Methotrexate	6-Mercaptopurine	5-Fluorouracil
Structure	Folate analog	Thio analog of hypoxanthine (purine)	Thymine analog
Toxicities	Myelosuppression[1] Oral ulceration Hepatotoxicity	Mild myelosuppression Hepatotoxicity Tumor Lysis Syndrome	Myelosuppression Alopecia GI toxicity Hand-foot syndrome
Antidote	Folinic acid Leucovorin		Uridine triacetate

[1] Dose-limiting



Both Methotrexate and Fluorouracil inhibit de novo synthesis of dTMP
→ Cell cycle arrest → Apoptosis in rapidly proliferating cells

1.3 – DNA Cross-linking and Intercalating Drugs

1.3.1 – DNA Cross-linking drugs

- DNA Cross-linking drugs, also known as alkylating agents, form permanent covalent bonds between alkyl groups and DNA bases, mainly guanine → Disrupting DNA replication and transcription → Cell arrest → Apoptosis

Alkylating drugs	Mechanism of Action	Clinical Indication	Toxicities
Cyclophosphamide Nitrogen mustards	Attaches to two guanine residues in the DNA strand[7] → Cell arrest	CLL Non-Hodgkin lymphoma (Burkitt´s lymphoma) Autoimmune disease	Hemorrhagic cystitis[5] Alopecia Emesis Myelosuppression[1]
Carmustine Nitrosourea		Brain tumors → Cross BBB	Myelosuppression[2] Interstitial lung disease Emesis[3] Veno-occlusive disease of liver
Cisplatin Platinum compound	Interact with water to form positively charged metabolites → Form intrastrand cross-links → Cell arrest	1st line in testicular, ovarian, cervical, bladder and lung cancer	NOPE - **N**ephrotoxicity[4] - **O**totoxicity - **P**eripheral neurotoxicity - **E**mesis[3] Mild myelosuppression
Busulfan Alkyl sulfonate	Act like a nitrogen mustard but has greater affinity toward myeloid cells	CML	Myelosuppression[1] Pulmonary Fibrosis Veno-occlusive disease of liver
Dacabazine	Alkylate DNA → inhibition of DNA, RNA and protein synthesis	Hodgkin lymphoma[6]	

[1] Dose limiting toxicity
[2] Causes more delayed and long-lasting suppression of leukocyte production
[3] Most emetic antineoplastic drugs, always given with an antiemetic drug
[4] Given with mannitol to increase urine flow and reduce binding of cisplatin to renal tubule proteins
[5] Prevented by coadministration of MESNA, because it binds to acrolein (the metabolite causing cystitis) and convert it to an inactive substance
[6] Used in combination therapy (ABVD)
[7] The guanine residues can either be on the same strand (intrastrand) or opposite strand (interstrand)

1.3.2 – Intercalating drugs

- Intercalating drugs slip between DNA base pairs, changing the DNA structure and therefore blocking replication and transcription.
- Doxorubicin and Bleomycin are antibiotics obtained from the Streptomyces species.

	Doxorubicin	**Bleomycin**
Mechanism of action	- Intercalation of DNA - Inhibition of Topoisomerase II - Formation of Free Radicals	Greatest effect in the G_2 phase - Intercalation of DNA - Iron-catalyzed free radical formation → DNA strand breaks
Clinical Indication	Breast cancer[1] Solid tumors Hodgkin lymphoma[3]	Widely used Non-Hodgkin lymphoma Hodgkin lymphoma[3] Solid tumors
Adverse Effects	Myelosuppression Cardiotoxicity[2] Nausea and Vomiting Extravasation[4] can cause necrosis and ulceration	Severe pulmonary toxicity Mucocutaneous reaction Alopecia

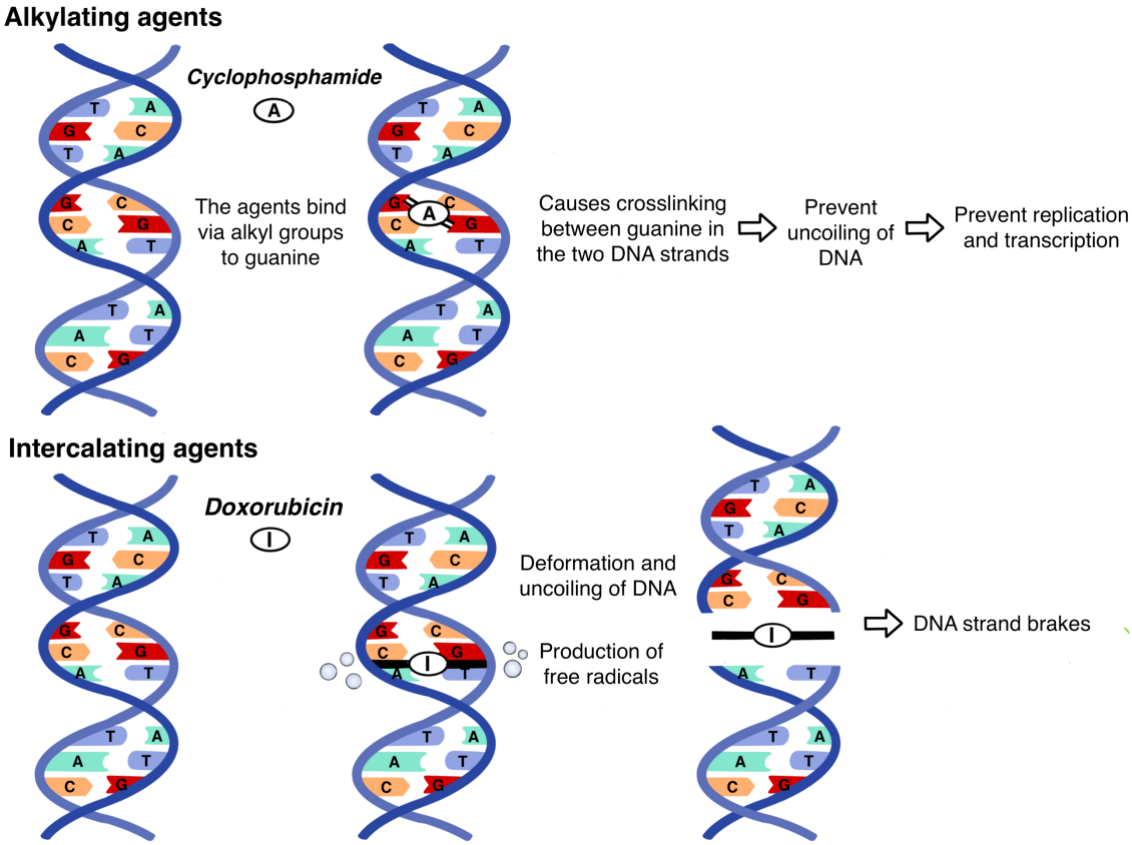
[1] One of the most active agents against breast cancer
[2] Chronic use can cause congestive cardiomyopathy (Irreversible and dose-dependent)
[3] ABVD – Adriamycin, Bleomycin, Vinblastine, Dacarbazine
[4] Leakage of the drug from the veins to the surrounding tissue

I. Doxorubicin

- Has an intense red color due to an anthracene ring found in the compound.
- Only given IV, as it is inactivated in the GI tract.
- DOXIL (Doxorubicin encapsulated in liposomes) reduce cardiotoxicity by reducing amount of drug taken up by cardiac tissue
- Also known as Adriamycin

II. Bleomycin

- Bleomycin is inactivated by aminohydrolase. Low levels of aminohydrolase in the skin and lungs cause higher toxicity.



CLINICAL CORRELATION

Busulfan lung

= interstitial pulmonary fibrosis with diffuse alveolar damage

- Busulfan causes alveolar damage and activation of fibroblasts, which may cause pulmonary fibrosis

- Causes nonproductive cough and difficulty breathing
- Occurs in 4% of patients treated long-term with busulfan

CLINICAL CORRELATION

"B symptoms"

= 3 distinct symptoms which are associated with lymphoma

- Fever
- Night sweats
- Weight loss

- Even though it is associated with lymphoma, these symptoms may occur in several forms of cancer

1.4 – DNA Topoisomerase Inhibitors

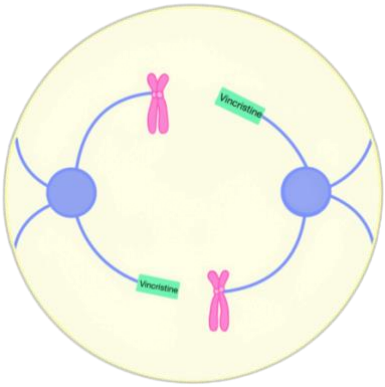
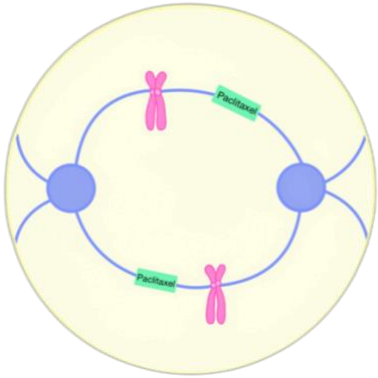
- Topoisomerase I cleave one strand of DNA, which relaxes the DNA supercoil before replication.
- Topoisomerase II cleaves both strands of DNA before replication.
- Inhibition of topoisomerase inhibit DNA replication, because the DNA strand will not be able to unwind from the supercoil.

	Etoposide	**Irinotecan**
Structure	Podophyllin analog	Camptothecin Analogs
Mechanism of Action	Topoisomerase II inhibitors S and G_2 phase specific	Topoisomerase I inhibitor Nonspecific
Clinical Indication	Testicular cancer Lung cancer Non-Hodgkin lymphoma Synergy with platinum compounds[2]	Colorectal carcinoma
Adverse Effects	Myelosuppression[1]	Myelosuppression[1]

[1] Dose-limiting
[2] Administered with cisplatin

1.5 – Mitotic Inhibitors

- Mitotic inhibitors disrupt microtubules, which are essential for proper nerve conduction and the release of neurotransmitters.
- As a result, it may cause neurotoxicity, commonly presented as peripheral neuropathy.
- Mutation in beta tubulin, which is the drug binding site, can make cancer cells resistant to to mitotic inhibitors

	Vinca alkaloids	**Taxanes**
Mechanism of Action	**Inhibit polymerization** of microtubules  → Chromosomes unable to align in the center of cell → Cell arrest in metaphase	**Promote polymerization** and inhibit disassembly of microtubules  → Chromosomes unable to align in the center of cell → Cell arrest in metaphase
Clinical Indication	Hematological cancers[4] Solid tumors[5]	1st line in metastatic ovarian cancer Non-small cell lung cancer Metastatic breast cancer
Toxicities	Peripheral neuropathy[1] Paralytic ileus SIADH	Myelosuppression[1] Hypersensitivity reactions[3]
Drugs	Vincristine Vinblastine[2]	Paclitaxel

[1] Dose-limiting
[2] Part of the ABVD regimen for Hodgkin disease
[3] Patients should be premedicated with steroids and antihistamine
[4] ALL, Hodgkin lymphoma, Non-Hodgkin lymphoma
[5] Rhabdomyosarcoma, Neuroblastoma, Wilms tumor

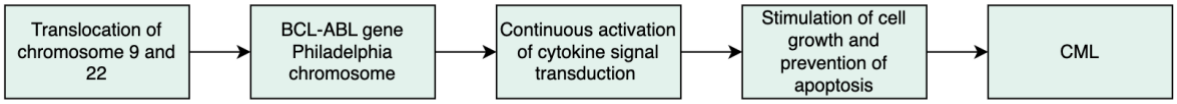
1.6 – Enzyme and Proteasome Inhibitors

1.6.1 – Imatinib

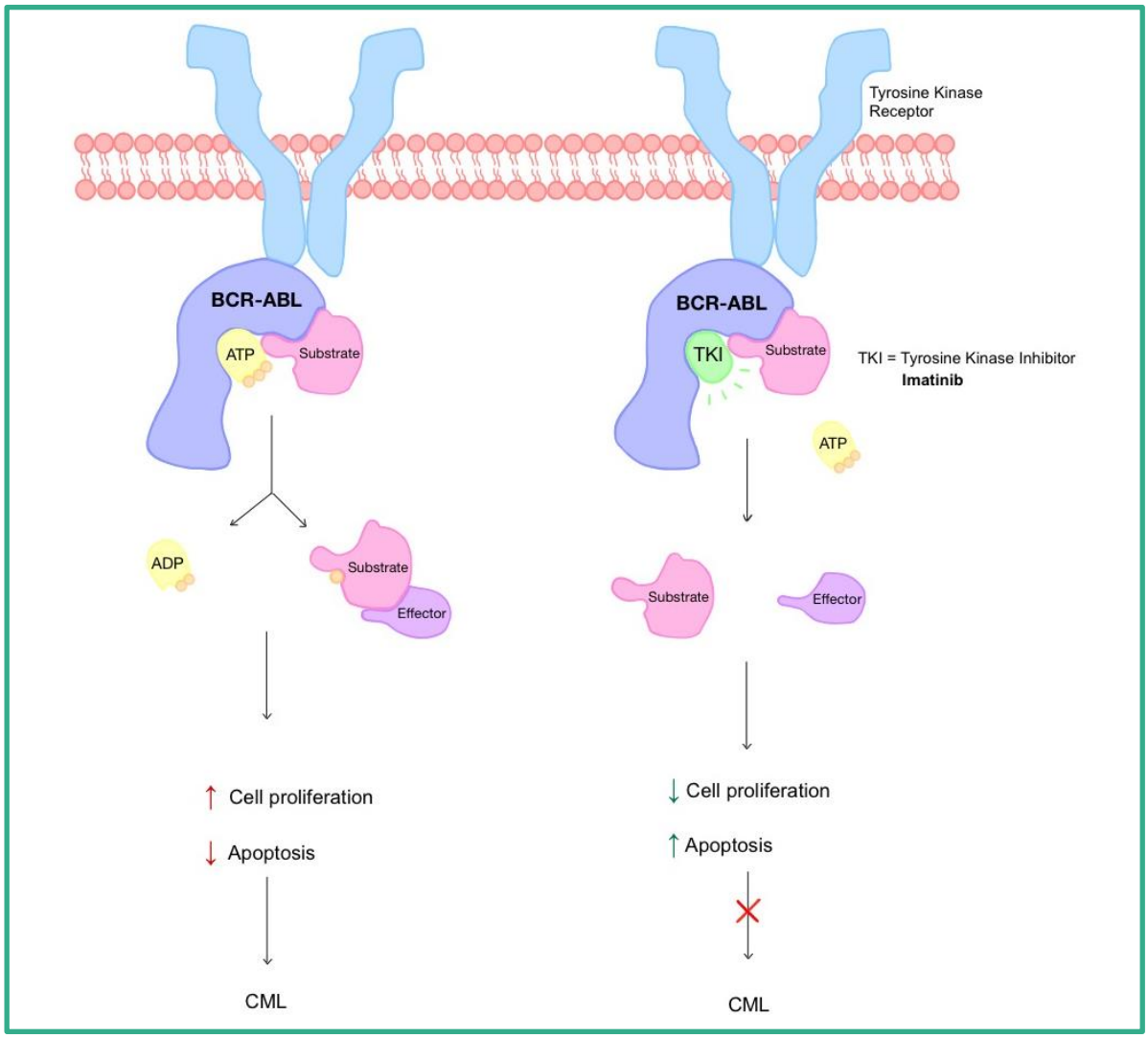
- Imatinib is a tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase.
- The BCR-ABL gene found on the Philadelphia chromosome creates a tyrosine kinase that is always “on”

SUFFIX

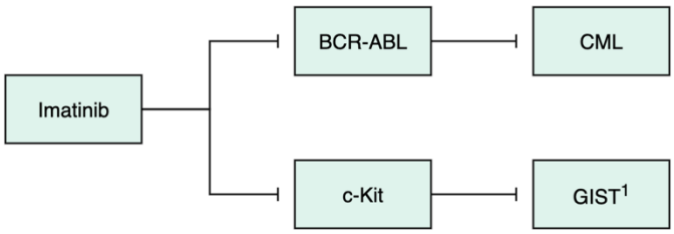
Tyrosine kinase inhibitors: -tinib



I. Mechanism of Action



II. Clinical Indications



[1] Gastrointestinal Stromal Tumor

III. Toxicities

- Fluid Retention
- Congestive Heart Failure

1.6.2 – Bortezomib and Vemurafenib

	Bortezomib	Vemurafenib
Mechanism of Action	Bind to catalytic site of 26S proteasome → Inhibit degradation of proapoptotic proteins → Protein accumulation and cell death	Inhibit B-RAF kinase with V600E mutation
Clinical Indication	Multiple Myeloma Mantle cell lymphoma	Metastatic Melanoma[1]

[1] Only effective in tumors with V600E mutation

1.7 – Cancer Immunotherapy Agents

1.7.1 – Monoclonal Antibodies

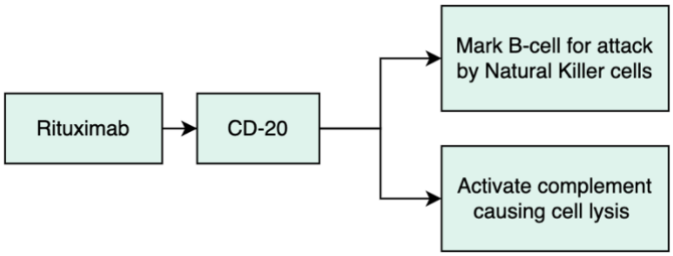
- Monoclonal antibodies are lab-made proteins that bind to specific targets to modulate immune responses or attack specific cells
- Toxicities usually include hypersensitivities and impaired immune function

	Target	Mechanism of Action	Clinical Indication	Toxicities
Rituximab	CD20 antigen[1]	Increased cancer cell lysis	Non-Hodgkin Lymphoma	Infusion Reaction Tumor Lysis Syndrome
Trastuzumab	HER2 receptor	Inhibit growth signals sent by HER2	Metastatic breast cancer, Gastric cancer	Congestive heart failure[5]
Cetuximab	EGFR[2]	Inhibit cell proliferation	Colorectal cancer, NSCLC[6]	Infusion Reaction Skin rash in 75%
Bevacizumab	VEGF[3]	Inhibit angiogenesis which halts tumor growth	Colorectal cancer	Infusion reaction Congestive HF Pulmonary hemorrhage GI perforation Proteinuria
Pembrolizumab	PD-1[4]	Reactivate T-cell apoptosis of cancer cells	Refractory melanoma, Renal cell carcinoma NSCLC[6]	Immune-related adverse effects Autoimmune reactions

[1] Found on 90% of B cells in non-Hodgkin lymphoma
[2] Epidermal growth factor receptor
[3] Vascular endothelial growth factor
[4] Programmed cell death protein 1
[5] Worse when given in combination with anthracyclines
[6] Non-small cell lung cancer

I. Rituximab

- CD-20 is a protein found on the surface of both cancerous and healthy mature B cells.
- Plasma cells and B-cell precursors do not have CD-20 and will therefore survive the treatment



II. Trastuzumab

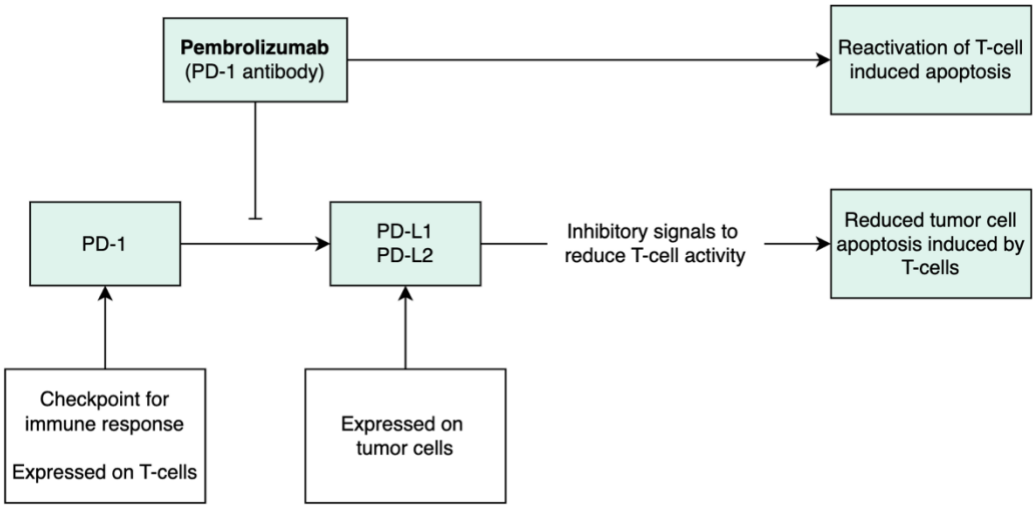
- HER2 is a tyrosine kinase that promotes growth and proliferation when activated
- Cancer cells may have an overexpression of HER2, which causes the receptor to always be activated
- This drug will therefore only be effective in cancers that have an HER2 overexpression
- Trastuzumab may cause congestive heart failure because the heart muscle uses HER2 for normal repair signaling

III. Bevacizumab

- Bevacizumab prevents the vascular endothelial growth factor from binding to its receptors and therefore prevents new vessels from forming
- Since bevacizumab cuts off the blood supply to the tumor, it will also decrease the risk of cancer cells reaching the blood stream and therefore reduce the risk of metastasis.

IV. Pembrolizumab

- Immune checkpoints like PD-1 are proteins found on the surface of healthy cells. They prevent T-cells from attacking healthy cells.
- Cancer cells can make programmed cell death-like proteins and therefore hide from the immune system.
- Checkpoint inhibitors will reactivate T cell action against cancer cells by inhibiting the function of PD-1.



- Autoimmune reactions may occur because you remove the “brakes” of immune cells

SUFFIX

Monoclonal antibody: -mab or -monab

Letters before -mab indicate the source of the antibody:

o → Mouse
u → Human
xi → Chimeric (Both human and mouse)

Internal letters indicate therapeutic use of the antibody:

tu → Tumor
vi → Virus
c / ci → Circulation

CLINICAL CORRELATION

Infusion reaction

Monoclonal antibodies in the bloodstream bind to target cells, causing the release of cytokines

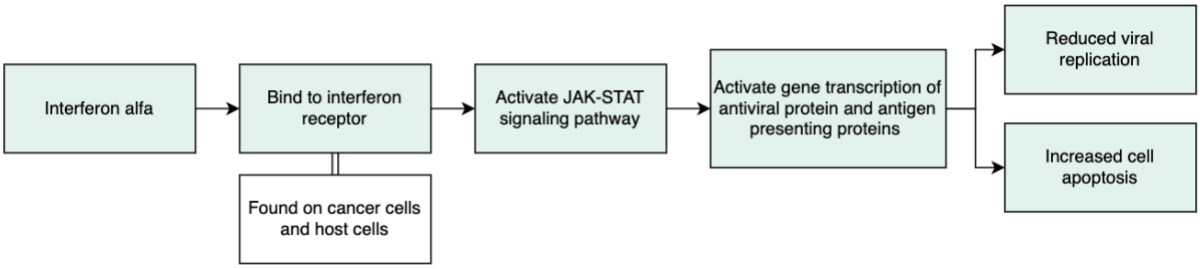
→ Hypotension
→ Bronchospasm
→ Angioedema
→ Fever and Chills

Especially common after the first infusion and rapid administration

Pretreatment with diphenhydramine (antihistamine), acetaminophen and corticosteroids can alleviate symptoms

1.7.2 – Interferon Alfa

- Interferon alfa is a cytokine that helps the immune system fight viruses and cancer



- Used to treat hairy cell leukemia, Kaposi sarcoma, and viral hepatitis
- Causes myelosuppression and flu-like symptoms

1.8 – Immunosuppressant Drugs

- Primary use of immunosuppressants:
    1. Prevent rejection of transplanted organs
    2. Autoimmune diseases
- Immunosuppressant drugs are rarely used to treat primary cancers, but may be indicated to manage complications like graft-versus-host disease and immune-related toxicities

1.8.1 – Antiproliferative Agents

- Prevent the proliferation of B and T lymphocytes
- Clinical indications
    1. To prevent acute rejection of organ transplants, especially kidney transplants
    2. Autoimmune diseases like SLE (systemic lupus erythematosus) and RA (rheumatoid arthritis)

I. Mycophenolate Mofetil

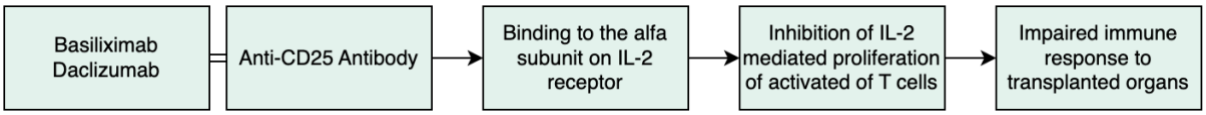
- Reversible and noncompetitive inhibitor of inosine monophosphate dehydrogenase, which is required in de novo synthesis of guanosine nucleotide.
  → Inhibit proliferation selectively in B and T lymphocytes because these cells depend on the novo synthesis, while other cells can use the salvage pathway.

II. Azathioprine

- Azathioprine is converted into 6-mercaptopurine, which inhibits de novo purine synthesis, thereby suppressing DNA and RNA production
- B and T lymphocytes are unable to use the salvage pathway to make purines → Inhibition of de novo purine synthesis will mainly affect the immune cells
- Metabolized by Xanthine Oxidase → Required to reduce dose when administered with allopurinol to avoid tumor lysis syndrome

1.8.2 – Inhibition of IL-2 receptor

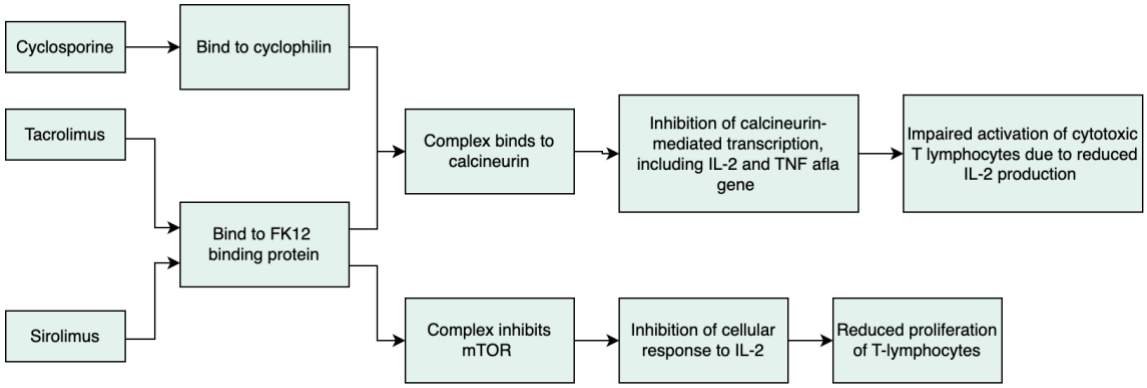
- Activated interleukin-2 receptor promotes activation, proliferation, and differentiation of T cells
- Inhibition of the IL-2 receptor will therefore inhibit T lymphocyte proliferation and reduce unwanted immune responses
- Administered IV
- Indicated as prophylaxis of acute rejection in renal transplants



1.8.3 – Inhibition of production and release of IL-2

- Interleukin 2 is a cytokine that binds to IL-2 receptors to enhance the immune system response
- Cyclosporine, Tacrolimus, and Sirolimus are examples of immunosuppressants that are derived from microbes

I. Mechanism of Action



- Cyclophilin and FK12-binding protein are intracellular proteins
- Calcineurin is a phosphatase enzyme
- mTOR is a serine/ threonine kinase

II. Clinical Indications

- Organ transplant rejection, usually in combination with corticosteroids
- Graft-versus-host disease, which may occur after bone marrow transplantation

III. Toxicities

- Cyclosporine is metabolized by CYP3A4, and will interact with drugs that inhibit or induce this enzyme

	Toxicities
Cyclosporine[1]	<u>Nephrotoxicity</u> Hyperkalemia Hypertension Muscle tremor Gingival hyperplasia Hirsutism
Tacrolimus	Nephrotoxicity[2] Neurotoxicity Post-transplant insulin-dependent DM
Sirolimus	Hyperlipidemia Impaired wound healing in patients with DM and obesity

[1] Most adverse effects are dose-dependent → Regular measurements of drug levels in blood
[2] More severe than in cyclosporine

1.9 – Test Yourself

1. Which drug can reduce adverse effects from Methotrexate?

a) Uridine triacetate

b) Leucovorin

c) Mannitol

d) Prednisone

2. Name the 4 drugs in ABVD combination therapy used to treat Hodgkin disease.

A –

B –

V –

D –

3. Fill out the table

	Methotrexate	Cyclophosphamide	Paclitaxel
Type of chemotherapeutic drug			
Mechanism of Action			
Cell cycle			
Indication			

4. Which of the following drugs is the most cardiotoxic?

a) Vincristine

b) Bleomycin

c) Cyclosporine

d) Doxorubicin

5. What are the most emetic anticancer drugs?

_____

_____

_____

6. Name 2 drugs causing severe pulmonary damage

_____

_____

7. What are the adverse effects caused by Cisplatin?

a) Nephrotoxicity, Oropharyngeal candidiasis, Pulmonary edema, Emesis

b) Neurotoxicity, Osteoporosis, Psoriasis, Emesis

c) Nephrotoxicity, Ototoxicity, Peripheral neuropathy, Emesis

d) Neurotoxicity, Osteoporosis, Pneumonia, Emesis

8. What is the difference between Tacrolimus and Sirolimus?

_____

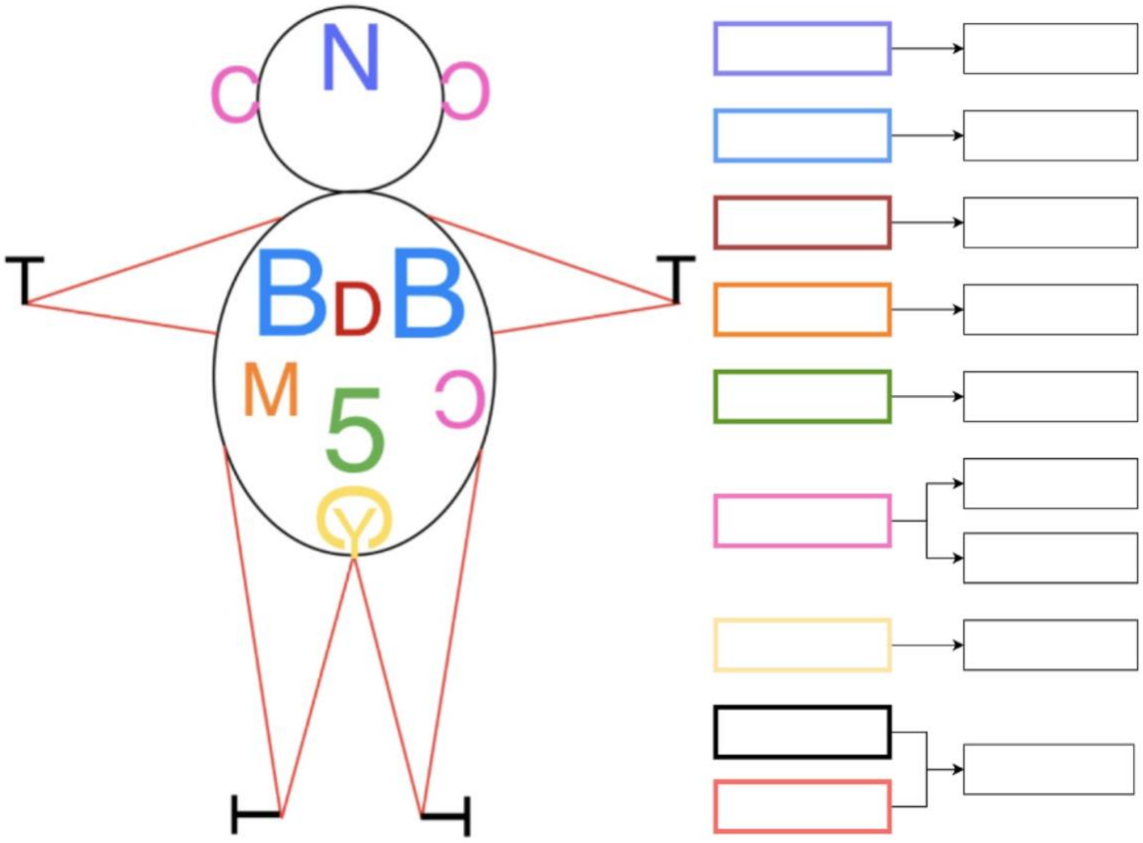
_____

_____

9. Match drug and mechanism of action

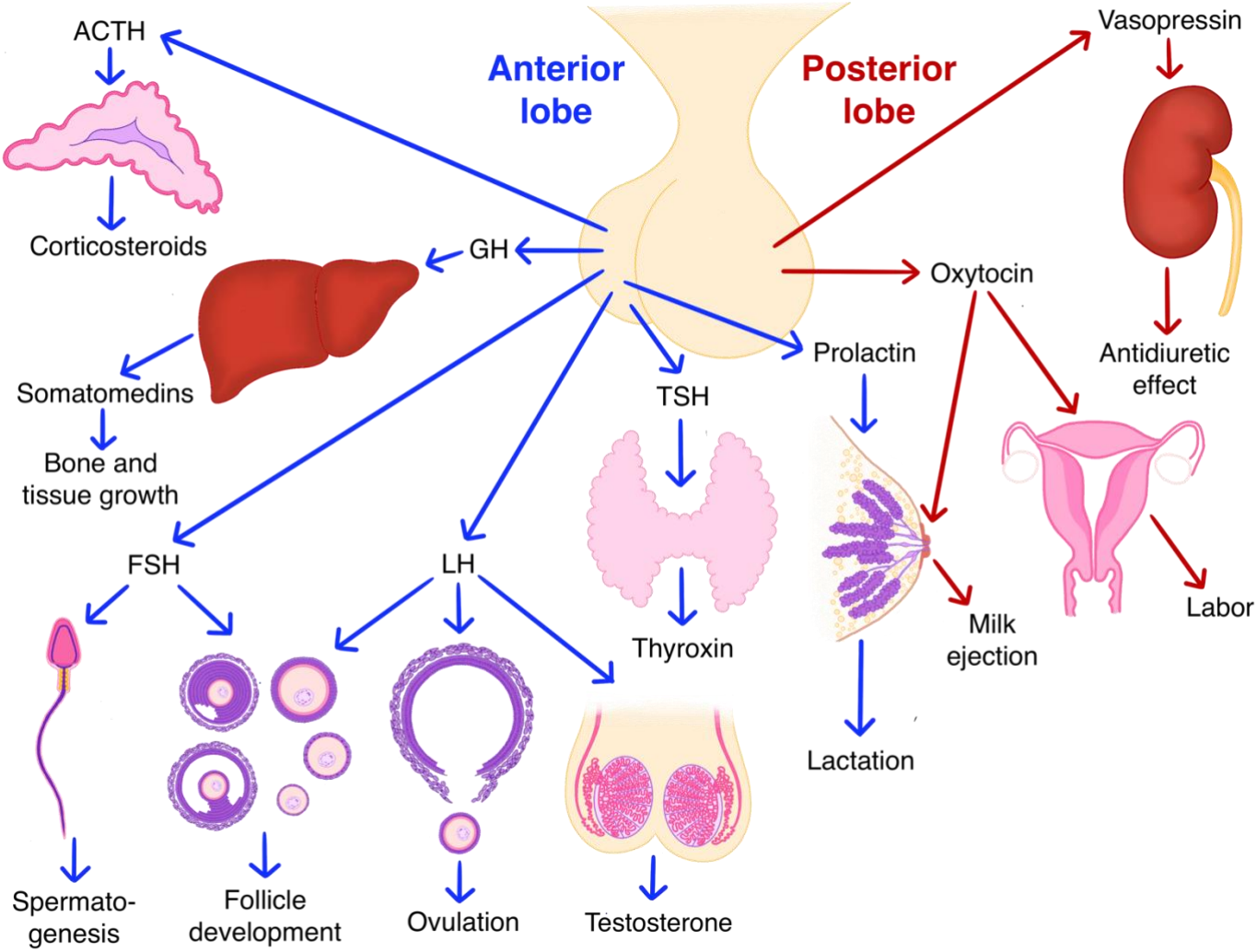
Vincristine	Binds HER2 receptor
Trastuzumab	Inhibits microtubule polymerization
Paclitaxel	Promote microtubules polymerization
Rituximab	Binds CD20 on B cells

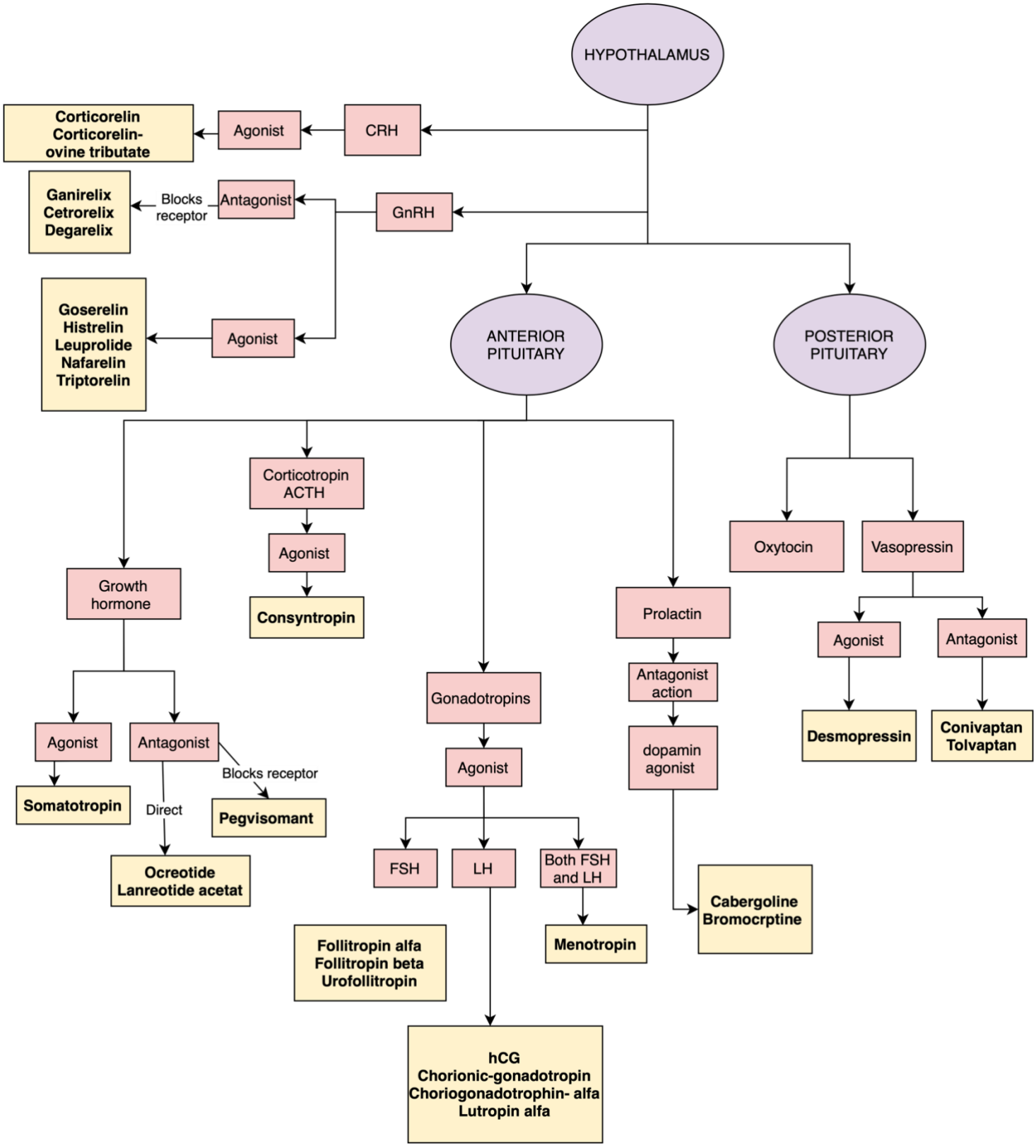
10. Fill out the drugs and toxicities in the "CHEMO-MAN"



Section 2 – Hypothalamic and Pituitary Drugs

2.1 – Overview of Hypothalamic Pituitary Axis and Related Hormones




HYPOTHALAMUS
CRH
Agonist
Corticorelin
Corticorelin-ovine tributate
GnRH
Antagonist
Blocks receptor
Ganirelix
Cetrorelix
Degarelix
Agonist
Goserelin
Histrelin
Leuprolide
Nafarelin
Triptorelin
ANTERIOR PITUITARY
POSTERIOR PITUITARY
Corticotropin ACTH
Agonist
Consyntropin
Growth hormone
Agonist
Somatotropin
Antagonist
Direct
Ocreotide
Lanreotide acetat
Blocks receptor
Pegvisomant
Gonadotropins
Agonist
FSH
LH
Both FSH and LH
Follitropin alfa
Follitropin beta
Urofollitropin
Menotropin
hCG
Chorionic-gonadotropin
Choriogonadotrophin- alfa
Lutropin alfa
Prolactin
Antagonist action
dopamin agonist
Cabergoline
Bromocrptine
Oxytocin
Vasopressin
Agonist
Desmopressin
Antagonist
Conivaptan
Tolvaptan

2.2 – Corticotropin and Related Drugs

RECALL

5.1.3 – Regulation of Adrenal Cortex Hormones, Endocrine booklet

- Corticotropin is secreted by the anterior pituitary in response to corticotropin-releasing hormone (CRH) secreted from the hypothalamus

- Production of cortisol, aldosterone, and adrenal androgens are stimulated by corticotropin.

2.2.1 – Corticotropin Preparations

- Two drugs mimic corticotropin effects: porcine corticotropin and cosyntropin.
- Cosyntropin is primarily used to diagnose adrenal insufficiency, but it can also be used to differentiate congenital adrenal hyperplasia from ovarian hyperandrogenism.

2.2.2 – Corticotropin-releasing Hormone

- Corticorelin ovine triflutate is a drug that mimics corticotropin-releasing hormone (CRH), which is released from the hypothalamus.
- Administered through IV
- Stimulates release of corticotropin and cortisol.
- Can be used as a diagnostic tool to determine the source of excessive levels of cortisol in Cushing syndrome.

CLINICAL CORRELATIONS

Adrenal insufficiency

Condition where the adrenal glands fail to produce adequate levels of steroid hormones.

Primary adrenal insufficiency→ something wrong with the adrenals

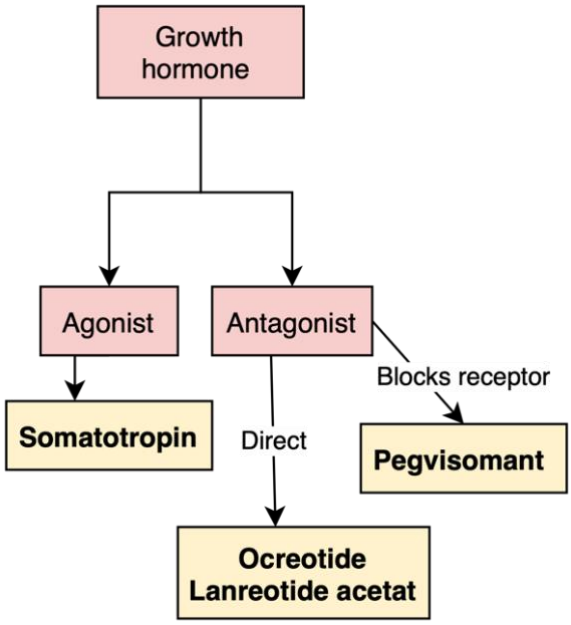
Secondary adrenal insufficiency→ something wrong with the pituitary.

Diagnostic testing with **cosyntropin**

Cortisol levels are increased in healthy individuals after **consytropin** administration, while there is no increase in individuals with adrenal insufficiency

2.3 – Growth Hormone and Related Drugs

- Growth hormone is also known as somatotropin, released from the anterior pituitary.
- Somatostatin inhibits the secretion of somatotropin from the anterior pituitary.



2.3.1 - Mechanism of Action of Growth Hormone

Type of effect	Action
Direct	- Stimulates lipolysis - Antagonizes insulin → ↑ blood glucose
Indirect *(mediated by IGF-1)*	- Skeletal growth - Amino acid transport - Protein synthesis - Nucleic acid synthesis - Cell proliferation

CLINICAL CORRELATIONS

Insulin-like growth factor-1 (IGF-1)

- Produced by the liver in response to stimulation from growth hormone.
- Promotes bone and muscle growth, cell proliferation and differentiation.

2.3.2 – Overview of Drugs Inhibiting and Stimulating Growth

Drug class	Action	Drugs	Route	Indications/clinical	Adverse effects
Recombinant somatotropin	<u>Stimulates growth</u>	**Somatotropin (synthetic)**	Subcutaneous	Used in various cases of growth hormone deficiency - Turner syndrome - Idiopathic growth hormone deficiency - Prader-Willi syndrome - Chronic renal failure	<u>In children</u> - Pseudotumor cerebri - Slipped capital femoral epiphysis - Scoliosis - Edema - Hyperglycemia
Recombinant IGF-1		**Mecasermin**	Subcutaneous	Growth failure in children unresponsive to growth hormone administration	Hypoglycemia
Somatostatin analogs	<u>Inhibit growth</u>	**Octreotide**	Subcutaneous	Patient with acromegaly[1] Hormone-secreting tumor[2]	- Nausea - Vomiting - Abdominal cramps - Steatorrhea
		Lanreotide acetate	Subcutaneous	Same as **octreotide** but a prolonged-release formulation	
Growth hormone receptor antagonist		**Pegvisomant**	Subcutaneous	Somatostatin resistant patients with acromegaly.	Elevated liver enzymes

[1]Acromegaly is a condition where you have excessive growth hormone secretion, most commonly because of pituitary adenoma.

[2] Tumors secreting insulin, glucagon, gastrin, thyrotropin, and vasoactive intestinal peptide. Carcinoid tumors secrete serotonin and kallikrein

2.4 – Gonadotropins and Related Drugs

- Pulsatile secretion of GnRH stimulates the release of FSH and LH from anterior pituitary.
- Continuous administration/secretion of GnRH inhibits FSH and LH release.

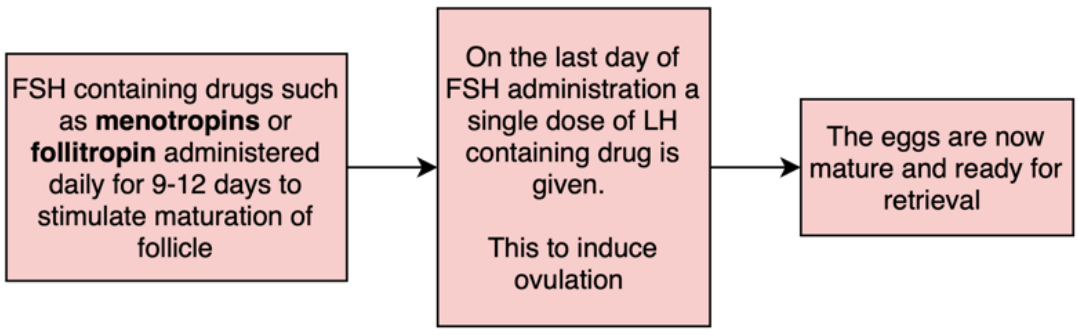
2.4.1 – Gonadotropins and Effect Differences in Males and Females

	FSH	LH
Females	- Ovarian follicle maturation - Estrogen production	- Induces ovulation - Stimulates corpus luteum to produce progesterone and androgens - Assist in follicle maturation
Males	Spermatogenesis	Stimulates the production of testosterone

2.4.2 – Gonadotropin Preparations

Gonadotropin preparations			
Drugs	Containing FSH	Containing LH	Containing both FSH and LH
	Follitropin alfa **Follitropin beta** **Urofollitropin**	**Chorionic gonadotropin** **Choriogonadotropin alfa** **Lutropin alfa**	**Menotropins**
Indication	Used in combination to induce ovulation in infertile women.		May be used as the first step in IVF treatment Treat infertility in men by stimulating spermatogenesis

4.3.2 – Basic Understanding of How Menotropin and Follitropin are Used



2.4.3 – Gonadotropin-releasing Hormone Agonist and Antagonist

<table>
<tr><td rowspan="2">Mechanism</td><td colspan="2">GnRH agonist</td><td colspan="2">GnRH antagonist</td></tr>
<tr><td colspan="2">Synthetic analogs of GnRH</td><td colspan="2">Competitive antagonist at GnRH receptor in the pituitary</td></tr>
<tr><td>Drugs</td><td colspan="2">Goserelin
Histrelin
Leuprolide
Nafarelin
Triptorelin</td><td colspan="2">Ganirelix
Cetrorelix
Degarelix</td></tr>
<tr><td>Effect</td><td>Pulsatile administration stimulates the release of FSH and LH</td><td>Continuous administration causes inhibition of FSH and LH release</td><td colspan="2">Inhibits secretion of FSH and LH</td></tr>
<tr><td rowspan="4">Indication</td><td>Goserelin</td><td rowspan="2">Prostate cancer
Breast cancer
Endometriosis</td><td colspan="2" rowspan="3">In IVF treatment, GnRH antagonists prevent premature ovulation, allowing for better timing of oocyte retrieval</td></tr>
<tr><td>Leuprolide</td></tr>
<tr><td>Histrelin</td><td>Treatment for children with CCP[1]</td></tr>
<tr><td>Nafarelin</td><td>Endometriosis
Precocious puberty</td><td>Degarelix</td><td>Prostate cancer</td></tr>
<tr><td rowspan="2">Adverse effect</td><td colspan="2">In women long-term use causes menopause symptoms such as hot flushes, sweats and headaches.</td><td colspan="2" rowspan="2">Similar as for agonists
Can cause hypersensitivity</td></tr>
<tr><td colspan="2">In men long-term use can cause hot flushes, sweats, gynecomastia, reduced libido, decreased hematocrit</td></tr>
<tr><td>Contraindication</td><td colspan="2">-</td><td colspan="2"><u>ABSOLUTE</u>
Pregnancy</td></tr>
</table>

[1]**Central precocious puberty (CPP)** is a condition where puberty starts earlier than usual. Before age 8 in girls and before age 9 in boys. Due to **early activation of the hypothalamic-pituitary-gonadal axis.**

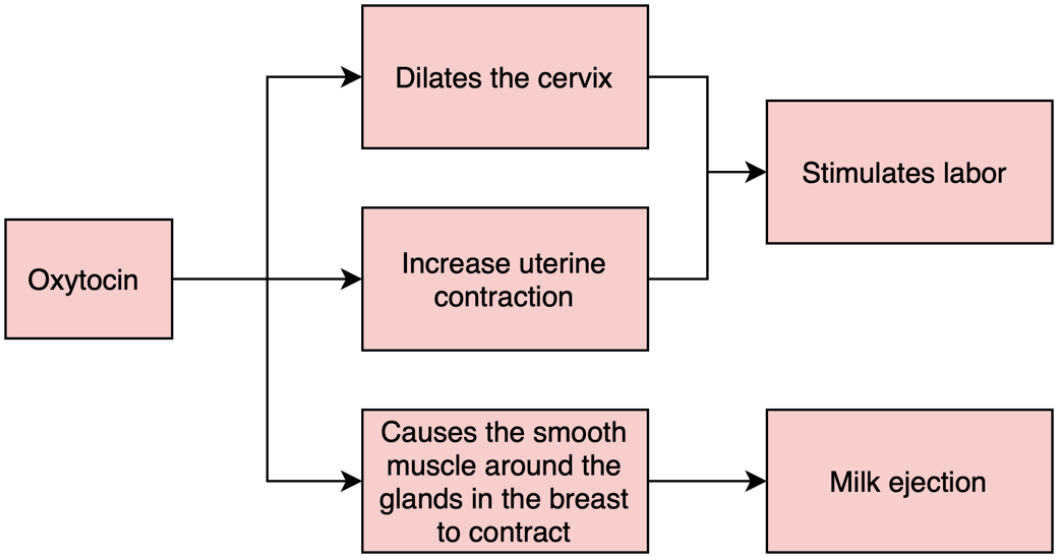
2.5 – Prolactin and Related Drugs

- Prolactin is secreted from the anterior pituitary and regulates lactation.
- Excessive release of prolactin can lead to galactorrhea, oligomenorrhea, or amenorrhea as well as infertility.
- Prolactin release is naturally inhibited by dopamine acting on D_2 receptors.
- For this reason, can hyperprolactinemia be treated with a dopamine agonist such as Cabergoline and Bromocriptine

	Cabergoline	**Bromocriptine**
Drug Class	Dopamine agonist Ergot alkaloid derivative	
Mechanism of Action	Selectively activates dopamine D2 receptors in the pituitary gland→ inhibiting prolactin secretion	Mimics dopamine action to inhibit prolactin secretion
Indications	- Hyperprolactinemia - Prolactin-secreting pituitary adenomas - Mixed growth hormone - Prolactin-secreting pituitary adenomas	
Duration of Action	Long duration of action	Shorter duration of action
Adverse effects	Better tolerated than Bromocriptine in hyperprolactinemia - Nausea - Dizziness - Headache	
Other Uses	-	Used to treat Parkinson's disease

2.6 – Oxytocin and Related Drugs

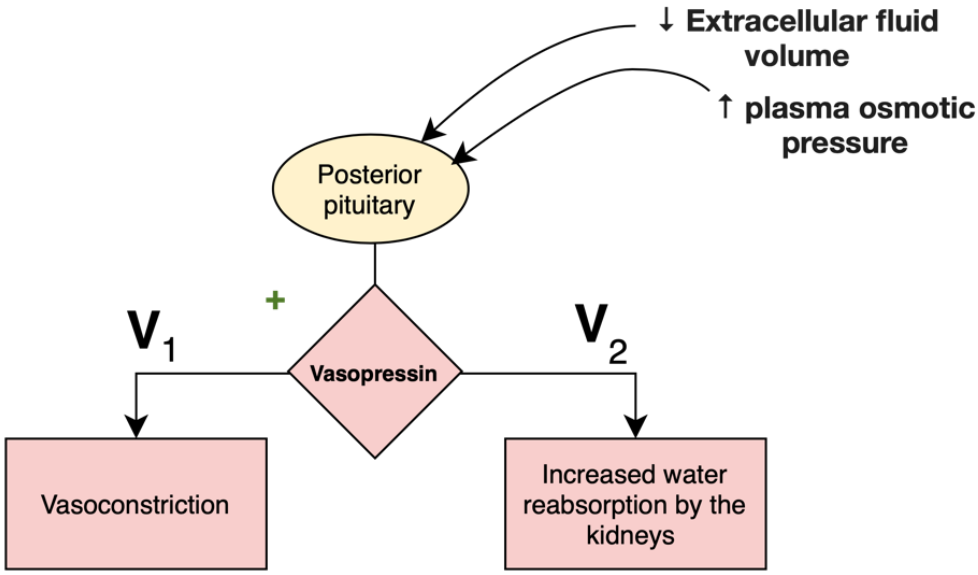
- Produced by the <u>posterior pituitary</u>



Drug	Clinical usage	Mechanism of action	Adverse effects	Contraindications
Synthetic **oxytocin**	- Enhance or induce uterine contraction during labor - Prevent postpartum uterine hemorrhage - Stimulate milk ejection in nursing mothers.	Same as for oxytocin	- Cardiac arrhythmias - CNS stimulation - Excessive uterine contraction - Hyponatremia	- Fetal distress - Abnormal fetal presentation - Prematurity - Cephalopelvic disruption

2.7 – Vasopressin and Related Drugs

- Vasopressin is secreted by the posterior pituitary and plays a crucial role in regulating the body's water balance



CLINICAL CORRELATION

Diabetes insipidus

One of the causes of diabetes insipidus is a deficiency in pituitary vasopressin secretion. It is a condition marked by excessive water excretion (polyuria) and increased thirst (polydipsia).

This condition is commonly treated with **Desmopressin**, a long-acting synthetic analog of vasopressin.

Desmopressin has strong antidiuretic effects but causes less vasoconstriction than natural vasopressin.

2.7.1 – Summarizing Table of Vasopressin and Related Drugs

Drug	Drug class	Route	Mechanism of action	Clinical usage	Adverse effects/cautions
Vasopressin	Endogenous hormone	-	Stimulates V1 receptors → vasoconstriction V2 receptors → ↑ aquaporins → water reabsorption in collecting ducts	Synthetic form of vasopressin can be used clinically - Septic shock - Cardiac arrest - Esophageal varices - Central diabetes insipidus	- GI disturbances - Headache - Hyponatremia - Allergic reaction
Desmopressin	Synthetic vasopressin analog	IV Nasal spray	Selective V2 receptor agonist → enhances water reabsorption without significant vasoconstriction	- Diabetes insipidus - Nocturnal enuresis - Von Willebrand disease - Mild hemophilia A - Control GI bleeding	- GI disturbances - Headache - Hyponatremia - Allergic reaction - Used with caution in CAD patients
Conivaptan	Vasopressin receptor antagonist	IV	Dual V1 and V2 antagonist → blocks vasopressin effects → ↑ free water excretion	Euvolemic and hypervolemic hyponatremia	Infusion site reaction
Tolvaptan	Selective V_2 receptor antagonist	**Orally**	V2 receptor antagonist → ↑ free water clearance, ↓ urine osmolality, ↑ serum sodium	Euvolemic and hypervolemic hyponatremia in patients with heart failure, cirrhosis, and SIADH.	Hepatotoxicity

2.8 – Test Yourself

1. What is the main clinical use of cosyntropin?

a) treat hyperthyroidism
b) diagnose adrenal insufficiency
c) induce ovulation
d) lower prolactin levels

2. Match the drug with the class

Drug	**Class**
A. Pegvisomant	1. Dopamine agonist
B. Cabergoline	2. Vasopressin receptor agonist
C. Desmopressin	3. Growth hormone receptor antagonist

3. What is the primary difference between the effects of GnRH when given pulsatile vs. continuous?

_____
_____
_____

4. Which of the following is a dopamine agonist **used to treat hyperprolactinemia?**

a) oxytocin
b) desmopressin
c) cabergoline
d) Octreotide

5. The liver produces _____ in response to stimulation from growth hormone, which promotes growth and cell proliferation.

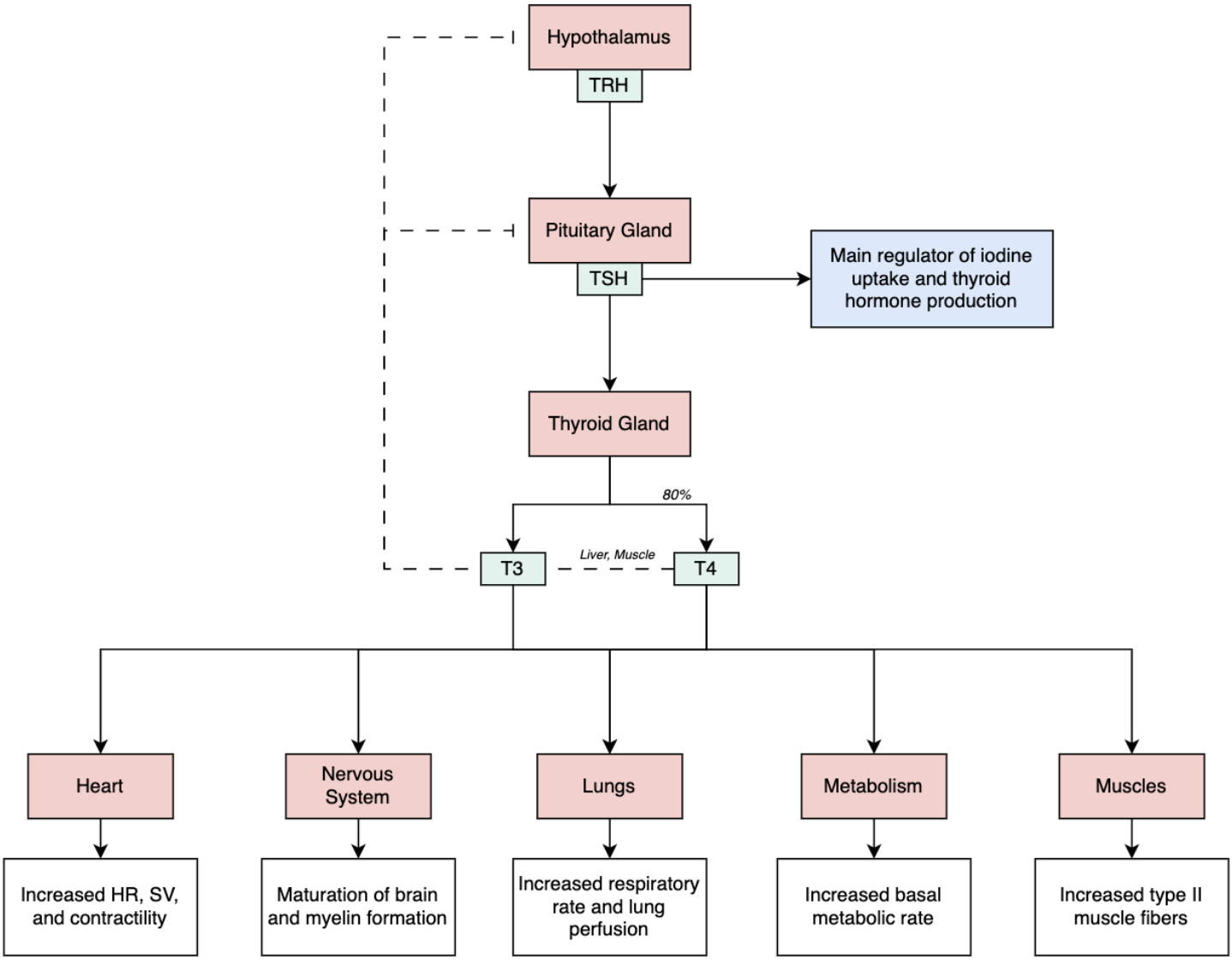
6. Match hormone with function

Hormone	**Function**
A. Vasopressin	1. Uterine contractions and milk ejection
B. Oxytocin	2. Water reabsorption via V2 receptors
C. Prolactin	3. Stimulates lactation

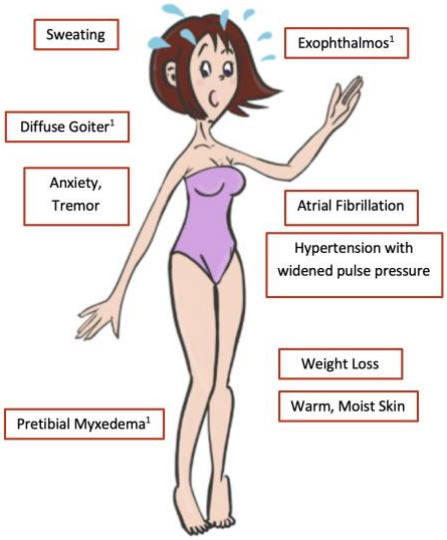
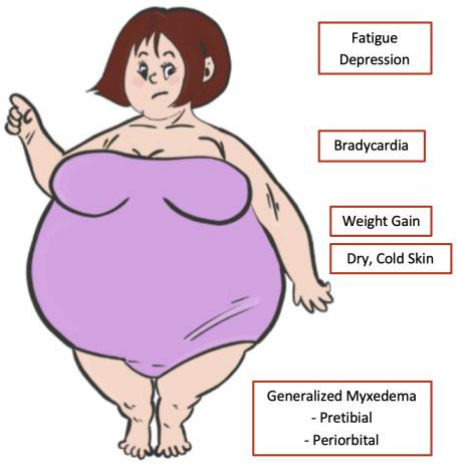
Section 3 – Thyroid and Parathyroid Drugs

3.1 – Thyroid Hormones and Axis

3.1.1 – Thyroid Axis



3.2 – Thyroid Diseases

	Hyperthyroidism	Hypothyroidism
Signs and Symptoms		
Causes	Graves' disease	Hashimoto Radioactive iodine Iodine deficiency[3]
Complications	Thyroid Storm[4]	Mental retardation[2]

[1] Triad of Graves' Disease
[2] In infants and children
[3] Most common cause of hypothyroidism worldwide
[4] Is the acute exacerbation of thyrotoxicosis (hyperthyroidism) which is a life-threatening condition

CLINICAL CORRELATION

Drug Induced Thyroid Disease

Lithium:
- Indicated in bipolar disease
- Inhibit release of thyroid hormones → can cause hypothyroidism

Amiodarone:
= Antiarrhythmic
Contain iodine → can cause hypo- or hyperthyroidism

CLINICAL CORRELATION

Thyroid Goiter

Thyroid goiter is the general term for any abnormal enlargement of the thyroid gland

Can be caused by several things, including Graves' disease, Hashimoto, Iodine deficiency and thyroid cancer

Patients may be asymptomatic or present with hypo/hyperthyroidism

3.3 – Thyrotropin Alfa

- Thyrotropin alfa (Thyrogen) is a recombinant form of TSH
- Increase thyroid gland uptake of radioactive iodine, making it easier to detect recurrence or metastasis
- Used in diagnosis and treatment of thyroid conditions

3.4 – Thyroid Hormone Preparations

	Levothyroxine	Liothyronine
Hormone	T4 *Thyroxine*	T3 *Triiodothyronine*
Clinical Indications	Replacement therapy - Hypothyroidism Suppressive therapy - Thyroid nodules - Diffuse goiter[1] - Thyroid cancer Myxedema coma[2]	Myxedema coma
Adverse Effects	Rare Excessive dose → Hyperthyroidism	Cardiac Hyperthyroidism[3]

[1] Uniform enlargement of the thyroid gland
[2] Medical emergency that require IV administration of loading dose
[3] At higher risk of hyperthyroidism than levothyroxine, because it is more potent and has a more rapid onset

3.4.1 – Levothyroxine

- Different brands have different bioavailability and should not be interchanged without measuring blood levels
- Different foods and drugs can reduce uptake so levothyroxine should be taken on an empty stomach
- Thyroxine is a non-peptide, which allows it to be taken orally without being degraded in the gastrointestinal tract.

3.4.2 – Liothyronine

- Rarely used because it has a short half-life requiring multiple daily doses and a rapid onset, thus causing symptomatic hormonal spikes.

CLINICAL CORRELATION

Levothyroxine
Can be used as suppressive therapy in thyroid cancer and thyroid goiter

It suppresses TSH release by negative feedback of the hypothalamic-pituitary-thyroid axis

TSH promotes thyroid tissue growth, so suppressing TSH levels can help prevent the growth of cancerous or overactive thyroid cells

CLINICAL CORRELATION

Myxedema Coma
Is a severe exacerbation of *hypothyroidism*

Clinical features include:
- Altered mental status
- Myxedema
- Hypothermia
- Hypoventilation
- Hypotension
- Bradycardia

This will require immediate IV therapy with levothyroxine and liothyronine
Have to coadminister hydrocortisone until adrenal insufficiency is ruled out

Myxedema is the collection of fluid in various tissues caused by buildup of glycosaminoglycans
Commonly found in behind the eyes and in the lower legs

CLINICAL CORRELATION

Thyroid Storm / Thyrotoxic crisis
Is a severe exacerbation of *hyperthyroidism*

Clinical features include:
- Severe agitation and anxiety
- Delirium
- Hyperpyrexia with profuse sweating
- Hypertension or hypotension
- Tachycardia

Treatment
- Propranolol for symptomatic relief
- PTU to inhibit synthesis of T3/ T4
- Iodine to inhibit release of T3/ T4
- Glucocorticoids to reduce T4 → T3 conversion peripherally
- Supportive therapy of hyperthermia and hypotension

Hyperpyrexia occurs when there is an extreme fever (> 41.5°C) due to an abnormally high hypothalamic setpoint

3.4.3 – Other thyroid hormone preparations

I. Liotrix
- 4:1 ratio with T4 and T3 respectively

II. Thyroid Desiccated
- Thyroid hormones from pigs
- Not used in treatment anymore

3.5 – Antithyroid Agents

- Used in the treatment of hyperthyroidism

3.5.1 – Thioamide Drugs

- Thioamide drugs are used in the treatment of hyperthyroidism because they inhibit the production of thyroid hormones

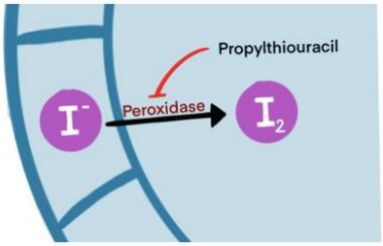
I. Mechanism of Action

- Methimazole and Propylthiouracil (PTU) inhibit thyroperoxidase
- PTU also inhibits the peripheral conversion of T4 to T3
- Delayed effect → Takes 4-8 weeks to deplete hormone stores and normalize circulating hormones

Recall

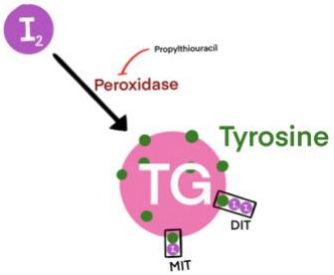
Thyroid Hormone Production

I^- is oxidized to I_2 by the enzyme peroxidase
→ Inhibited by Methimazole and Propylthiouracil
→ Reduces I_2 available to synthesize thyroid hormones



I_2 binds tyrosine moieties on thyroglobulin to form mono- and diidotyrosine (MIT and DIT respectively)
→ Action is inhibited by Methimazole and PTU
→ Reduced synthesis of thyroid hormones

The process where I_2 binds to thyroglobulin is called *organification*



II. Indications and Adverse Effects

Clinical Indication	Adverse Effects
Graves' Disease Thyrotoxicosis	Agranulocytosis Maculopapular rash Transient Leukopenia GI disturbances Fatal liver failure[1] Birth defects in 1st trimester[2]

[1] Higher incidence with PTU
[2] Methimazole

3.5.2 – Other Antithyroid Agents

I. Beta Blockers

- Propranolol is the 1st line treatment in symptomatic thyrotoxicosis
- Acute reduction of adrenergic symptoms of thyrotoxicosis (arrhythmia, tachycardia, anxiety)
- Does *not* treat the underlying cause of thyrotoxicosis

II. Iodide Salts

- Lugol Solution = elemental iodine and potassium iodide
- Symptomatic improvement: 2-7 days after administration
- The effect of iodine salts is limited to a few weeks, so treatment is typically continued with a thioamide drug to maintain inhibition of thyroid hormone synthesis

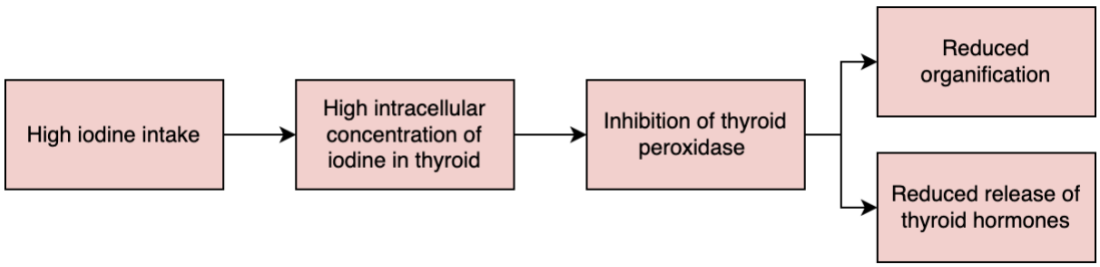
Mechanism of Action	Inhibits the release of thyroid hormones by the Wolff-Chaikoff Effect Reduce the size and vascularity of the thyroid gland
Clinical Indication	Acute thyrotoxicosis Preparation for thyroid surgery Inhibit the release of thyroid hormones after RAI

CLINICAL CORRELATION

Wolff-Chaikoff Effect

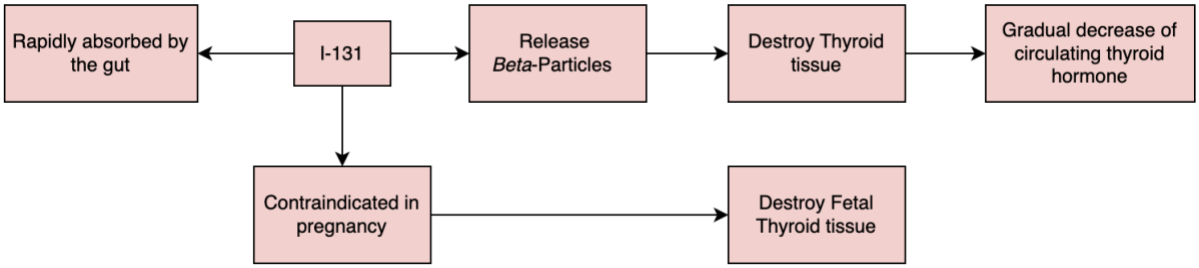
= Transient decrease of thyroid hormone production following iodine ingestion

This protective response prevents the thyroid from producing dangerously high levels of hormones during sudden iodine overload



III. Radioactive Iodine (RAI)

- Consists of Sodium Iodide I-131, which is a radioactive isotope of iodine
- I-131 has a half-life of 8 days, which means it would take weeks for circulating thyroid hormone levels to normalize after exposure
- Pretreatment with thioamide drugs should be withdrawn several days before RAI treatment, because it reduces the efficacy of RAI treatment and increases the risk of post-treatment recurrence
- Posttreatment with iodine salts to avoid release of radioactive thyroid hormones



Clinical Indications	Graves´ disease[1] Toxic multinodular goiter Thyroid cancer[2] Diagnostic imaging[3]
Toxicities	Salivary gland problems Transient worsening of hyperthyroidism Radiation-induced thyroiditis Post-treatment hypothyroidism

[1] Where other medications are not tolerated or fail to treat
[2] To destroy the remaining thyroid tissue after removal of cancer
[3] To visualize potential metastasis or remnants of thyroid cells after thyroidectomy

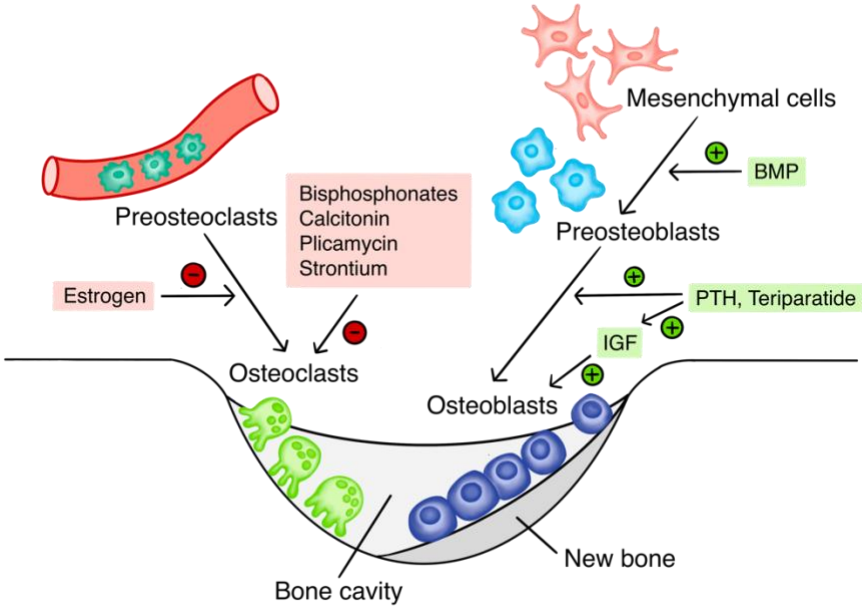
CLINICAL CORRELATION

Nuclear Bomb Explosion

Iodine salts can be used to competitively block RAI uptake by the thyroid gland in case of a nuclear bomb explosion

3.6 – Parathyroid and Bone

3.6.1 – Overview



- Osteoclasts = Break down bone and increase calcium in the blood
- Osteoblasts = Promote bone formation and decrease calcium in the blood

CLINICAL CORRELATION

Osteoporosis

Loss of bone mineral density causes increased susceptibility to fractures

Vertebral fracture is the most common finding

Several risk factors
- Postmenopausal women have ↓ Estrogen
→ Increased activity of osteoclasts
→ Increased bone resorption
- Corticosteroid use

Use DXA scan (type of x-ray) to diagnose osteoporosis

1st line treatment is bisphosphonates

CLINICAL CORRELATION

Paget Disease of Bone

Increased bone remodeling
↑ Osteoclast and ↑ Osteoblast activity
→ Formation of disorganized bone

Clinical features include:
- Bone pain
- Saber shin[1]
- Skull enlargement
- Impaired hearing

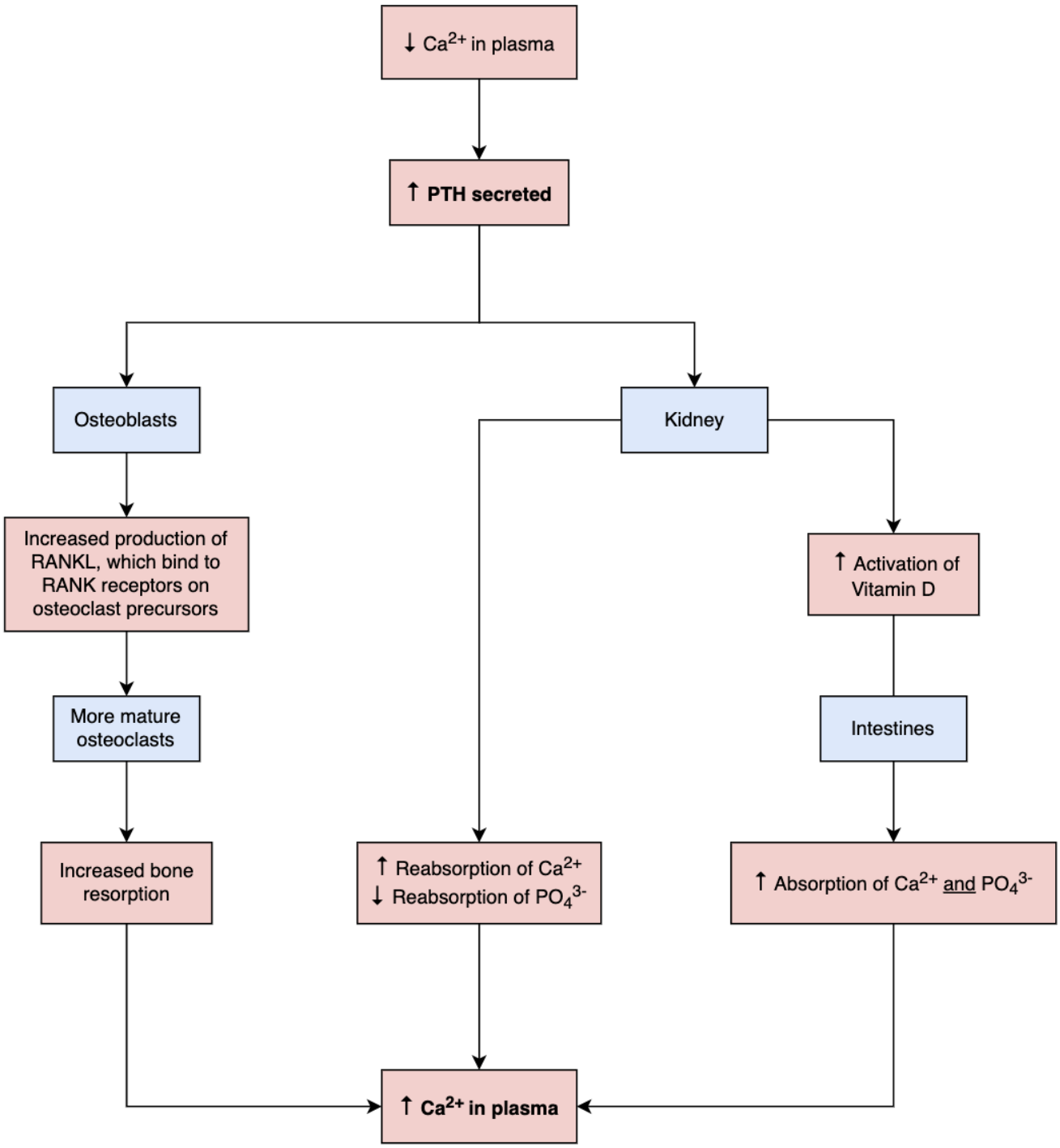
Pharmacological goal: Reduce bone pain and prevent progressive bone deformity

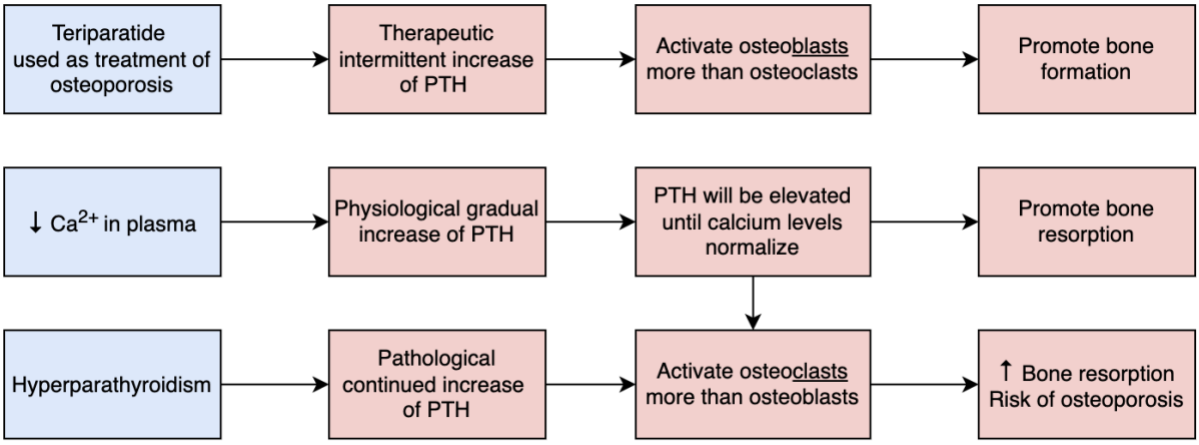
Drug of Choice: Calcitonin and/ or Bisphosphonates (Zoledronic acid)

[1]Also seen in Rickets and Congenital Syphilis

3.6.2 – Parathyroid hormone

I. Actions of Parathyroid Hormone



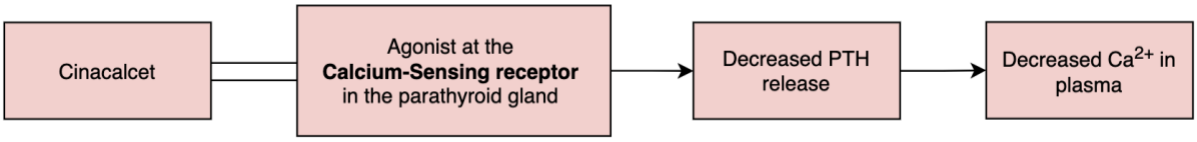


II. Teriparatide

- = Recombinant form of human PTH
- Increase bone formation by stimulating osteoblast activity
- Indicated in postmenopausal women with osteoporosis and hypogonadal men with a high risk of fracture.
- Teriparatide is contraindicated in patients with increased risk of osteosarcoma, such as Paget disease, because it stimulates bone formation and increases bone turnover, which may promote bone malignancy.

III. Cinacalcet

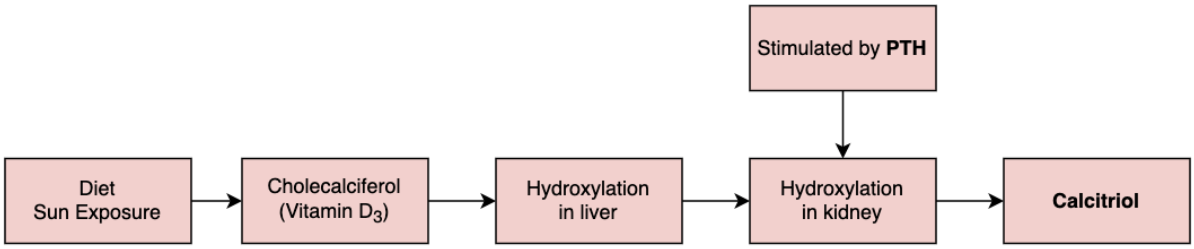
- Cinacalcet increases the sensitivity of calcium-sensing receptors in the parathyroid gland, making the parathyroid cells think there is more calcium in the blood than it actually is.
- Used to treat hypercalcemia due to hyperparathyroidism and parathyroid carcinoma



3.6.3 – Calcium and Vitamin D

	Calcium Supplementation	Vitamin D Supplementation
Types	Calcium Carbonate[1] Calcium Citrate[2]	Cholecalciferol – D_3 Ergocalciferol – D_2 Calcitriol (active form of Vitamin D)
Clinical Indication	Osteoporosis Hypocalcemia	Osteoporosis Hypocalcemia[3] Rickets Vitamin D Deficiency in CKD[4]
Adverse Effects	<u>Constipation</u> Myocardial Infarction	Hypercalcemia / Hypercalciuria
Drug interaction	Reduce absorption of some drugs → should be taken 2 hours before other drugs	

[1] Require stomach acid to be absorbed
[2] Do NOT require stomach acid → Preferred in elderly
[3] From Hypoparathyroidism
[4] Require Calcitriol because they lack the ability to hydroxylate precursors



<u>CLINICAL CORRELATION</u>

Vitamin D supplement
Most individuals will require supplementation to obtain Recommended Daily Amount (400-800 IU)

Melanin-rich skin has a slower uptake of Vitamin D from the sun
→ Dark skinned individuals living in the north should therefore take supplements to achieve RDA

<u>CLINICAL CORRELATION</u>

Dihydrotachysterol
= Vitamin D analog that does not require renal hydroxylation
→ Given to patients with CKD

<u>IMPORTANT TO DIFFERENTIATE</u>

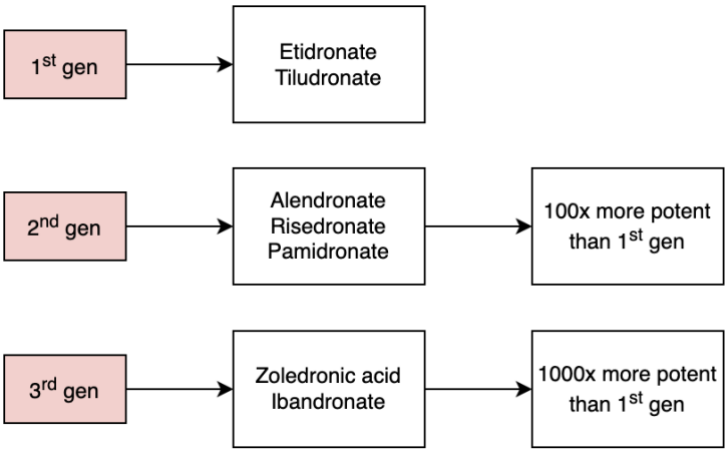
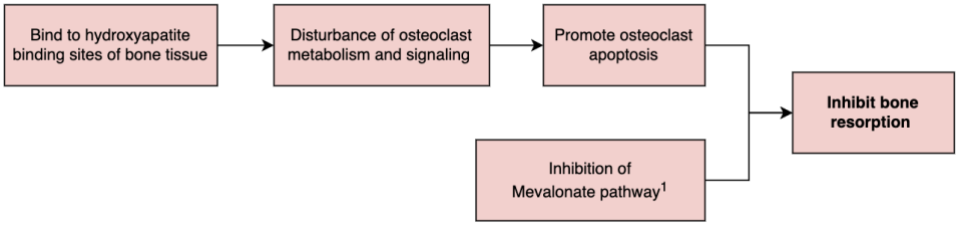
Calcitonin → Decrease serum Calcium
Calcitriol → Increase serum Calcium

3.6.4 – Bisphosphonates

- Bisphosphonates are a class of drugs that reduce bone loss by inhibiting osteoclast activity
- Most bisphosphonates are given orally → About 5% is absorbed into bone
- Half-life in bone > 10 years
- May require 6 months to be effective

SUFFIX

Bisphosphonates: -dronate

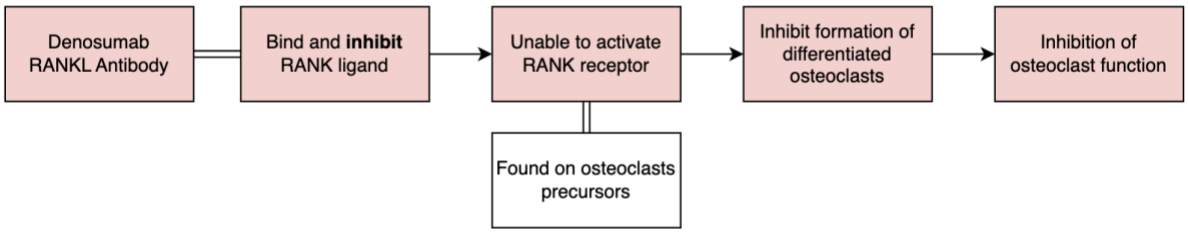
	Bisphosphonates
Drug Name	
Mechanism of Action	
Clinical Indication	Osteoporosis Paget´s Disease of Bone Hypercalcemia Osteolytic bone lesions of metastatic cancer
Adverse Effects	GI distress (Esophageal erosion[2]) Atypical femur fracture Hypocalcemia Osteonecrosis of the jaw

[1] Pathway in cholesterol synthesis → Statins also inhibit bone resorption
[2] Tablets should not be taken with food or while lying down

3.6.5 – RANKL Antibodies

- RANKL is a signaling molecule produced by osteoblasts, which binds to RANK receptors on osteoclast precursors.
- When RANKL binds to RANK receptors, it stimulates osteoclast maturation and will eventually cause increased bone resorption.
- RANKL antibodies bind to the RANK receptor, and inhibit the maturation of osteoclasts and thereby inhibiting the bone resorption

I. Mechanism of Action



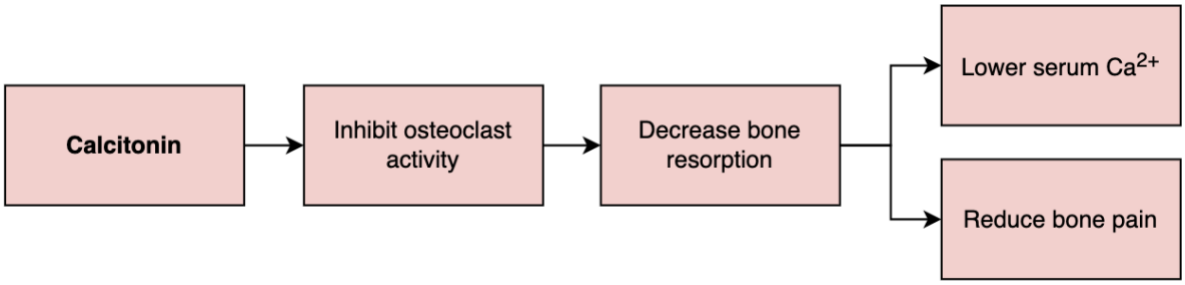
Clinical Indications	Adverse Effects
Osteoporosis	Muscle and joint pain Increased risk of infection[1] Hypocalcemia[2]

[1] May be due to RANKL´s role in immune cell function
[2] Because more Calcium is used in bone formation than is released from bone resorption

3.6.6 – Calcitonin

- Calcitonin is a hormone produced by the parafollicular cells (C cells) in the thyroid gland
- It opposes the effects of parathyroid hormone, and will decrease serum Ca^{2+} and PO_4^{3-}
- Administered subcutaneous or intranasal → Due to poor absorption after oral intake

I. Mechanism of Action



II. Clinical Indication

- Osteoporosis
- Paget´s Disease of Bone
- Hypercalcemia
- Can be used as a tumor marker in medullary thyroid cancer

III. Adverse Effects

- Nasal irritation and bleeding after nasal administration
- Hypocalcemia

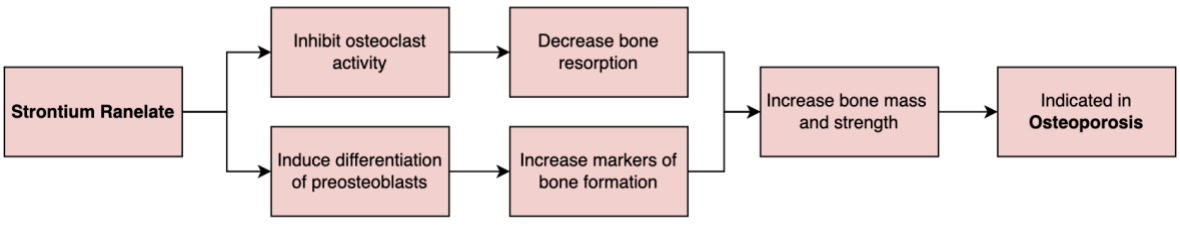
3.6.7 – Other

I. Sodium Fluoride

- Sodium fluoride is an inorganic salt of fluoride
- It is used to prevent tooth decay and dental caries
- Fluoride replaces the hydroxyl group in hydroxyapatite to form fluorapatite, which is more resistant to acid erosion in the tooth than hydroxyapatite

II. Strontium Ranelate

- Strontium Ranelate is a salt that was formerly used to treat osteoporosis
- Rarely used now as it is found to have an increased risk of blood clots



3.7 – Test Yourself

1. Methimazole is used in the treatment of hyperthyroidism because it …

a) Inhibit secretion of TSH

b) Inhibit biosynthesis of thyroglobulin

c) Inhibit thyroperoxidase and therefore reducing I_2 available for production of thyroid hormones

d) Inhibit uptake of I^- into the thyroid gland

2. A woman with hyperthyroidism is pregnant in the 1st trimester. Which drug should be prescribed?

a) Methimazole

b) PTU

c) Radioactive iodine

d) Lugol Solution

3. A 43-year-old woman comes to the GP due to intermittent episodes of heart palpitations and chest pain over the last weeks. On examination you notice irregular heart rhythm, excessive sweating and fine tremor of both hands. Which drug can reduce her symptoms?

a) Propranolol

b) Amiodarone

c) Thyroxine

d) Epinephrine

4. Fill out the table for thioamides

Clinical Indication	Adverse Effects

5. A 78-year-old woman comes to the ER due to progressively worsening pain and swelling of the left side of her face. She has had several fractures during the last years and is therefore undergoing treatment for osteoporosis. Which drug can be responsible for her symptoms?

a) Calcitonin

b) Zoledronic Acid

c) Calcitriol

d) Teriparatide

6. Fill out the table with ↑ and ↓

	Bone	Intestine	Kidney		Blood	
	Bone resorption	Ca^{2+} absorption	Ca^{2+} reabsorption	PO_4^{3-} reabsorption	Serum Ca^{2+}	Serum PO_4^{3-}
Calcitriol	-					
PTH		-				
Calcitonin						

7. Cinacalcet decrease PTH level by

a) Inhibiting parafollicular cells of the thyroid gland

b) Indirectly by increasing Ca^{2+} reabsorption in the distal convoluted tubule

c) Inhibiting expression of the PTH gene

d) Activating calcium-sensing receptors in the parathyroid gland

8. A 68-year-old man presents with bone pain and hearing impairment. He reports that his helmet has recently become too tight. X-rays reveal findings consistent with Paget disease of bone. Which of the following is the most appropriate first-line treatment?

a) Zoledronic acid

b) Calcitriol

c) Teriparatide

d) Strontium Ranelate

9. What is the most appropriate treatment for a patient with Vitamin D deficiency and chronic kidney disease?

a) Ergocalciferol

b) Cholecalciferol

c) Calcitriol

d) Calcium carbonate

Section 4 – Drugs for diabetes

4.1 – Pancreatic Hormones Physiological Effects

- *This booklet will focus on insulin and glucagon as these are the two hormones connected to test nr.4. If you want to remind yourself further, use the endocrine booklet section 7.*

4.1.1 – Overview of Insulin and Glucagon

	Produced by	Main mechanism	Release is activated by	Effect
Insulin	β-cells in the pancreas	Promotes glucose uptake in skeletal muscle and adipose tissue by activating **GLUT4**	Rise in blood glucose concentration	**Promotes storage** of glycogen, triglycerides, and protein. **Inhibits breakdown** of glycogen, triglycerides, and protein. Stimulates glycogen synthesis, inhibits glycogenolysis and gluconeogenesis→ reducing glucose output from the liver
Glucagon	α-cells in the pancreas.	Increase blood glucose levels during fasting or hypoglycemia	Response to decreased blood glucose	Stimulates glycogenolysis and gluconeogenesis and **Inhibits glycogen synthesis** in the liver →Promoting glucose release from the liver. Promotes lipolysis in adipose tissue

4.2 – Diabetes Classification

	Diabetes Mellitus type 1	Diabetes mellitus type 2
Etiology	Autoimmune destruction of pancreatic β-cells that causes insulin deficiency	Insulin resistance with a relative insulin deficiency because of β-cells dysfunction, often associated with obesity
Genetic predisposition	Moderate	Very strong
Onset	May occur at any age, however it is most common in children and adolescents	Typically in adults
Treatment + pharmacological management	Multiple daily insulin injections or insulin pump	- Lifestyle changes - Oral antidiabetic drugs - Subcutaneous antidiabetic drugs

CLINICAL CORRELATIONS

Ketoacidosis

- Medical emergency caused by not enough or absent insulin administration.
-More commonly affects those with diabetes type 1 and less frequently in those with diabetes type 2.

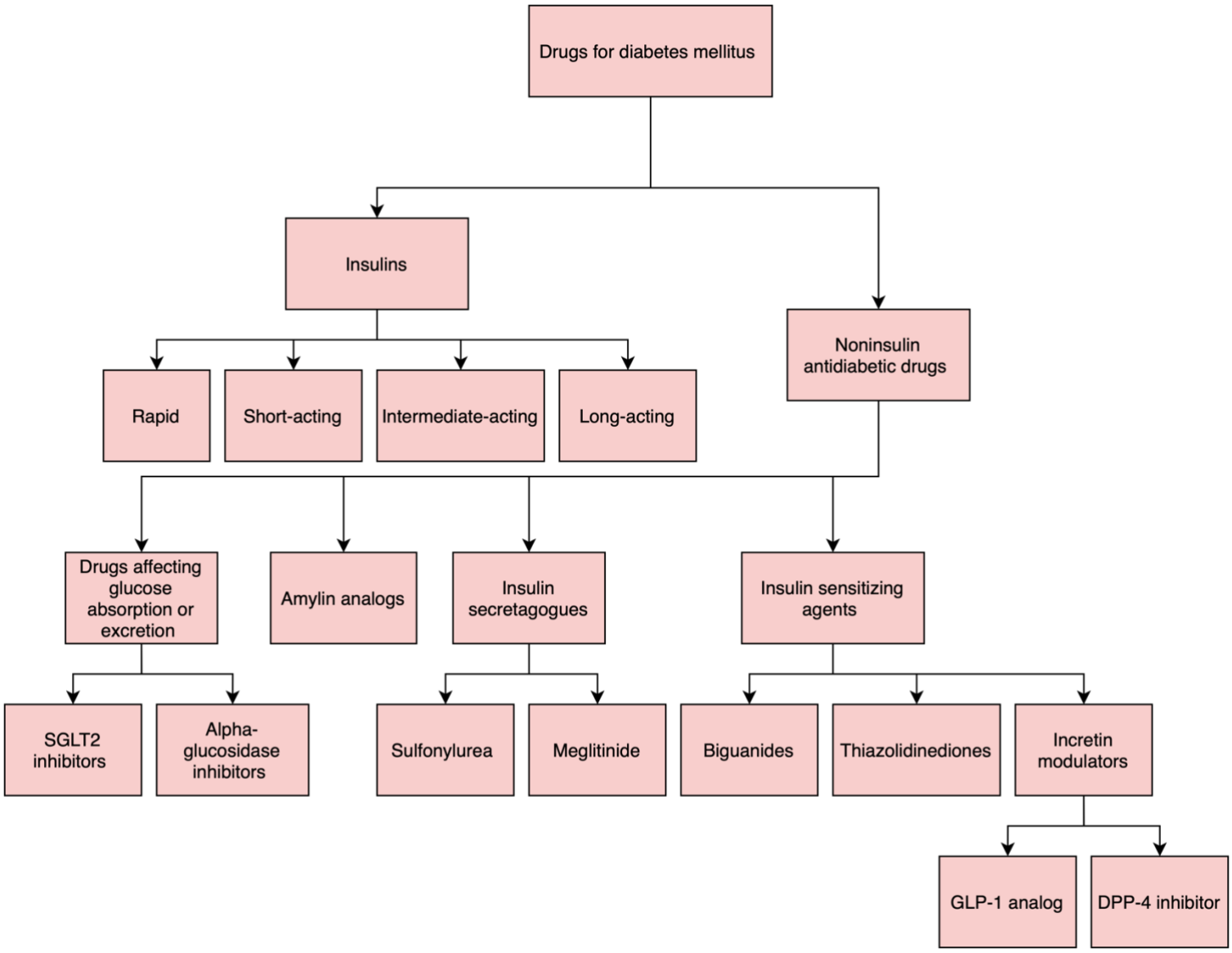
Insulin deficiency→glucose will not be taken up by the cells→ increased lipolysis and free fatty acid release→liver converts free fatty acid→accumulation of ketones→ decrease in pH

Treatment includes:

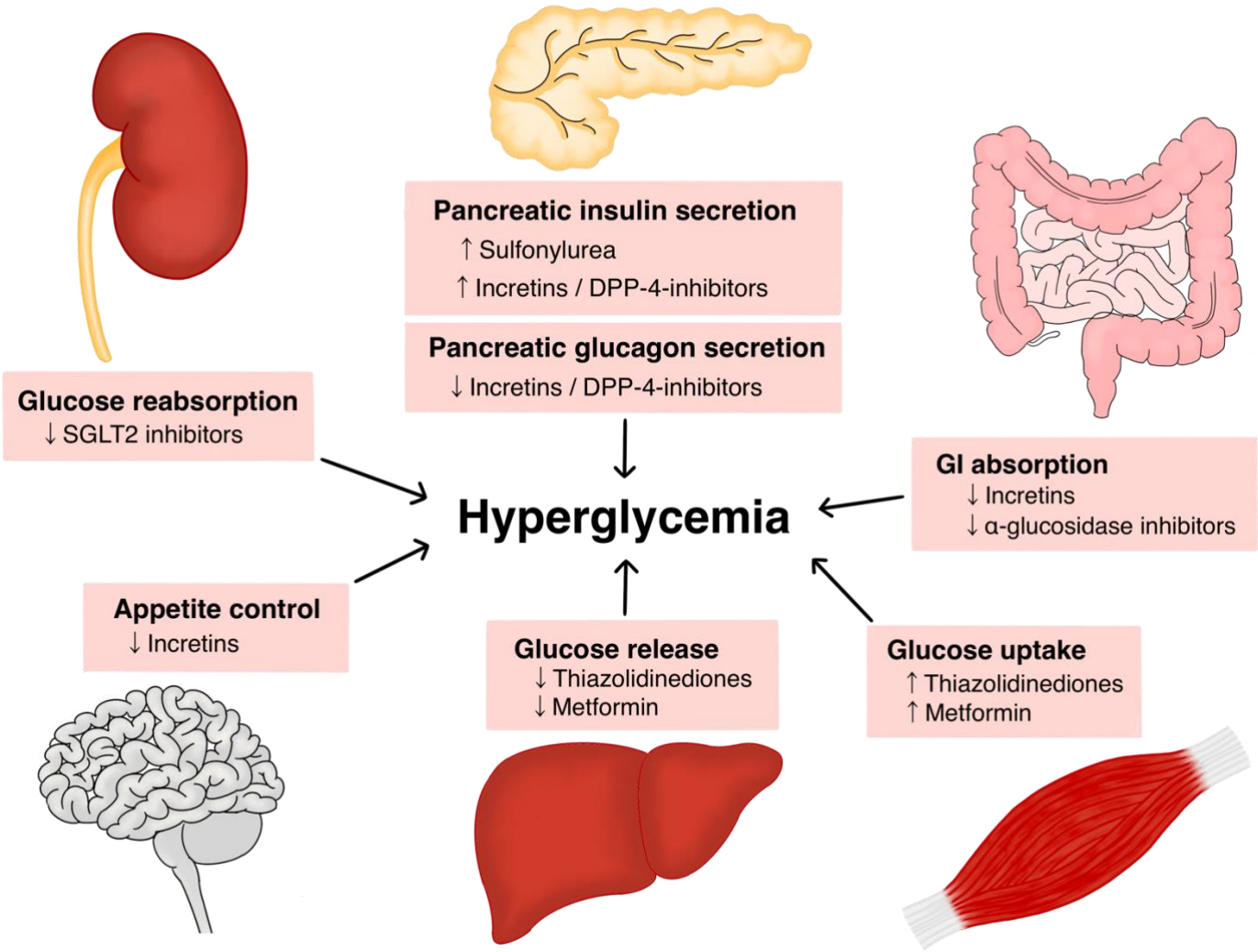
- Insulin→ stimulate glucose uptake from the blood to the cells
- Potassium → insulin shifts potassium into cells. This can induce hypokalemia. Therefor supplementation of potassium is often necessary.
- Isotonic fluid treatment → to replace fluid loss from increased voiding

4.3 – Overview of Antidiabetic Agents and Mechanism of Action

4.3.1 – Overview of Drugs Used in Diabetes Mellitus



4.3.2 – Effect of Antidiabetic Drugs on Various Tissues



4.4 – Insulin Preparation

- All patients with type 1 diabetes are treated with insulin preparations and about one-third of patients with type 2 diabetes
- Insulin therapy is used to control both basal and postprandial glucose levels while minimizing the risk of hypoglycemia.
- Human insulin is preferred over pork or beef insulin as it is less likely to make the patient develop insulin resistance and less likely to cause allergic reaction or lipodystrophy at the injection site.
- Differences in the amino acid composition of insulin give different preparations different pharmacokinetic properties.
- Administration of insulin is usually injected subcutaneously or by continuous subcutaneous infusion with an insulin pump.

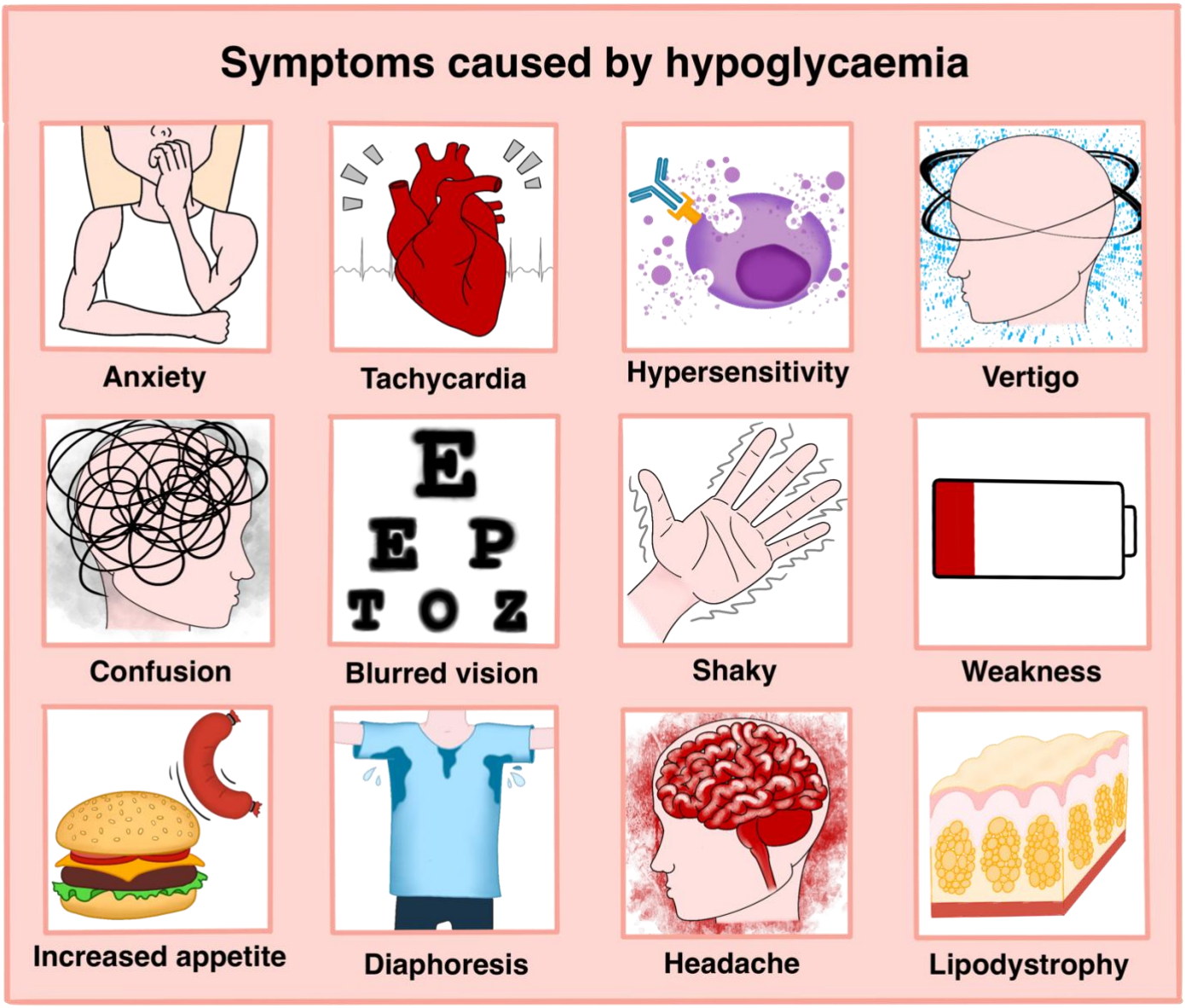
	Rapid-acting insulin	**Short-acting insulin**	**Intermediate-acting insulin**	**Long-acting insulin**
Usage	Taken right before eating	Used in IV form for treating diabetic ketoacidosis.	Provides basal control of blood glucose.	Provides basal control of blood glucose.
Mechanism	Human insulin analogs with amino acid substitution These modifications prevent insulin molecules from clumping together, allowing for faster absorption.	Regular insulin consists of hexamers surrounding a zinc molecule. After injection, the hexamers dissociate into dimers and monomers. This process takes longer time, hence later onset of action.	Formed by the addition of zinc and protamine. Protamine forms a less soluble structure that is resulting in delayed absorption.	Steady, peak less release. Mimics basal insulin secretion
Drugs	**Aspart (NOVOLOG)** **Lispro (HUMALOG)** **Glulisine (APIDRA)**	**Regular (HUMULIN R)**	**Isophane**	**Glargine (LANTUS)** **Detemir (LEVEMIR)** **Degludec (TRESIBA)**

4.4.1 – Hypoglycemia

I. Key Reasons for Hypoglycemia in Type 1 Diabetes

- Too much insulin → Overdosing short- or long-acting insulin lowers glucose too far
- Skipped/delayed meals → No food after insulin → blood sugar drops
- Increased physical activity → Exercise uses glucose → insulin effect becomes too strong
- Alcohol → Suppresses liver gluconeogenesis → worsens hypoglycemia
- Wrong insulin timing/type → E.g. giving rapid-acting insulin too early or mixing up doses

II. Symptoms Caused by Hypoglycemia

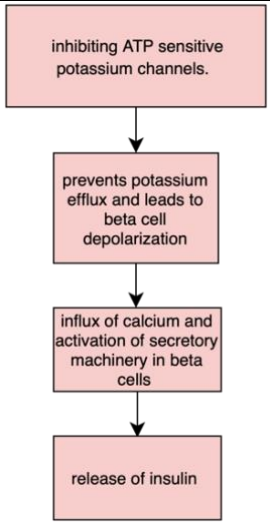


4.5 – Insulin Secretagogues

- Insulin secretagogues are a class of medications used to treat type 2 diabetes.
- They stimulate the pancreatic beta cells to release insulin, regardless of blood glucose levels.

4.5.1 – Sulfonylurea drugs

- Sulfonylureas are oral antidiabetic drugs that lower blood glucose by stimulating insulin secretion and decreasing the secretion of glucagon

<table>
<tr><th colspan="3">Sulfonylurea drugs</th></tr>
<tr><td>Mechanism</td><td colspan="2"> 
</td></tr>
<tr><td>Route</td><td colspan="2"> 
</td></tr>
<tr><td>Effect</td><td colspan="2">- Increasing the amount of insulin secreted
- Decreasing glucagon secretion</td></tr>
<tr><td>Indications</td><td colspan="2">Can be used alone or in combination with metformin in patients with type 2 diabetes</td></tr>
<tr><td>Adverse effects</td><td colspan="2">- Weight gain
- Hypoglycemia
- Few cases of hematological reactions such as leukopenia, thrombocytopenia, hemolytic anemia</td></tr>
<tr><td>Interaction</td><td>Drugs that increase the effect
- ACE- inhibitors
- sulfonamides
- salicylates and other NSAIDs
- Gemfibrozil</td><td>Drugs that decrease the effect
- Thiazides
-Corticosteroids
- Estrogens
- Thyroid Hormones
Phenytoin</td></tr>
<tr><td>Drugs</td><td><u>First generation</u>
Tolbutamide
Chlorpropamide
Tolazamide</td><td><u>Second generation</u>
Glimepiride
Glipizide
Glyburide</td></tr>
</table>

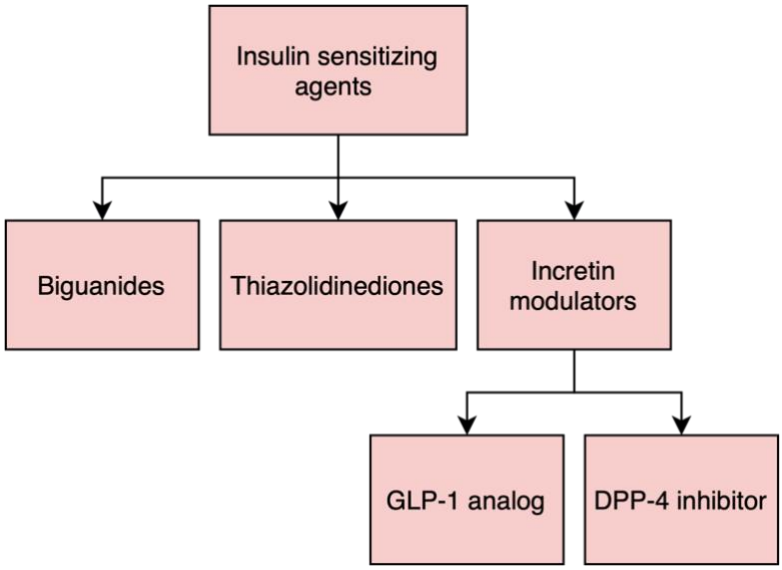
4.5.2 – Meglitinide compounds

- Meglitinide drugs stimulate insulin secretion through blockade of ATP-sensitive potassium channels on the pancreatic beta cells.
- Have a shorter duration of action, which allows for more flexible dosing around meals, reducing the risk of hypoglycemia compared to sulfonylureas.

Meglitinide compounds	
Mechanism	Same as for sulfonylurea drugs
Effect	Increase the amount of insulin release
Benefit	Achieve peak effectiveness in about 1 h perfect to control postprandial glycemia. Duration of action is relatively short→ insulin concentrations return to basal levels before the next meal
Indications	Taken before meals to control postprandial glycemia Can be taken alone or in combination with metformin Useful in patients with irregular meal intervals
Adverse effects	Hypoglycemia
Interactions	SHOULD NOT be used with other oral antidiabetic drugs or with insulin
Drugs	**Repaglinide** **Nateglinide**

4.6 – Insulin Sensitizing Agents

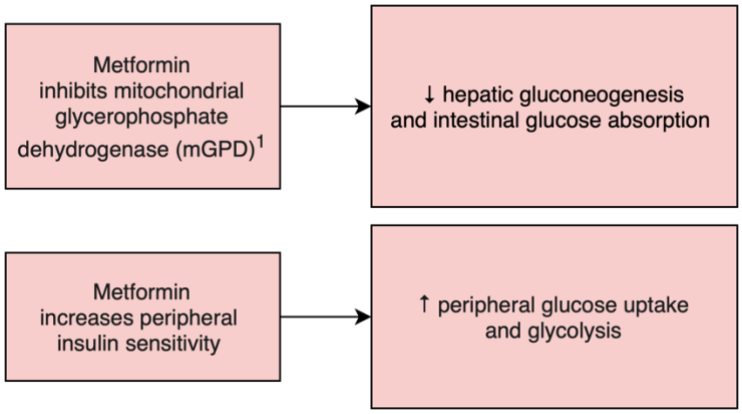
- Works by decreasing the insulin resistance and increasing glucose uptake.
- Metformin, thiazolidinedione compounds, and incretin mimetics are included in this group
- Unlike insulin secretagogues agents these drugs do not increase insulin secretion, therefor the risk of hypoglycemia is far less.



4.6.1 – Metformin

- Metformin belongs to the biguanide drug class.
- Recommended as <u>first-line treatment for type 2 diabetes.</u>
- Metformin primarily enhances the effects of insulin by reducing insulin resistance and altering glucose metabolism.
- Works well in combination with other oral antidiabetic drugs. Commonly combined with a sulfonylurea, meglitinide, alpha glucosidase inhibitor or incretin mimetic.

I. Main Mechanism of Action

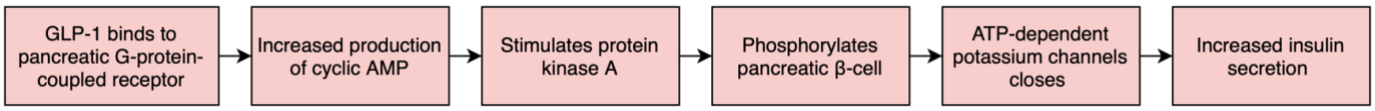


[1] mGPH supports gluconeogenesis in the liver by allowing the conversion of glycerol into glucose

4.6.2 – Thiazolidinediones

- Also known as glitazones
- Greater effect on skeletal muscle and adipose tissue, rather than the liver compared to metformin.
- Metabolites of pioglitazone have pharmacological activity.

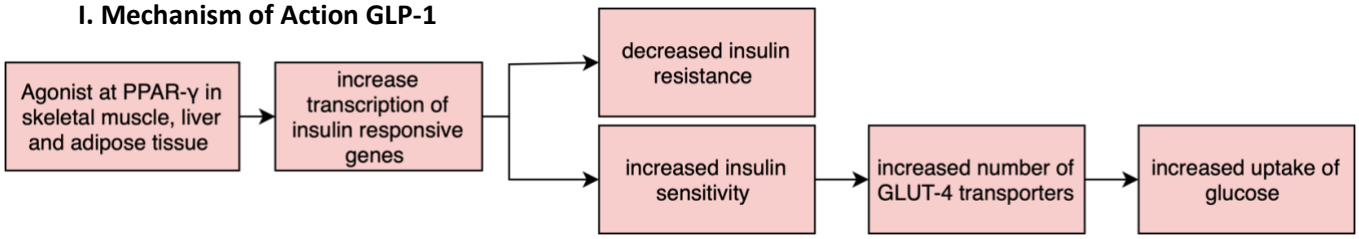
I. Mechanism of Action



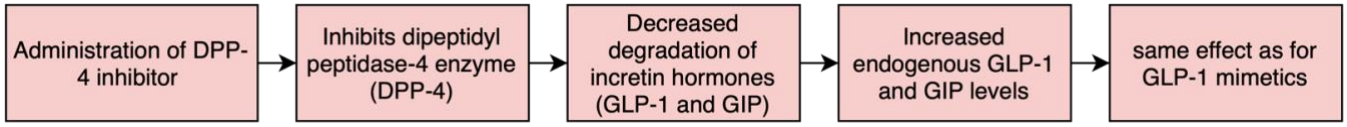
4.6.3 – Incretin Mimetics

- Incretins are a group of metabolic hormones released from the small intestine in response to food intake.
- The two main incretin mimetics are glucagon-like-peptide-1 (glp-1) and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors).
- GLP-1-like peptides are administered subcutaneously.

I. Mechanism of Action GLP-1



II. Mechanism of Action DPP-4 Inhibitor



CLINICAL CORRELATIONS

"OZEMPIC" / Semaglutide

Probably best known today for its effectiveness in promoting weight loss. Ozempic is a GLP-1 receptor agonist originally developed for treating type 2 diabetes.

It enhances glucose-dependent insulin secretion, suppresses glucagon, slows gastric emptying, and reduces appetite.

Clinically, it improves glycemic control, supports weight reduction, and lowers cardiovascular risk in patients with type 2 diabetes.

4.6.4 – Comparison of Insulin Sensitizing Agents

	Metformin	Thiazolidinedione/Glitazones	Incretin mimetics	
			GLP-1	DPP-4 inhibitor
Route	Orally→ renal excretion	Orally	Mostly injected	Orally
Effect	- Inhibition of gluconeogenesis in the liver - Increasing insulin sensitivity in peripheral tissue - Promotes glucose uptake in skeletal muscle and adipose tissue - Inhibits glucose absorption from the intestine	- Increases insulin sensitivity of skeletal muscle and adipose tissue -Suppresses hepatic glucose output	- Stimulation of glucose-dependent insulin secretion - Inhibition of glucagon secretion - Increased glucose uptake by adipose tissue and skeletal muscle - Slowed gastric emptying	
Indications	Especially useful in patients with insulin resistance, obese patients or for patients with hyperlipidemia[1]	The role of this drug in treating DM 2 is uncertain due to its limited efficacy	DM 2 patients that does not respond well to oral treatment	Suited for older and frail patients[5]
Adverse effect	- Diarrhea - Rare cases of lactic acidosis[2]	- Fluid retention[3] - increase in body weight - rare cases of bladder cancer and osteoporosis	Nausea Pancreatitis[4]	GI symptoms
Interactions	Cimetidine can inhibit the metabolism of metformin.	-	-	-
Drugs	**Metformin**	**Pioglitazone** **Rosiglitazone**	**Exenatide** **Liraglutide** **Lixisenatide** **Albiglutide** **Dulaglutide**	**Sitagliptin** **Alogliptin** **Linagliptin** **Saxagliptin**

[1] Metformin is often associated with weight loss.

[2] Patients with hepatic/ renal diseases or patients with a high intake of alcohol should therefore not be treated with metformin.

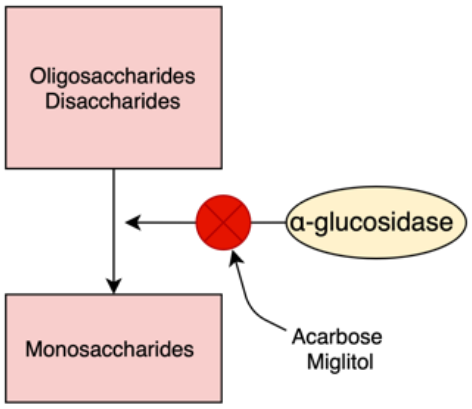
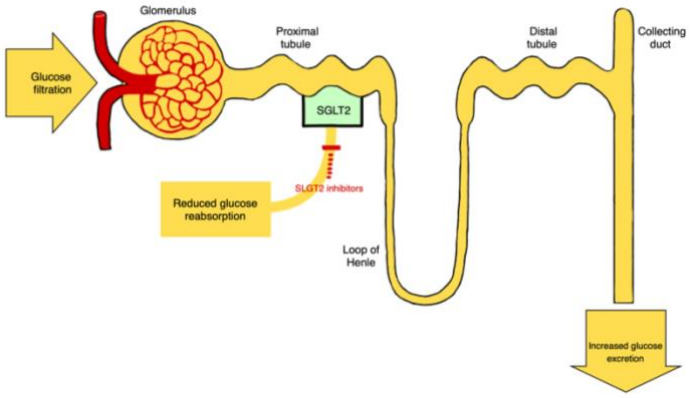
[3] Increasing the risk of heart failure, therefore, people with heart failure or people at risk of developing it should not use this drug.

[4] Slightly increased risk, especially in people with hypertriglyceridemia or gallstones

[5] Can also be used in patients with renal insufficient, and it does not cause hypoglycemia or GI symptoms

4.7 – Drugs Affecting Glucose Absorption or Excretion

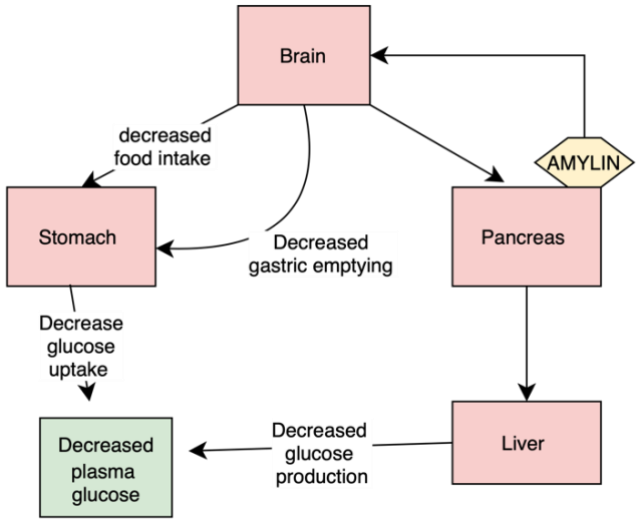
- α-glucosidase inhibitors, SGLT2 inhibitors, and amylin mimetic goes to this category.
- α-glucosidase is an enzyme located in the brush border of the intestine. It converts oligosaccharides and disaccharides to monosaccharides

<table>
<tr><th></th><th>α-glucosidase inhibitors</th><th>SGLT2 inhibitors (Gliflozins)</th></tr>
<tr><td>Mechanism</td><td>Acts locally in the GI tract
 
</td><td> 
</td></tr>
<tr><td>Effect</td><td>Decreases the rate of glucose absorption</td><td>Decreases renal glucose absorption and increases renal glucose excretion</td></tr>
<tr><td>Indication</td><td>Usually in combination with another oral antidiabetic drug to control type 2 diabetes</td><td>Patients with type 2 diabetes
Should <u>not</u> be used in patients with kidney insufficiency</td></tr>
<tr><td>Adverse effect</td><td>- Flatulence
- Abdominal bloating</td><td>UTI
- genital yeast infections
- AKI</td></tr>
<tr><td>Interactions</td><td>Acarbose
- Can enhance the absorption of metformin
-Decrease iron absorption

Miglitol
Decreases absorption of ranitidine[1] and propanolol[2]</td><td>-</td></tr>
<tr><td>Drugs</td><td>Acarbose
Miglitol</td><td>Canagliflozin
Dapagliflozin
Empagliflozin</td></tr>
</table>

4.8 – Amylin Mimetic

- Amylin is a hormone co-secreted with insulin by beta cells in the pancreas, and it plays a key role in the postprandial glucose control
- Given as subcutaneous injections

Pramlintide	
Mechanism	
Route	Subcutaneously
Effect	- Slows gastric emptying - Suppresses glucagon secretion - Reduces glucose output by the liver - Reduces appetite
indication	Can be used in patients with both type 1 and 2 diabetes who are being treated with insulin.
Adverse effects	- Nausea -Anorexia -Headache -hypoglycemia[1]
Interactions	In coadministration with insulin increases the risk of hypoglycemia
Drugs	**Pramlintide acetate**

[1] coadministration of pramlintide and insulin increases the risk of hypoglycemia

4.9 – Test Yourself

1. Insulin is produced by the _____ cells, while glucagon is produced by the _____ cells in the pancreas.

2. Which of the following is <u>not</u> an effect of insulin?
A. Promotes glucose uptake in skeletal muscle
B. Inhibits glycogenolysis
C. Promotes gluconeogenesis
D. Stimulates glycogen synthesis

3. Match the insulin preparation to its classification:

A. Aspart	1. Short-acting insulin
B. Regular	2. Intermediate-acting insulin
C. Isophane	3. Long-acting insulin
D. Glargine	4. Rapid-acting insulin

4. Which of the following drugs is a sulfonylurea?
A. Tolbutamide
B. Chlorpropamide
C. Glipizide
D. Repaglinide

5. Name two GLP-1 receptor agonists used in diabetes management.

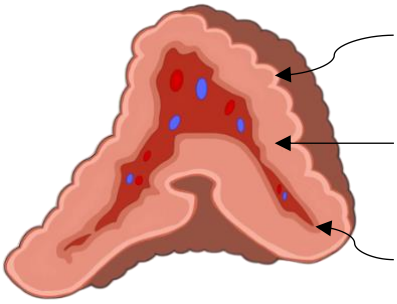
_____
_____

6. Which oral drug is associated with rare cases of lactic acidosis and should be avoided in patients with renal dysfunction?
A. Glipizide
B. Metformin
C. Sitagliptin
D. Rosiglitazone

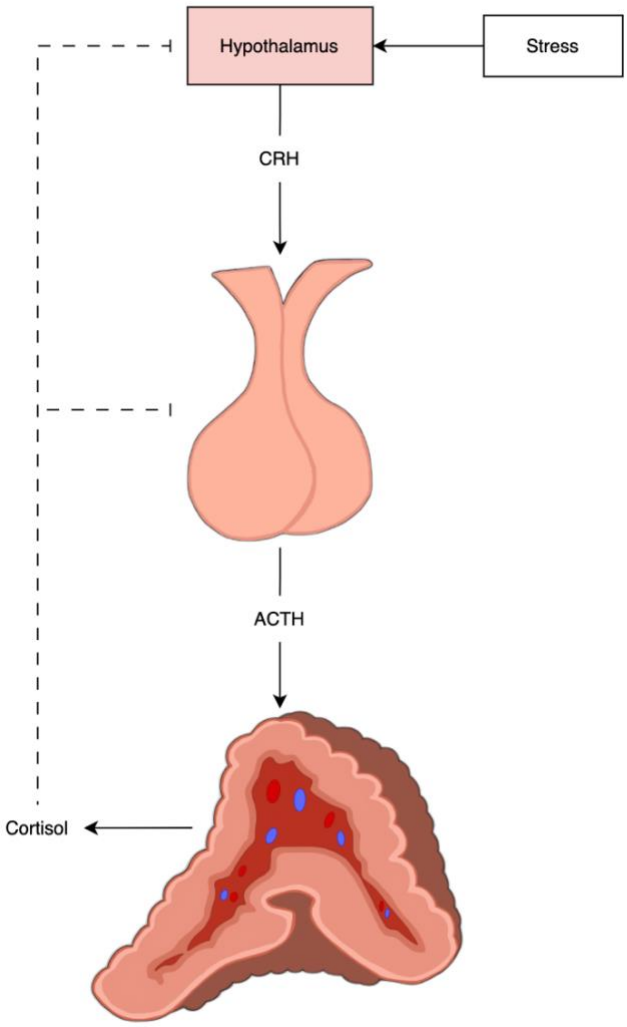
7. _____ and _____ are SGLT2 inhibitors that promote renal glucose excretion.

Section 5 – Adrenal Steroid Drugs

5.1 – Adrenal Steroids

Layer	Hormone	Function
 Zona Glomerulosa	**Mineralocorticoids** (Aldosterone)	Salt balance in blood
Zona Fasciculata	**Glucocorticoids** (Cortisol)	Sugar balance in blood
Zona Reticularis	**Androgens** (DHEA)	Male sex characteristics

5.1.1 – Hypothalamic-pituitary-adrenal axis (HPA axis)



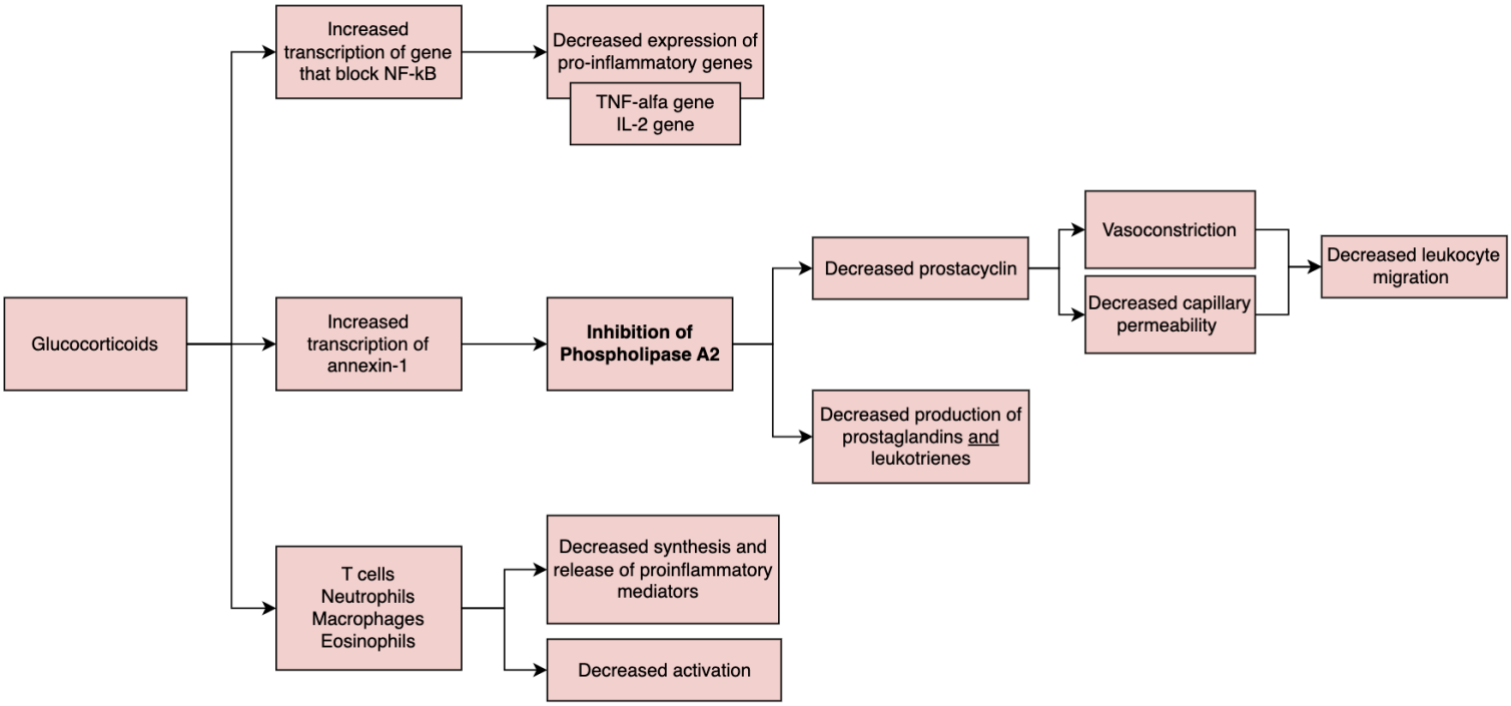
5.2 – Adrenal Steroid Drugs

5.2.1 – Glucocorticoids

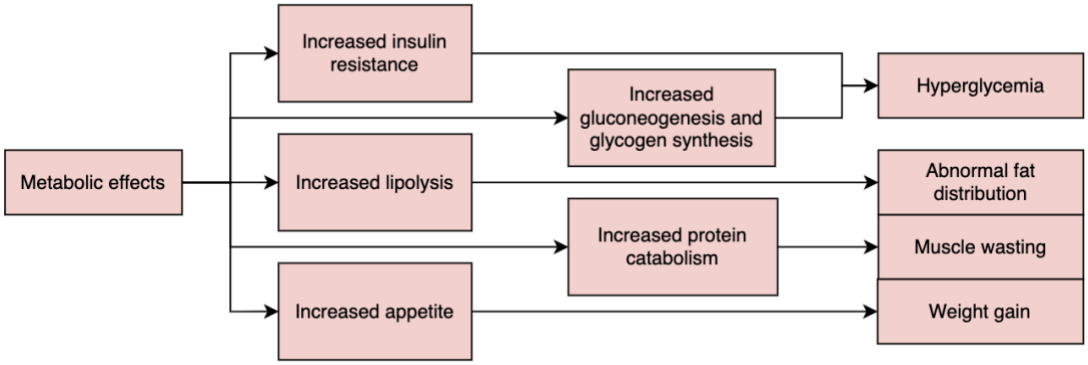
- Glucocorticoids are steroid hormones that reduce inflammation and suppress the immune system by altering gene expression and inhibiting pro-inflammatory pathways
- Generally, glucocorticoids with longer duration of action tend to have higher glucocorticoid potency and lower mineralocorticoid potency
- Production of cortisol is diurnal, meaning that it peaks in the morning and decreases during the day

	Hydrocortisone Cortisol	**Prednisone**	**Dexamethasone Betamethasone**
Duration of Action	Short-Acting (8-12h)	Intermediate Acting (12-36h)	Long Acting (24-72h)
Mineralocorticoid Potency	1	0.7	-
Glucocorticoid Potency	1	3.5	30

I. Anti-inflammatory and Immunosuppressive Effects

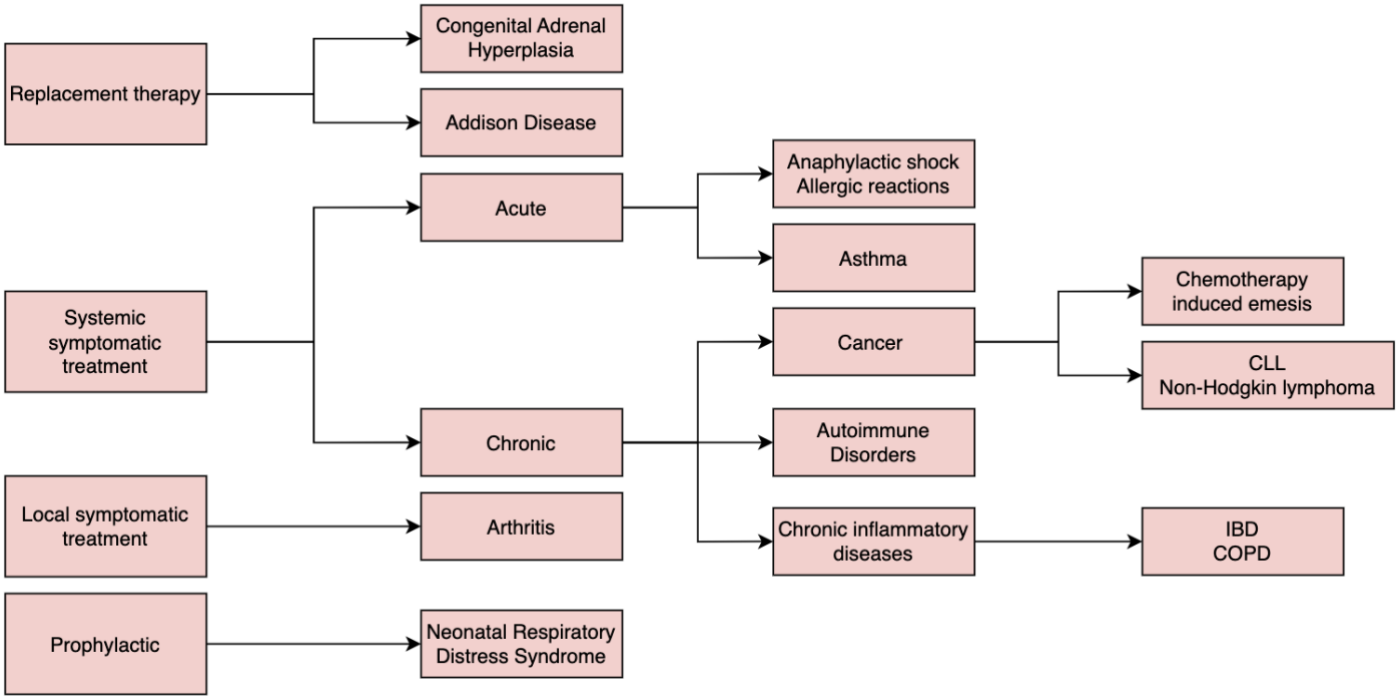


II. Metabolic Effects



III. Clinical Indications

- Glucocorticoids have several clinical indications, including most systems of the body
- Desoximetasone is a high-potency topical steroid that is used to treat different skin conditions



CLINICAL CORRELATION

Neonatal Respiratory Distress Syndrome

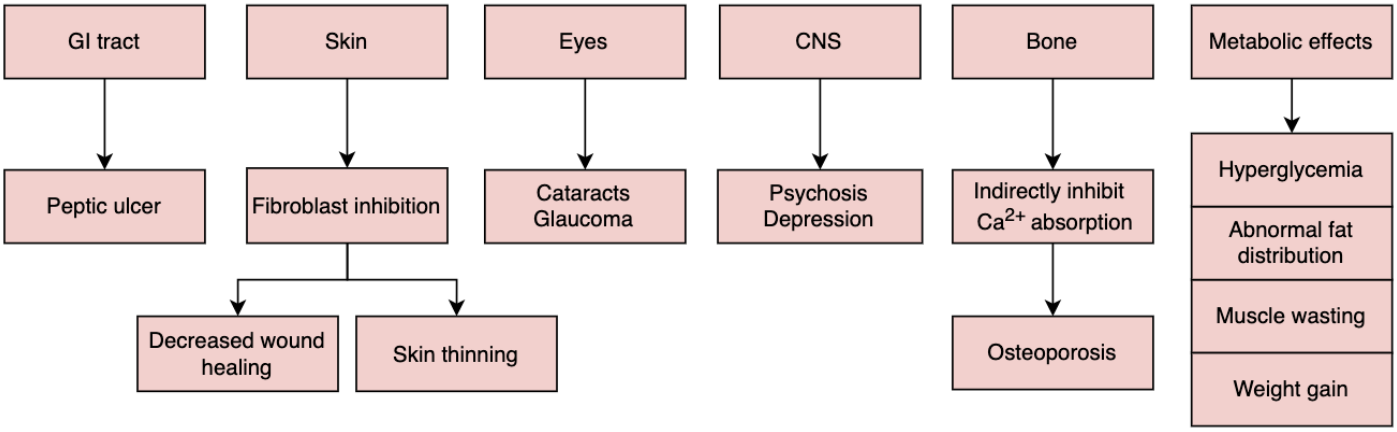
= Lung disorder found in preterm infants

- Caused by deficiency of surfactant, which causes the alveoli to collapse

Betamethasone, which crosses the placenta, is given to the mother 48h before delivery to stimulate lung maturation which may prevent NRDS

IV. Adverse Effects

- Long-term systematic administration of steroids (>3 weeks) requires tapering to avoid adrenal crisis
- Administering glucocorticoids over physiological level will eventually cause Cushing Syndrome
- Toxicities depend on dosage and duration of treatment → One time treatment will rarely cause adverse effects



CLINICAL CORRELATION

Adrenal Crisis

= Acute, severe glucocorticoid deficiency

- Can occur after long term steroid therapy, secondary to HPA axis suppression
- Life-threatening condition; Severe hypotension, electrolyte disturbances, and abdominal pain

Treated with high doses of hydrocortisone

MNOMIC

Adverse Effects of Corticosteroids:

CUSHINGOID

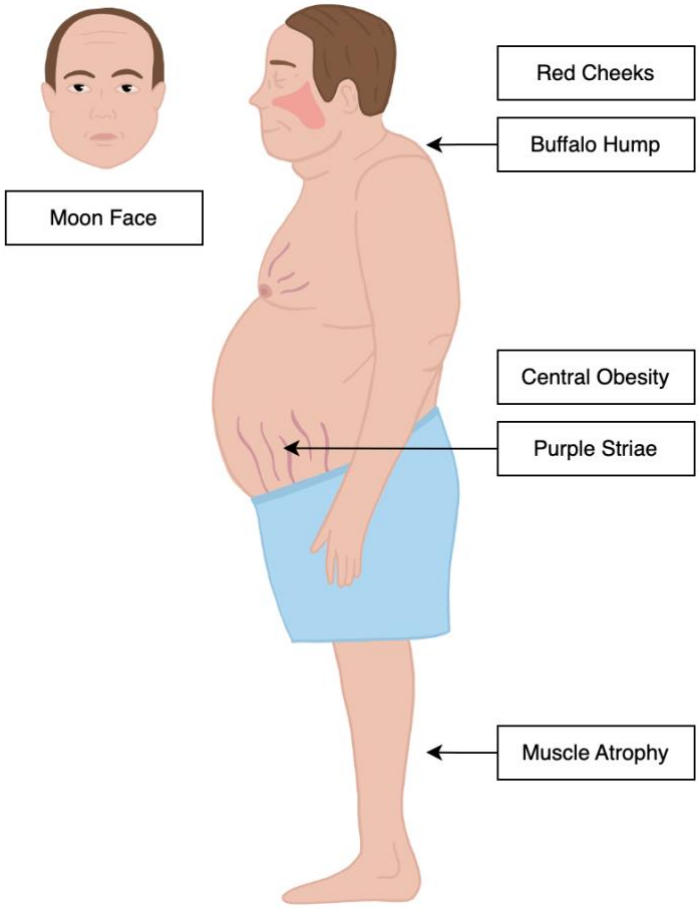
C – **C**ataract
U – **U**lcers
S – **S**triae, **S**kin thinning
H – **H**ypertension, **H**irsutism
I – **I**nfections
N – **N**ecrosis
G – **G**lucose elevation
O – **O**steoporosis, **O**besity
I – **I**mmunosuppression
D – **D**epression, **D**iabetes

CLINICAL CORRELATION

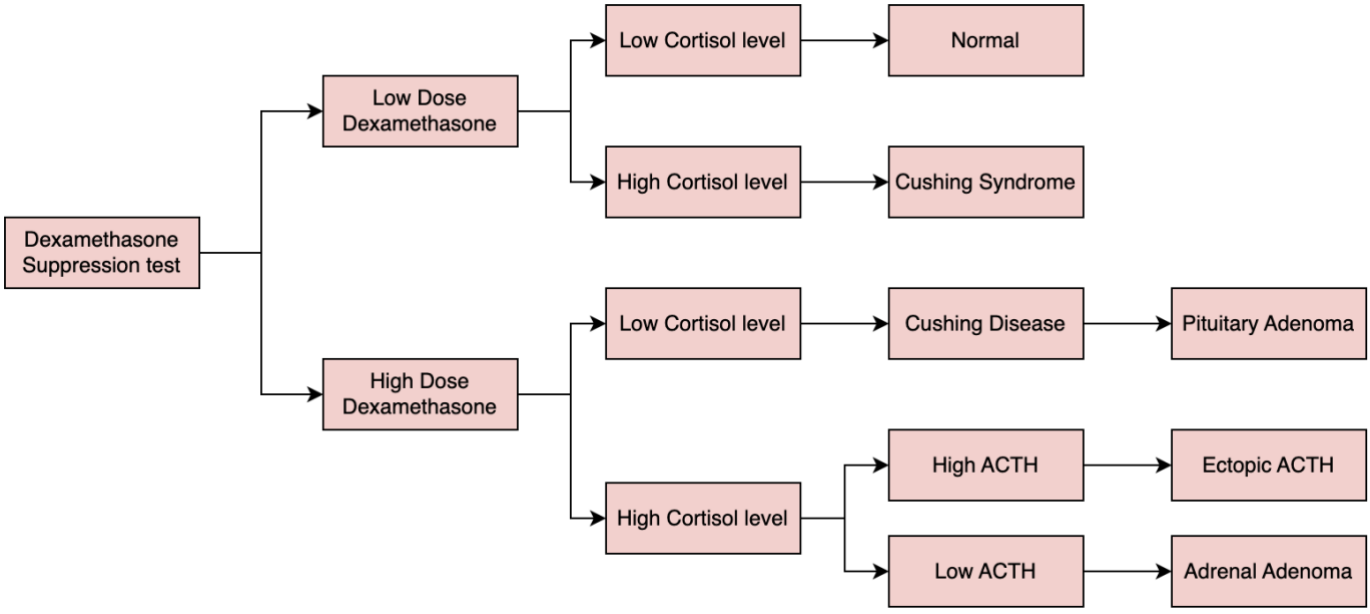
Cushing Syndrome

= Symptoms of hypercortisolism
- Due to exogenous administration or endogenous overproduction of glucocorticoids

- Prolonged glucocorticoid therapy (exogenous) is the most common cause of Cushing Syndrome
- 1st line treatment is surgical resection in cases where a tumor is the cause



Dexamethasone Suppression test
- Used to diagnose cause of Cushing Syndrome
- In healthy individuals, where the HPA axis is functional, low-dose dexamethasone will suppress cortisol secretion due to negative feedback



5.2.2 – Mineralocorticoids

- Mineralocorticoids, like aldosterone, are steroid hormones that regulate salt and water balance by promoting sodium retention and potassium excretion in the kidneys
- Aldosterone is produced by the adrenal cortex and activates the mineralocorticoid receptors
- Fludrocortisone = Synthetic analog of aldosterone

- Indicated as replacement therapy in Primary Adrenal Insufficiency (Addison Disease)

CLINICAL CORRELATION

Primary Adrenal Insufficiency
Is a condition where the adrenal glands are unable to produce adequate amounts of cortisol and aldosterone

Common causes include
- Autoimmune adrenalitis
- Infectious adrenalitis (Tuberculosis)
- Adrenal Hemorrhage

Clinical features
- Hypotension
- Hyperpigmentation (because ACTH is elevated which activates melanocytes)
- Hyponatremia, Hyperkalemia and metabolic acidosis (due to decreased aldosterone)

Treated with both glucocorticoids and mineralocorticoids

5.2.3 – Adrenal Androgens

- Adrenal androgens are weak male sex hormones produced by the adrenal cortex that contribute to the development of secondary sexual characteristics, especially in females
- DHEA is the major androgen secreted by the adrenal cortex
- Part of DHEA secreted will get converted into testosterone
- Although DHEA has been marketed as a “wonder drug”, its pharmaceutical effects remain unclear
- Should not be given to men with prostate cancer as it might stimulate tumor growth

5.3 – Androgen Steroid Inhibitors

5.3.1 – Corticosteroid Synthesis Inhibitors

I. Metyrapone

- Inhibit 11β-hydroxylase, which catalyzes the final step in the glucocorticoid pathway
- Clinical Indication: Cushing syndrome refractory to other treatments/ surgery

II. Ketoconazole and Fluconazole

- Ketoconazole and fluconazole are antifungals that inhibit several steps in the glucocorticoid pathway, including 11β-hydroxylase
- Does also inhibit androgen synthesis → may cause gynecomastia in males
- Clinical indication: Cushing syndrome

5.3.2 – Corticosteroid Receptor Antagonist

I. Spironolactone

- Is a potassium sparing diuretic

Mechanism of Action	Clinical Indication	Adverse Effects
Competitive inhibitor of mineralocorticoid receptors in the renal tubule → Inhibit Na^+ reabsorption → Inhibit K^+ secretion	Hyperaldosteronism Severe heart failure	Hyperkalemia[1] Gynecomastia

1 Exaggerated by ACE inhibitors

II. Mifepristone

- Mifepristone is an antagonist at both progesterone and glucocorticoid receptors
- It can reduce some effects of Cushing syndrome, including hyperglycemia

5.4 – Test Yourself

1. Which of the following drugs have NO mineralocorticoid receptor activity?

a) Prednisone
b) Dexamethasone
c) Cortisone
d) Hydrocortisone

2. A patient on long-term corticosteroids suddenly stops taking them and presents with hypotension and abdominal pain. What condition is this, and what is the 1st line treatment?

_____
_____
_____

Question 3-5

A 30-year-old woman comes to the clinic complaining of weight gain, acne, and irregular menstrual cycles. She also reports muscle weakness, especially when climbing stairs or getting up from a chair. On examination you observe central obesity, moon face and stretch marks on the abdomen.

3. What is the most likely diagnosis in her case?

_____
_____

4. Which test can help determine the cause of her symptoms?

a) Dexamethasone suppression test
b) Serum TSH
c) Serum aldosterone
d) Serum cortisol

5. What would you suspect if she has low cortisol level after high dose dexamethasone?

a) Exogenous glucocorticoid administration
b) Adrenal adenoma
c) Pituitary adenoma
d) Ectopic ACTH production

6. Which of the following has the *least* mineralocorticoid activity?

a) Hydrocortisone
b) Prednisone
c) Fludrocortisone
d) Dexamethasone

7. What is the primary mechanism of action of glucocorticoids in inflammatory conditions?

a) Inhibit phospholipase A_2

b) Inhibit cyclooxygenase (COX) enzymes

c) Inhibit maturation of B cells

d) Increased breakdown of macrophages

8. Which of the following is NOT an adverse effect of glucocorticoids

a) Osteoporosis

b) Decreased wound healing

c) Hypotension

d) Depression

9. A patient with Cushing syndrome has low serum ACTH and high cortisol. Which is the most likely cause?

a) Adrenal adenoma

b) Ectopic ACTH secretion

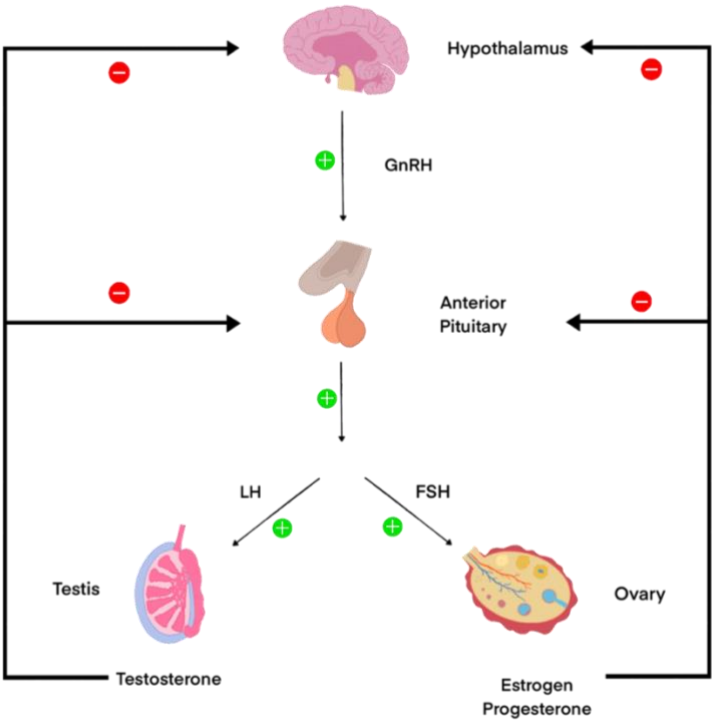
c) Pituitary adenoma

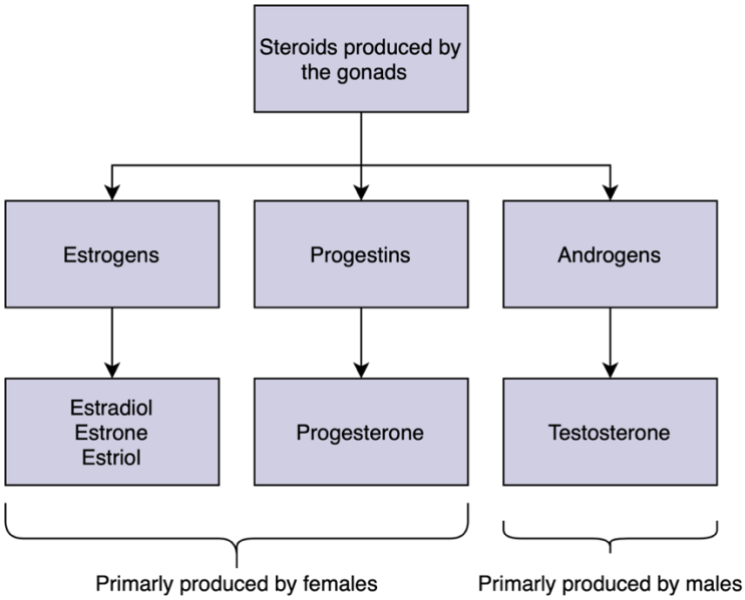
d) Long-term steroid therapy

Section 6 – Drugs affecting fertility and reproduction

6.1 – Overview of Gonadal Steroids

"tips": try to think about what effects the specific hormone has on the body. It will make it easier to remember both the desired effects and the adverse effects.





6.1.1 – Hormonal Actions of Estrogens and Progesterone

Effect	Estrogen	Progesterone
Reproduction	- Stimulates follicles - Regulates cycle - Thickens endometrium	- Prepares uterus for pregnancy - Maintains pregnancy - Reduces contractions
Breast & Lactation	Develops breast tissue	Prepares for lactation but inhibits milk production
Cardiovascular	- ⇑HDL - ⇓LDL - Vasodilation	Mild diuretic
Bone Health	Prevents bone loss→ inhibits osteoclasts	Supports bone maintenance
Metabolism	- Fat distribution - Regulates insulin	- Increases body temp - Promotes fat storage
CNS & Mood	- Neuroprotective - Mood regulation	- Calming - Sedative
Skin & Hair	- Collagen production - Skin elasticity - Hair protection	Minimal effect
Fluid Balance	Mild water retention	Diuretic effect

6.1.2 – Hormonal Actions of Testosterone

Effect	Testosterone
Sexual Development	Develops primary and secondary male characteristics
Reproductive System	Stimulates growth of: penis, scrotum, seminal vesicles, prostate
Voice & Hair	- Deeper voice→Enlarges larynx, thickens vocal cords - Promotes facial, axillary, and pubic hair growth
Muscle & Bone	- Increases lean mass + skeletal growth - Accelerates epiphyseal closure
Skin	Increases sebaceous activity→ contributes to acne
Blood & Metabolism	- Boosts erythropoietin production - Lowers HDL cholesterol

6.2 – Estrogen and Progestin Drugs

6.2.1 – Estrogens

- Estradiol (17beta-estradiol) primary estrogen in premenopausal women
- Estrone is a metabolite of Estradiol, and it is the primary estrogen after menopause
- Estriol is a metabolite of Estradiol and is the primary estrogen during pregnancy produced by the placenta
- Combination estrogen-progestin preparations contain either ethyl estradiol or mestranol.
- Conjugated equine estrogens are used in hormonal replacement therapy for postmenopausal women and to treat hypogonadism. They contain sulfate forms of estrone and equilin.

6.2.2 – Progestins

- Refers to progesterone and its ester derivatives. These include Megestrol, Hydroxyprogesterone caproate and Medroxyprogesterone acetate.
- High progesterone levels inhibit GnRH, FSH, and LH release through negative feedback, helping regulate the menstrual cycle and prevent multiple ovulations
- Progesterone has a very short plasma half-life (around 5 min) and therefore these derivatives have been developed.

I. Progesterone and ester derivatives

Drug	Route of administration	Mechanism of action	Usage	Adverse effects
Progesterone	Orally	Uses feedback inhibition by suppressing the release of (GnRH) from the hypothalamus and (LH) and (FSH) from the pituitary.	- Contraception - Treatment of hormone deficiency - Uterine bleeding - Dysmenorrhea - Endometriosis - Infertility	- Headache - Depression -Weight gain - Changes in libido
Megestrol	Orally			
Hydroxyprogesterone caproate	IM			
Medroxyprogesterone acetate	Orally and IM			

II. Synthetic progestins

- Synthetic progestins are primarily used as oral contraceptives.
- In the same manner as the progesterone esters, synthetic progestins are also used to treat dysmenorrhea, endometriosis, and uterine bleeding.
- They can have estrogenic, antiestrogenic, or androgenic effects.
- Norgestrel, Desogestrel, Norgestimate, and Drospirenone are synthetic progestins.

Drug	**Norgestrel**	**Desogestrel**	**Norgestimate**	**Drospirenone**[1]
Effect	Adrenergic activity	Progestational	Progestational	Antiandrogenic

[1] Drospirenone is a spironolactone derivative

CLINICAL CORRELATION

Menopause

Menopause is defined as the cessation of menstruation. Typically occurring between ages 45 and 55, due to the decline in ovarian function and estrogen production. As estrogen levels fall→ FSH levels rise. A level above 40 IU/L indicates menopause.

In women without a uterus, estrogen-only hormone replacement therapy can be used. However, in women with a uterus, combined estrogen-progestin therapy is recommended. This to reduce the risk of endometrial cancer, which is increased with estrogen-only treatment.

Therapeutic use of estrogens relieves menopausal symptoms in up to 90% of women, especially hot flashes, night sweats, tachycardia, and headaches

6.3 – Contraceptives

- Contraceptives are drugs that is used to prevent conception.

6.3.1 – Estrogen-Progestin Contraceptives

- All oral contraceptives are usually administered once daily for 21 days → packed in a calendar format to facilitate proper usage.
- Acts by feedback inhibition of GnRH secretion.
- Estrogen reduces the FSH secretion, and progestin inhibits LH spike mid-cycle (at ovulation).
- Estrogen-progestin oral contraceptives can be divided into two subgroups monophasic and multiphasic preparations.

I. Monophasic and Multiphasic

	Amount of progestin	Amount of estrogen
Monophasic	The same amount of progestin throughout the whole cycle of administration	Constant amount
Multiphasic	The amount of progestin is increased in the pill after 7 and 14 days of the cycle→ mimic the natural ratio of estrogen to progestin during the menstrual cycle.	Constant amount in most

II. Contraindications, Usage and Adverse Effects

Contraindication

- Thromboembolic disease
- History of MI or CAD
- Active liver disease
- Breast cancer or carcinomas of the reproductive tract.

Usage

- Contraceptive
- Acne vulgaris
- Dysmenorrhea

Adverse effects

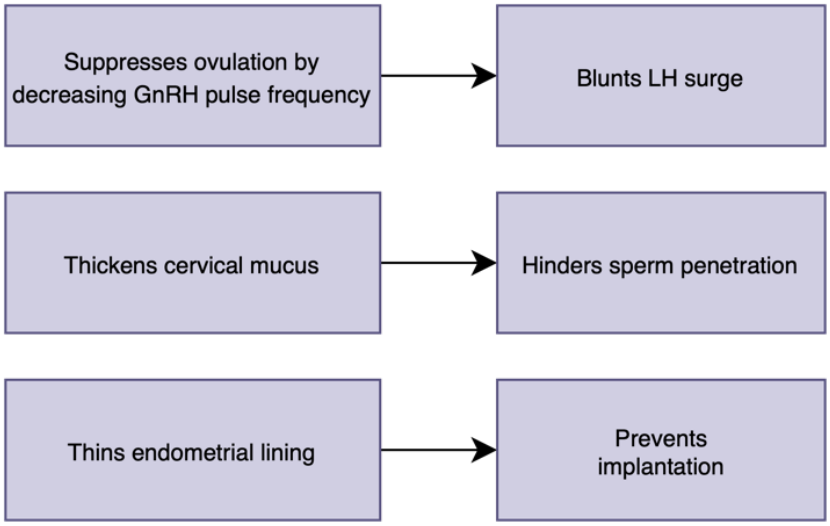
- Increased risk of stroke
- DVT
- MI
- and a lot more ☺

6.3.2 – Progestin-Only Contraceptives

- Indications → Women who smoke, older women and women where estrogen are contraindicated.
- Adverse Effects → Frequent spotting, amenorrhea, and increased risk of ectopic pregnancy.
- In contrast to estrogen-progestin preparations progestin-only preparations **MUST** be taken **DAILY** without interruptions to prevent pregnancy

Progestin-only contraceptives
- Minipills (Norethindrone) - Subdermal implants - IUDs

I. Progestin-Only Mechanism of action



6.3.3 – Long-Acting reversible contraceptives (LARCs)

- LARCs improve patient compliance, making them a more effective form of contraception compared to daily birth control pills.

	Method	Hormonal Component	Duration	Mechanism of Action	Side Effects/ considerations
NuvaRing ***(Etonogestrel/ Ethinyl Estradiol)***	Ring inserted into vagina	Estrogen + Progestin	3 weeks in, 1 week out	- Suppresses ovulation - Thickens cervical mucus	Similar to combined oral contraceptives
Ortho Evra Patch ***(Norelgestromin/ Ethinyl Estradiol)***	Patched applied to the skin	Estrogen + Progestin	1 patch per week for 3 weeks, 1 week off	- Inhibits ovulation - Thickens cervical mucus	May be **less effective in women >90 kg**
Etonogestrel Implant ***(Nexplanon)***	“p-stav”	Progestin	3 years	-Prevents ovulation - Thickens cervical mucus - Alters endometrial lining	**Most effective** LARC method; irregular bleeding may occur
Copper IUD ***(Paragard T 380A)***	“kobberspiral”	Non-hormonal	Up to 10 years	- Sperm toxicity - Prevents fertilization and implantation	May cause heavier and painful periods initially
Levonorgestrel IUD ***(Mirena, Skyla, Liletta)***	”Spiral”	Progestin	3–7 years (varies by device)	- Thickens cervical mucus - Inhibits ovulation - Thins endometrial lining	**Lighter periods or amenorrhea** common

6.3.4 – Emergency contraceptives

- Emergency contraceptives are used after unprotected sex to prevent pregnancy

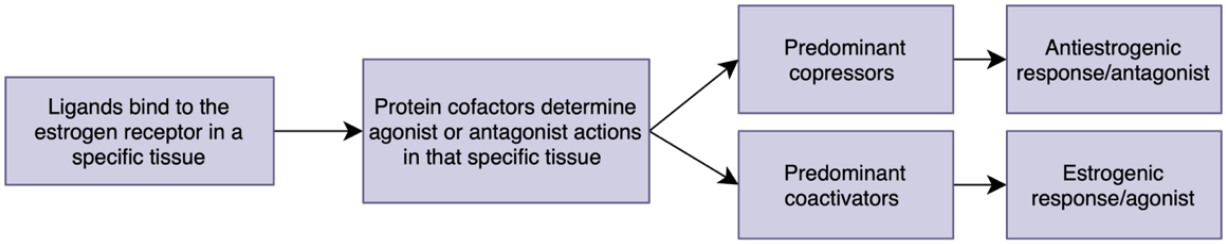
Drug	Type	Mechanism of Action	Dosage	Time Frame	Side Effects	Availability
Levonorgestrel (Plan B One-Step)	Progestin only	- Inhibits ovulation - Thickens cervical mucus	1.5 mg single dose	Within 72 hours	- Nausea - Vomiting - Dizziness - Headache - Leg cramps	OTC[1] or Prescription
Levonorgestrel (Plan B, Next Choice)			0.75 mg x 2 doses (12h apart)			
Ulipristal acetate (Ella)	Progestin agonist/antagonist[2]	Delays/inhibits ovulation	30 mg single dose	Within 120 hours (5 days)	- Nausea - Headache - Abdominal pain - Menstrual irregularities	Prescription-only

[1] OTC= over the counter

[2] Ulipristal acetate is a Selective Progesterone Receptor Modulator. This means it can bind to progesterone receptors and act in two different ways, depending on:
- The tissue type
- The local concentration of progesterone
- The presence of co-regulator proteins in the cell

6.4 – Selective estrogen receptor modulators (SERMS)

- Are drugs that work both as agonists and antagonists depending on the tissue that expresses the estrogen receptors.



Drug	Agonist effect	Antagonist effect	Mechanism	Indications	Adverse Effects
Clomiphene	-	Hypothalamus Pituitary	Blocks ERs in hypothalamus → inhibit estrogen feedback inhibition →increasing FSH and LH	Anovulatory infertility	Multiple births→ twins most common.
Tamoxifen	Uterus	Breast tissue	Converted to active metabolite in liver (4-hydroxytamoxifen)→ act as an estrogen receptor antagonist→ inhibit expression of HER2	Estrogen receptor-positive breast cancer treatment/prevention.	- Hot flashes - Nausea - Menstrual irregularities - Endometrial cancer risk
Toremifene	Uterus	Breast tissue	Similar to tamoxifen	Metastatic breast cancer in postmenopausal women.	- Hot flashes - Nausea
Raloxifene	- Bone - Lipid metabolism	- Breast tissue - Uterus	Look at the effect	- Osteoporosis prevention - Reduces breast cancer risk in postmenopausal women.	- Stroke - Pulmonary embolism - Deep vein thrombosis
Ospemifene	Endometrium	Breast tissue	Look at the effect	Dyspareunia (painful intercourse) due to menopause.	Similar to other SERMs, but fewer risks known.
Bazedoxifene	Bone	Breast tissue	Only available in combination with conjugated estrogens.	Menopausal symptoms (VMS) and osteoporosis prevention.	Similar to other SERMs but used only in combination therapy.

6.5 – Aromatase Inhibitors

- Aromatase is an enzyme of the cytochrome p450 family that is produced in the ovaries, adipose tissue, and placenta.
- Aromatase is responsible for conversion of testosterone to estradiol, and androstenedione to estrone.
- Aromatase inhibitors are Anastrozole and Letrozole.

6.5.1 – Mechanism of Action for Inhibitors

Inhibition of aromatase → ↓ conversion of androstenedione to estrone → ↓ conversion of testosterone to estradiol →↓ tumor growth

CLINICAL CORRELATION

Breast Cancer

Many breast cancers are estrogen and/or progesterone receptor positive and respond to therapies that decrease estrogen levels or inhibit estrogen effects.

Aromatase inhibitors like **anastrozole** and **Letrozole** are used to block the enzyme aromatase, which converts androgens into estrogens.

These drugs reduce circulating levels of estrogen and is therefore indicated as first line treatment for locally

6.6 - Antiprogestins

- Antiprogestins act as competitive inhibitors of progesterone receptors that causes inhibition or delay of ovulation, suppression of endometrial maturation, and pregnancy termination.

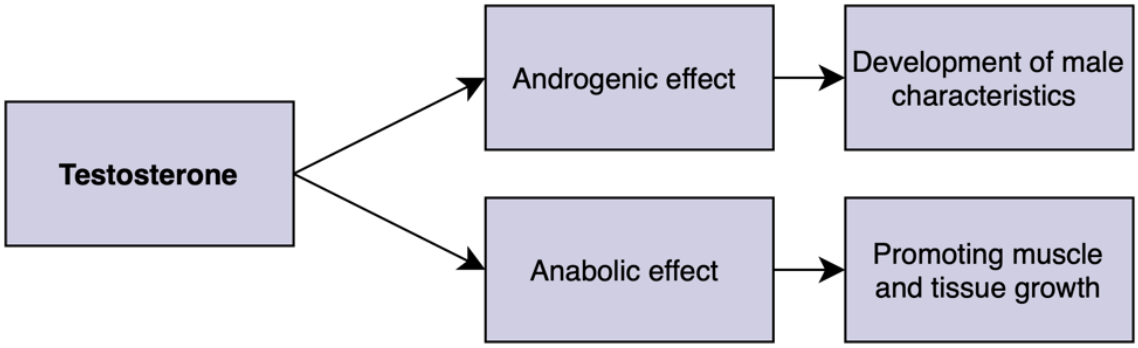
Drug	Class	Mechanism of action	Clinical application	Adverse effects	Administration
Mifepristone	Synthetic steroid compound	Antagonist of glucocorticoid and progesterone receptors	Medical abortion→causes breakdown of the endometrium	- Vaginal bleeding - Abdominal pain - Diarrhea - Headache	Orally Single dose

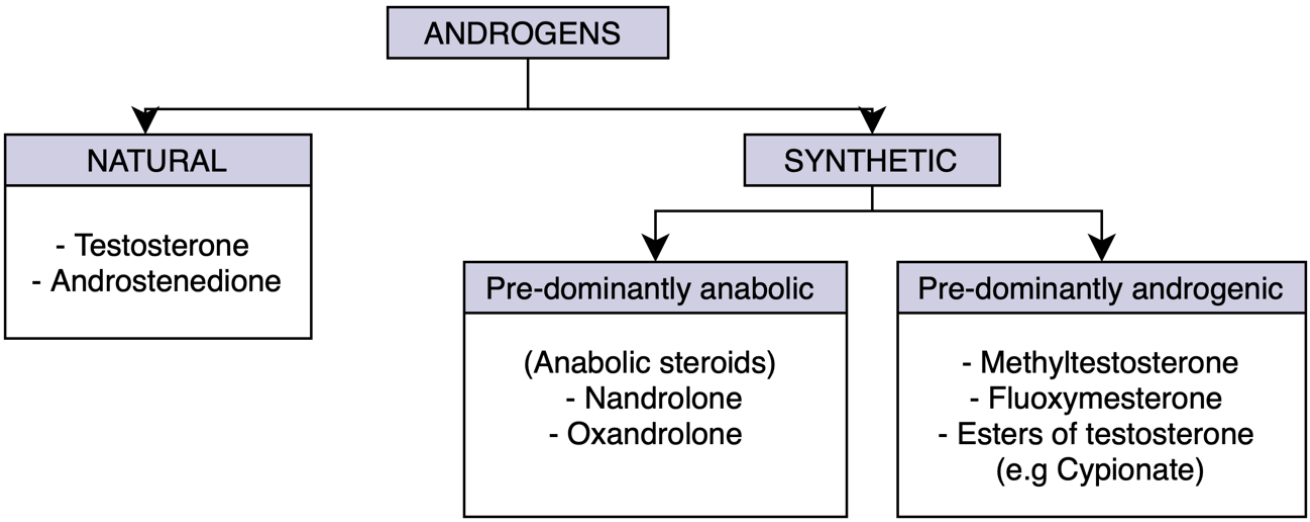
CLINICAL CORRELATION

Induced abortion

- Induced abortion involves medical procedures used to terminate a pregnancy and remove the products of conception from the uterus.
- Common reasons for seeking an abortion include the individual's choice, potential harm to their health, and fetal genetic or anatomical abnormalities.
- Induced abortion can be divided into procedural or medication abortion
- A combined regimen of mifepristone and misoprostol is recommended for medication abortion in the first and second trimester of pregnancy.
- Administration of mifepristone once → 24-48h later

6.7 – Androgens and Antiandrogens





6.7.1 – Testosterone, methyltestosterone, Anabolic steroids and Danazol

- Anabolic steroids are synthetic derivatives of testosterone that have more anabolic than androgenic effects.

Category	Drug	Administration/ Pharmacokinetics	Clinical Uses	Adverse Effects
Testosterone & Derivatives	**Testosterone**	Extensively metabolized via first-pass effect → not effective orally Administered via transdermal, IM or buccaly	Treatment of hypogonadism	<u>In Males:</u> - Priapism - Impotence - Decreased spermatogenesis - Gynecomastia <u>In females</u> - Masculinization - Acne - Facial hair - Deepening of the voice - Excessive muscle development - Male pattern baldness
	Methyltestosterone	Given orally		Same as for testosterone + liver failure
Anabolic Steroids (synthetic derivative of testosterone)	**Oxandrolone**	Orally anabolic:androgenic ratio (3:1)	- Weight gain post-surgery, infection, trauma. - Reverses corticosteroid-induced catabolism. - Alleviates osteoporosis-related bone pain.	Same as for testosterone + - Tendon rupture - Hepatic dysfunction - Cholestatic jaundice - Increased aggressiveness
	Fluoxymesterone	Orally	Treatment of hypogonadism	
Synthetic androgenic anabolic steroid hormone	**Danazol**	weak androgenic activity. Inhibits pituitary gonadotropin release → reduces estrogen secretion.	- Endometriosis - Fibrocystic breast disease. - Heavy menstrual bleeding - Hereditary angioedema[1]	- Mild hirsutism - Acne and oily skin - Menstrual irregularities -Hypercholesterolemia - Hepatotoxicity - Stroke - Teratogenic

1 Hereditary angioedema is a disorder caused by a deficiency of an inhibitor of the first component of the complement system, a group of plasma proteins involved in immune defense. This deficiency leads to episodes of swelling in the face, airways, arms, and legs.

6.7.2 – Antiandrogens

- Antiandrogens are a group of medications that block the effect of testosterone and dihydrotestosterone.
- This group includes: Gonadotropin-releasing hormone analogs, Androgen receptor antagonist
- and 5α-reductase inhibitors

Drug Class	Drugs	Mechanism of Action	Indications		Adverse Effects
GnRH Analog/agonist	**Leuprolide**	Continuous administration → suppresses LH secretion → reducing testosterone production	Inoperable metastatic prostate carcinoma		- Hypogonadism - Decreased libido - Vaginal dryness - Hot flashes - Nausea, vomiting - Decreased bone mineral density
Androgen Receptor Antagonists	**Flutamide, Bicalutamide, Enzalutamide, Nilutamide**	Compete with testosterone at the androgen receptor.	Inoperable metastatic prostate carcinoma		- Nausea - Gynecomastia - Impotence - Hot flashes - Hepatitis
5α-Reductase Inhibitors	**Finasteride**	↓Dihydrotestosterone (DHT) synthesis in prostate and other tissues	Benign prostatic hyperplasia (BPH) Off-label for prostate cancer prevention.	Male pattern baldness	- Erectile dysfunction - Decreased Libido - Gynecomastia
	Dutasteride				

6.8 – Test Yourself

1. Aromatase inhibitors like _____ and _____ are used in the treatment of breast cancer.

2. Which drug is a 5α-reductase inhibitor used to treat BPH?
a) Leuprolide
b) Finasteride
c) Flutamide
d) Anastrozole

3. Why are LARCs considered more effective than daily contraceptive pills?
a. They release higher hormone doses
b. They don't alter cervical mucus
c. They eliminate user compliance issues
d. They increase sperm motility

4. What drug is not an example of an antiandrogenic drug?
a. Flutamide
b. Finasteride
c. Leuprolide
d. Danazol

5. What is the mechanism of action of aromatase inhibitors like anastrozole?

a. Increase estrogen production
b. Block conversion of androgens to estrogens
c. Stimulate ovulation
d. Inhibit LH release from pituitary

6. Match drug with primary usage

Drug	**Primary Use**
a) Mifepristone	1) Emergency contraception
b) Ulipristal acetate	2) Medical abortion
c) Leuprolide	3) Prostate cancer treatment
d) Anastrozole	4) Breast cancer treatment