SAM's Guide

A Clinical Pharmacology and
Community Pharmacy Practice
approach, based on human body systems
More than 500+ drugs added
New Oncology Chapter,
All Chapters content updated
And for the first time; head-to-head,
drug to drug comparisons

Authored/Edited By:
Salam Daoud Salem
Clinical Pharmacy GP, B.Sc. Pharm.

ISBN

9 789922 955537

3.1 Ed. - Enhanced Ver.

رقم الإيداع في دار الكتب والوثائق ببغداد
(1682) لسنة 2023

Self-Assessment Medication's Guide

Table of content:

رقم الإيداع في دار الكتب والوثائق ببغداد (2483) لسنة 2015

Deposit No. in the House of books and documents in Baghdad (2483) for the year 2015

RESPIRATORY SYSTEM

Chapter 1: Respiratory System

Part One: Introduction

Part Two:

1.1- Bronchodilators and Anti-Asthmatic Drugs:

1.1-1. Selective Beta2 agonists

1.1-2. Inhaled corticosteroids
- Combination Products

1.1-3. Anti-Muscarinic bronchodilators
- Combination Products
- Triple Products

1.1-4. Theophylline and Xanthine's derivatives

1.1-5. Leukotriene Receptor Antagonists
- Combination Products

1.1-6. Cromoglicate & Nedocromil

1.1-7. Other Asthma Therapies

1.2- Antihistamines

1.2-1. First Generation

1.2-2. Second & Third Generation

1.2-3. Topical Antihistamines

1.2-4. Other Antihistamines

1.3- Cough preparations, Common Cold and Flu

1.3-1. Topical Sympathomimetics

1.3-2. Common cold & Flu Preparations

1.3-3. Expectorants and Antitussive

1.3-4. Cough medication (Suppositories)

1.3-5. Herbal Mixtures for Cough

1.4- Respiratory Stimulants

1.5- Pulmonary Surfactant

1.6- Drugs for Cystic Fibrosis
- Combination Products
- Aerosolized Antibiotics

Chapter one: Respiratory System

Part One:

1. Introduction:

- The respiratory system consists of the lungs and the air passages, such as the trachea (windpipe) and bronchi, by which air reaches them; Through the process of inhaling and exhaling air (breathing) the body obtains the oxygen necessary for survival, and to expel carbon dioxide, which is the waste product of the basic human biological process.
- Air enters the trachea, which branches into two main bronchi, one for each lung. Within the lungs, the air passes into bronchioles, smaller tubes whose muscular walls may contract or dilate in response to drugs and nerve signals; The bronchioles open out into tiny, blood-vessel lined air sacs (alveoli), which allow oxygen to pass into the bloodstream and carbon dioxide to pass from the bloodstream for expiration.

2. How do we breathe?

- Breathing occurs when the contraction or relaxation of muscles around the lungs changes the total volume of air within the air passages (bronchi, bronchioles) inside the lungs, when the volume of the lungs changes, the pressure of the air in the lungs changes in accordance with Boyle's Law, if the pressure is greater in the lungs than outside the lungs, then air rushes out. If the opposite occurs, then air rushes in; Here is a summary of the process:
  - **Inspiration** occurs when the inspiratory muscles (the diaphragm and the external intercostal muscles) contract; contraction of the diaphragm (the skeletal muscle below the lungs) causes an increase in the size of the thoracic cavity, while contraction of the external intercostal muscles elevates the ribs and sternum; Thus, both muscles cause the lungs to expand, increasing the volume of their internal air passages, and in response, the air pressure inside the lungs decreases below that of air outside the body; because gases move from regions of high pressure to low pressure, air rushes into the lungs.
  - **Expiration** occurs when the diaphragm and external intercostal muscles relax, in response, the elastic fibers in lung tissue cause the lungs to recoil to their original volume, the pressure of the air inside the lungs then increases above the air pressure outside the body, and air rushes out; During high rates of ventilation, expiration is facilitated by contraction of the expiratory muscles (intercostal muscles and abdominal muscles).
- Lung compliance is a measure of the ability of the lungs and thoracic cavity to expand, due to the elasticity of lung tissue and the low surface tension of the moisture in the lungs (from the surfactant), the lungs normally have high compliance.
- **Boyle's Law** describes the relationship between the pressure (P) and the volume (V) of a gas. The law states that if the volume increases, then the pressure must decrease (or vice versa). This relationship is often written algebraically as PV = constant, or P1V1 = P2V2, both equations state that the product of the pressure and volume remains the same; (Boyle's Law applies only when the temperature does not change).

3. Control of Respiration

- Respiration is controlled by these areas of the brain that stimulate the contraction of the diaphragm and the intercostal muscles. These areas, collectively called respiratory centers, are summarized here:
  1. **The medullary inspiratory center**, located in the medulla oblongata, generates rhythmic nerve impulses that stimulate contraction of the inspiratory muscles (diaphragm and external intercostal muscles). Normally, expiration occurs when these muscles relax, but when breathing is rapid, the inspiratory center facilitates expiration by stimulating the expiratory muscles (internal intercostal muscles and abdominal muscles).
  2. **The pheumotaxic area**, located in the pons, inhibits the inspiratory center, limiting the contraction of the inspiratory muscles, and preventing the lungs from overinflating.
  3. **The apneustic area**, also located in the pons, stimulates the inspiratory center, prolonging the contraction of inspiratory muscles.

- The respiratory centers are influenced by stimuli received from the following three groups of sensory neurons:
  1. **Central chemoreceptors** (nerves of the central nervous system), located in the medulla oblongata, monitor the chemistry of cerebrospinal fluid. When CO_2 from the plasma enters the cerebrospinal fluid, it forms HCO_3^- and H^+, and the pH of the fluid drops (becomes more acidic). In response to the decrease in pH, the central chemoreceptors stimulate the respiratory center to increase the inspiratory rate.
  2. **Peripheral chemoreceptors** (nerves of the peripheral nervous system), located in aortic bodies in the wall of the aortic arch and in carotid bodies in the walls of the carotid arteries, monitor the chemistry of the blood. An increase in pH or pCO_2, or a decrease in pO_2, causes these receptors to stimulate the respiratory center.
  3. **Stretch receptors in the walls of bronchi and bronchioles** are activated when the lungs expand to their physical limit. These receptors signal the respiratory center to discontinue stimulation of the inspiratory muscles, allowing expiration to begin. This response is called the inflation (Hering-Breur) reflex.

4. What Can go wrong in the Respiratory tract?

- **Difficulty in breathing** may be due to narrowing of the air passages, from spasm, as in asthma and bronchitis, or from swelling of the linings of the air passages, as in bronchiolitis and bronchitis; Breathing difficulties may also be due to an infection of the lung tissue, as in pneumonia and bronchitis, or to damage to the small air sacs (alveoli) from emphysema or from inhaled dusts or molds, which cause pneumoconiosis and farmer's lung.
- **Smoking** and **air pollution** can affect the respiratory system in many ways, leading to diseases such as lung cancer and bronchitis.
- Sometimes difficulty in breathing may be due to **congestion of the lungs from heart disease**, to an inhaled object such as a peanut, or **to infection or inflammation of the throat**.
- Symptoms of breathing difficulties often include a cough and a tight feeling in the chest.
- The usual cause of a **blocked nose** is swelling of the delicate mucous membrane that lines the nasal passages and excessive production of mucus as a result of inflammation. This may be caused by an infection (for example, a common cold) or it may be caused by an allergy (for example, to pollen – a condition known as allergic rhinitis or hay fever). Congestion can also occur in the sinuses (the air spaces in the skull), resulting in sinusitis.
- **Coughing** is a natural response to irritation of the lungs and air passages, designed to expel harmful substances from the respiratory tract. Common causes of coughing include infection of the respiratory tract (for example, bronchitis or pneumonia), inflammation of the airways caused by asthma, or exposure to certain irritant substances such as smoke or chemical fumes. Depending on their cause, **coughs may be productive – that is, phlegm producing – or they may be dry**. In most cases, coughing is a helpful reaction that assists the body in ridding itself of excess phlegm and substances that irritate the respiratory system; suppressing the cough may actually delay recovery. However, repeated bouts of coughing can be distressing, and may increase irritation of the air passages. In such cases, medication to ease the cough may be recommended. There are two main groups of cough remedies, according to whether the cough is productive or dry.
- **Asthma** is a chronic lung disease that is characterized by episodes in which the bronchioles constrict due to oversensitivity. The attacks are usually, but not always, reversible; asthma is also known as reversible airways obstruction. About 5 per cent of adults and 10 per cent of children have the disease. Sometimes the inflammation causing the constriction is due to an identifiable allergen in the atmosphere, such as house dust mites, but often there is no obvious trigger. Breathlessness is the main symptom, and wheezing, coughing, and chest tightness are common. Asthma sufferers often have attacks during the night and wake up with breathing difficulty. The illness varies in severity, at its most severe, it can even be life threatening.

- **Chronic Obstructive Pulmonary Disease (COPD)** is an umbrella term used to describe progressive lung diseases including emphysema, chronic bronchitis, and refractory (non-reversible) asthma. This disease is characterized by increasing breathlessness.
  - Damage to the alveoli (air sacs) causes **Emphysema**. The walls inside the alveoli disappear, making many small sacs become larger, single sacs. These larger sacs do not absorb oxygen as well. So, less oxygen is absorbed into the blood; Also, when the alveoli are damaged, the lungs become stretched out and lose their springiness. The airways become flabby, and air is trapped in the lungs. It becomes hard to breathe out. This creates a feeling of shortness of breath.
  - Damage to the bronchial tubes causes **Chronic Bronchitis**. Bronchitis occurs when the bronchial tubes are irritated and swollen. This causes coughing and shortness of breath. If mucus comes up with the cough and the cough lasts at least three months for two years in a row, the bronchitis has become chronic bronchitis; There are hair-like fibers lining the bronchial tubes of the lungs. These tiny hairs are called cilia. The cilia help move mucus up the tubes so it can be coughed out. In chronic bronchitis, the tubes have lost their cilia. This makes it hard to cough up mucus, which causes more coughing. More coughing makes the tubes more irritated. This creates more mucus. The tubes then become swollen, making it hard to breathe. Smoking even just a little keeps the cilia from working normally. Mucus can build up in the lungs. This can cause more damage.
  - **Refractory (non-reversible) asthma** is a type of asthma that does not respond to usual asthma medications. In an asthma attack, bronchial airways tighten up and swell. Medications can usually reverse this, opening up the airways and returning them to how they were before the asthma attack. In refractory asthma, medications cannot reverse the tightening and swelling of the airways.

5. Spirometry

- Spirometry is a common clinical test used to assess how well the lungs work by measuring how much air they inhale; how much they exhale and how quickly they exhale.
- Spirometry is used to diagnose asthma, chronic obstructive pulmonary disease (COPD) and other conditions that affect breathing; Spirometry may also be used periodically to monitor the lung condition and check whether a treatment for a chronic lung condition is helping the patient to breathe better.
- Key spirometry measurements include the following:
  - **Forced vital capacity (FVC):** This is the largest amount of air that the patient can forcefully exhale after breathing in as deeply as he can, a lower than normal FVC reading (less than 80%) indicates restricted breathing.
  - **Forced expiratory volume (FEV1)**: This is how much air the patient can force from his lungs in one second, this reading helps the doctor to assess the severity of the breathing problems; lower FEV-1 (less than 80% in 6 seconds) readings indicate significant breathing obstruction.
  - **FEV1/FVC ratio:** represents the percentage of the lung capacity to exhale in one second.
    - ☒ Usually used to differentiate between obstructive and restrictive diseases.
    - ☒ Decreased in obstructive diseases (Asthma, COPD), less than 75%.
    - ☒ Normal or high in restrictive diseases (Pulmonary Fibrosis).

6. Asthma Vs COPD

Sign	Asthma	COPD
Cough	Usually non-productive; worsen at night and early morning	Usually Productive, and occurs throughout the day
FEV1	Reversible	Irreversible
Lung Damage	Reversible	Irreversible

7. Medications Range and Types:

1. Air entering the lungs passes through narrow tubes called bronchioles, in asthma and bronchitis the bronchioles become narrower, either as a result of contraction of the muscles in their walls, or as a result of mucus congestion.
2. This narrowing of the bronchioles obstructs the flow of air into and out of the lungs and causes breathlessness; **Bronchodilators are prescribed to widen the bronchioles and improve breathing.**
3. Drugs with a variety of actions are used to clear the air passages, soothe inflammation, and reduce the production of mucus:
   - **Decongestants**; oral or topical **(Phenylephrine, Pseudoephedrine, Xylometazoline)** reduce swelling inside the nose, thereby making it possible to breathe more freely.
   - If the cause of the congestion is an allergic response, an **antihistamine** is often recommended to relieve symptoms or prevent attacks.
   - **Bacterial infections** of the respiratory tract are usually treated with **antibiotics**, although **most respiratory tract infections are viral**.
   - **Bronchodilators (Salbutamol, Salmeterol, Terbutaline)** are drugs that widen the bronchi. They are used to prevent and relieve asthma attacks.
   - **Leukotriene antagonists (Montelukast, Zafirlukast)** reduce the inflammation and bronchoconstriction of asthma.
   - **Corticosteroids (Beclomethasone, Budesonide)** reduce inflammation in the swollen inner layers of the airways. They are used to prevent asthma attacks.
   - Other drugs, such as **Sodium Cromoglicate**, may be used for treating allergies and preventing asthma attacks but are not effective once an asthma attack has begun.
   - **Biological therapies** (Monoclonal antibodies), used to manage severe asthma
   - A variety of drugs are used to relieve a cough, depending on the type of cough involved. Some drugs make it easier to **eliminate phlegm (Expectorants** or **Mucolytics)**; others **suppress the cough (cough suppressants)** by inhibiting the cough reflex.

8. Drug Delivery available for Respiratory tract

A. Inhalation devices:

- This route delivers the drug directly to the airways; the dose required is smaller than when given by mouth and side effects are reduced.
- Inhaler devices include pressurized **metered-dose inhalers (MDI)**, **breath actuated inhalers (BAI)**, and **dry powder inhalers (DPI)**. Many patients can be taught to use a pressurized MDI effectively but some patients, particularly the elderly and children, find them difficult to use. Spacer devices can help such patients because they remove the need to co-ordinate actuation with inhalation, DPI may be useful in adults and children over 5 years who are unwilling or unable to use a pressurized MDI, breath-actuated inhalers are suitable for adults and older children.
- On changing from a pressurized MDI to a DPI dry powder inhaler, patients may notice a lack of sensation in the mouth and throat previously associated with each actuation, Coughing may also occur during the change.
- Spacer devices remove the need for coordination between actuation of a pressurized MDI and inhalation. Spacer devices are particularly useful for patients with poor inhalation technique, for children, for patients requiring high doses of inhaled corticosteroids, for nocturnal asthma, and for patients prone to candidiasis with inhaled corticosteroids.

B. Nebulizers:

- A nebulizer converts a solution of a drug into an aerosol for inhalation. Solutions for nebulization are available for use in severe acute asthma or COPD
- They are administered over 5–10 minutes from a nebulizer usually driven by oxygen in hospital, Nebulization may be carried out using an undiluted nebulizer solution or it may require dilution beforehand, the usual diluent is sterile sodium chloride 0.9%.

C. Oral Route

- The oral route is used when administration by inhalation is not possible. Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation.

D. Parenteral Route

- Drugs such as β2 agonists, corticosteroids, and aminophylline can be given by injection in acute severe asthma when administration by nebulization is inadequate or inappropriate.

9. Drugs Available

Drugs used for asthma and/or COPD			
Drug classification		**Examples**	**Route**
Bronchodilators	β2-agonists	Salbutamol, Terbutaline, Formoterol, Salmeterol	**Systemic, Inhaled**
	Antimuscarinic	Ipratropium, Tiotropium	**Inhaled**
	Xanthines	Theophylline, aminophylline	**Systemic**
Corticosteroids	Inhaled	Beclometasone, Budesonide, Fluticasone	**---**
	Systemic	Prednisolone, Hydrocortisone	**---**
Leukotriene Receptor Antagonists (Leukotriene Modifiers)		Montelukast, Zafirlukast	**Oral**
Mast Cell Stabilizers		Cromolyn sodium	**Inhaled**
Immunosuppresants (monoclonal antibodies)		Omalizumab, Mepolizumab	**S.C inj.**
		Reslizumab	**I.V infusion**
Phosphodiesterase type-4 inhibitor		Roflumilast	**Oral**
Combination Products			
Bronchodilators + Corticosteroids		Formoterol + Budesonide	**Inhaled**
Leukotriene Modifiers + Antihistamines		Montelukast + Desloratidine	**Oral**

Drugs used for Cough			
Drug classification		**Examples**	**Route**
Decongestants	Used topically	Oxymetazoline, Xylometazoline	**Nasal Drops, Spray**
	Used orally	Phenylephrine, Ephedrine, Pseudoephedrine	**Oral**
Expectorants		Ammonium chloride, Guaifenesin	**Oral**
Mucolytics		Carbocysteine, Bromhexine, Ambroxol	**Oral , Inj.**
Cough Suppressants	**Opioid**	Codeine, Dextromethorphan, Methadone, Pholcodine	**Oral**
	Non-Opioid	Anti-Histamines	**Oral , Inj.**

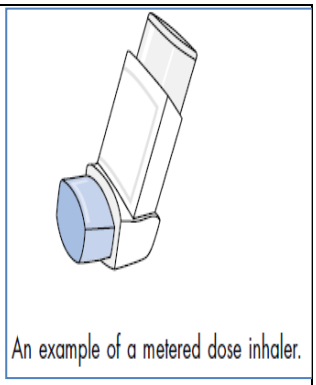
Part 2:

1.1-Bronchodilators and Anti-Asthmatic Drugs

1. Administration of drugs by the **inhaled route** delivers the drug directly to the Airways with **fewer systemic side effects** than either the parenteral or oral routes.
2. Commonly inhalation dosage forms available are **inhaler**, **nebulizer**, **Diskus** and **turbohaler** (the use of turbohaler is much easier than inhaler).

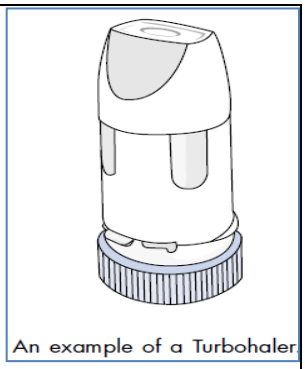
Teach the Patient

Using a metered dose inhaler (MDI)


An example of a metered dose inhaler.

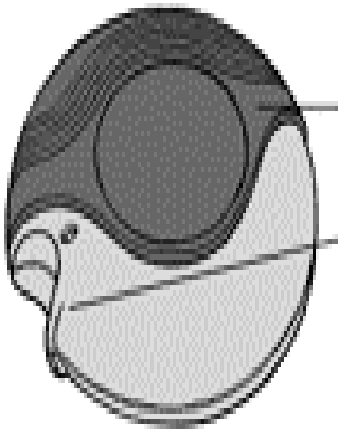
1. Remove the cap covering the mouth piece and check that there is no fluff or dirt in the mouthpiece, then Shake the inhaler.
2. If the inhaler is new or has not been used for some time it will need to be tested. To test: Hold the inhaler away from body. Press the top of the aerosol canister once, a fine mist should be puffed into the air. The inhaler is now ready to use.
3. Tilt head back slightly and Breathe out gently.
4. Place the mouthpiece in the mouth between the teeth (do not bite). Close lips around the mouthpiece.
5. Start to breathe in slowly through the mouth, at the same time press down on the inhaler to release the medicine in to the lungs.
6. Hold breath for between 5 and 10 seconds, and then breathe out slowly.
7. If a second dose is required, wait approximately 30 seconds and repeat the process.
8. Replace the cap and if the inhaler is a corticosteroid inhaler, rinse the mouth out with water.

Using a Turbohaler


An example of a Turbohaler

A Turbohaler is a dry powder inhaler. To load it prior to use:
1. Unscrew the cover and remove it.
2. Hold the Turbohaler upright with one hand and with the other twist the grip in one direction as far as it will go.
3. Now twist back as far as it will go – a click should be heard, showing the inhaler is primed and ready for use.
4. Breathe out gently by Placing the mouthpiece between the lips and breathe in through the mouth as deeply and as hard as possible.
5. Remove the inhaler from the mouth and breathe out slowly.
6. Replace the cover or Repeat the above steps if more than one puff is required.

Using a DISKUS

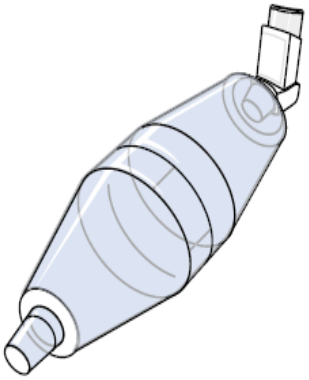


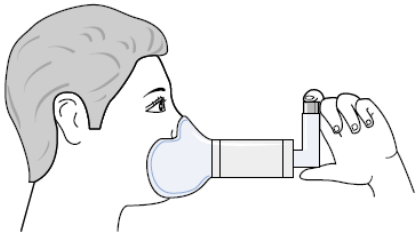
1. Open your DISKUS and Hold it in the palm of your hand, put the thumb of your other hand on the thumb grip and push the thumb grip until it "clicks" into place
2. Slide the lever away from you as far as it will go to get your medication ready
3. Breathe out away from the device by placing the mouthpiece gently in your mouth and close your lips around it
5, Breathe in deeply until you have taken a full breath
6. Remove the DISKUS from your mouth
7. Hold your breath for about ten seconds, then breathe out

Always check the number in the dose counter window to see how many doses are left.

Using a metered dose inhaler with the aid of a spacer device

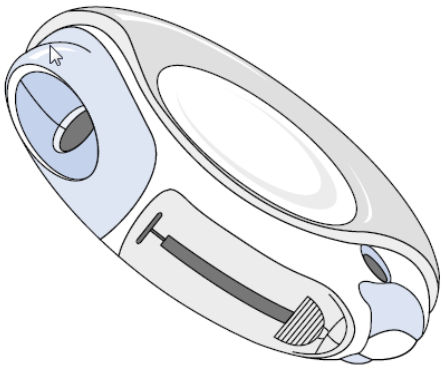
1. First assemble the spacer device if necessary as directed by the manufacturer (with or without a face mask).
2. Remove the cap from the inhaler and insert the mouthpiece of the inhaler into the opening at the end of the spacer.
3. Hold the spacer and inhaler together and shake.
4. Breathe out.
5. Put the spacer mouthpiece in the mouth and seal with the lips.
6. Press the inhaler once and then breathe in and out four or five times.
7. Further doses may be taken waiting a few seconds between puffs.
8. Separate the spacer and inhaler. Replace the inhaler cap and store until next dose.





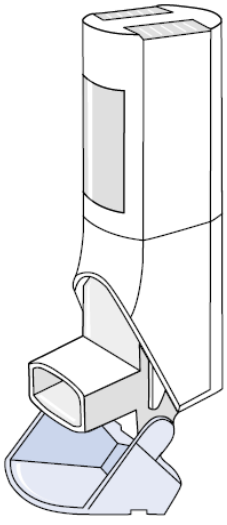
Using an Accuhaler

1. With the Accuhaler mouthpiece facing you, slide the lever away until it clicks. This will have loaded a dose ready for inhalation and the Accuhaler will move the dose counter on.
2. Hold the Accuhaler flat and breathe out away from the inhaler.
3. Seal lips around the Accuhaler mouthpiece and inhale deeply.
4. Remove inhaler from the mouth and hold breath as long as is comfortable.
5. Slide the thumb grip back towards you to close the inhaler.
6. For further doses repeat above steps.



Using a Breath actuated inhaler

1. Shake the inhaler.
2. Hold the inhaler upright and open the cap.
3. Breathe out, away from the inhaler.
4. Put the mouthpiece in the mouth, seal lips around the mouthpiece.
5. Breathe in steadily through the mouthpiece.
6. Hold breath for about ten seconds.
7. Keeping the inhaler upright, close the cap.
8. For further doses repeat the above steps.



1.1.1-Selective Beta2 agonists

1. **Beta2-Adrenergic agonists** are a class of drugs that act on the beta2-adrenergic receptor, thereby **causing smooth muscle relaxation, resulting in dilation** of bronchial passages, vasodilation in muscle and liver, relaxation of uterine muscle, and release of insulin.
    - They are primarily used to treat asthma and chronic pulmonary obstructive disease.
    - usually improve breathing within a few minutes of administration.
    - Divided into: Short acting, Long acting and Ultra-Long acting
2. **Short-acting beta2 agonists (SABAs),** (such as **Salbutamol** or **Terbutaline**) are considered the first choice for **the treatment of acute asthmatic attack** (and other conditions associated with airways obstruction), Because of their rapid onset of action – within 15 minutes.
    - Inhaled **SABAs** are given '**as required'** and **NOT as Regular treatment**.
    - **Salbutamol** may be used by some gynecologist as a **uterine relaxant for pregnant women**. (Also is used in the treatment of hyperkalemia).
3. **Long-acting beta2 agonists (LABAs),** (such as **Formoterol and Salmeterol**)**,** they are taken **regularly as prophylaxis (usually twice per day)** for chronic asthma or chronic obstructive pulmonary disease (COPD).
    - **Formoterol** is full agonist whereas **Salmeterol** is partial agonist; therefore, if poor response to one, try the other, **Formoterol** has more rapid onset (5 minutes) of action than **Salmeterol** (20 minutes)
4. **Ultra-Long-acting beta2 agonists (U-LABAs),** are a new generation approved on 2011, which is used once daily. Unfortunately, they are licensed only for the treatment of chronic obstructive pulmonary disease (COPD), (Not FDA approved for asthma yet)
5. **Adverse Effects** include **tremor**, **tachycardia**, ↑ Risk of **hypokalemia** & **hyperglycemia**.
6. **They are not recommended during the first 18 months of life because β2 receptors are not well developed during that age**

Scientific name	Dosage form	Trade name	concentration
Short-acting beta2 agonists (SABAs)			
***Salbutamol** *	Inhaler	Ventolin® , Vental®	100 mcg (0.1 mg/puff)
	Tab , Syr.	Butadin®	2mg , 2 mg/5 ml
	Nebulizing Solu.	Aloprol® , Ventolin®	5 mg/1 ml
	Inj.		0.5 mg
Levo-Salbutamol *	Inhaler	Respira®	50 mcg
	Nebulizing Solu.	Xopenex®	1.25 mg/3 ml
Terbutaline	Inhaler	Bricanyl® , Brethaire®	0.2 mg/puff
	Tab	Brethine®	2.5 mg , 5 mg
Fenoterol	Inhaler	Berotec N®	100 mcg
Pirbuterol	Inhaler	Maxair Autohaler®	0.2 mg/puff
Long-acting beta2 agonists (LABAs)			
***Formoterol** **	Inhaler	Oxis® , Aerolizer®	20 mcg/2 ml
	Inhale Powder (cap)	Foradil®	12 mcg , 20 mcg
Salmeterol	Inhaler	Serevent®	25 mcg/puff
	Inhale Powder (cap)	Serevent Diskus®	50 mcg/inhale
Arformoterol	Nebulizing Solu.	Brovana ®, Erdotin®	15 mcg/2 ml
Bambuterol	Tab	Bambec® , Oxeol®	10 mg , 20 mg
Ultra-Long-acting beta2 agonists (U-LABAs)			
Indacaterol	Cap (inhale Powder)	Arcapta Neohaler®, Onbrez®	150 mcg , 300 mcg/cap
Olodaterol	Inhaler	Striverdi®	2.5 mcg

*** Salbutamol** is Called **Albuterol** in USA and Canada (they are the same Drug).

** **Levo-Salbutamol** is also called **Levalbuterol**, also **Formoterol = Eformoterol.**

1.1.2 - Inhaled corticosteroids

1. Corticosteroids are used for the management of reversible and irreversible airways disease. An inhaled corticosteroid used for 3–4 weeks may help to distinguish asthma from chronic obstructive pulmonary disease; clear improvement over 3–4 weeks suggests asthma.
   - Corticosteroids are used for their anti-inflammatory properties**, by suppressing airway inflammation, they reduce swelling (edema)** inside the bronchioles, complementing relaxation of the walls by the bronchodilators in opening up the tubes.
   - **Reducing the inflammation also has the effect of reducing the amount of mucus** produced, and this again helps to clear the airways.
2. An inhaled corticosteroid is used **regularly for prophylaxis of asthma**, but they are **ineffective for acute asthmatic attack**.
   - For Acute Asthmatic attack (Hydrocortisone Injection) is preferred.
3. Inhaled corticosteroid may cause **oral candidiasis** (**oral fungal infection**), hoarseness; and these side effect can be **reduced by rinsing the mouth with water** after inhalation of a dose. [4].
4. High doses of inhaled corticosteroids used for prolonged periods can **induce adrenal suppression;** Inhaled corticosteroids have been associated with adrenal crisis and coma in children; **excessive doses should be avoided**.
   - Note that oral and systemic corticosteroids are also used in the treatment of asthma and COPD, for more information about corticosteroids see chapter 11.

Scientific name	Dosage form	Trade name	concentration
Beclomethasone	Inhaler	Qvar®, Beclosone®, Becotid®	50 mcg , 100 , 200 , 250 mcg
Budesonide	Inhaler , Nebul.	Pulmicort®	200 mcg
	Inhale Cap	Miflonide®	200 mcg
Fluticasone	Aerosol	Flixotide® , Flovent®	110 mcg , 100 mcg (Diskus)
Ciclesonide *	Inhaler	Alvesco®	80 mcg
Flunisolide	Aerosol	Aerospan®	80 mcg
Mometasone	Inhaler	Asmanex® , Twist-haler®	110 mcg , 220 mcg
Triamcinolone	Inhaler	Azmacort®	55 mcg , 100 mcg

Combinations of inhaled corticosteroid and long acting Beta2 agonist			
Symbicort®, Foracort® Pulmoton®	Inhaler (Turbohaler)	***Budesonide + Formoterol***	(80 mcg + 4.5 mcg), (160 mcg + 4.5 mcg), **(200 mcg + 6 mcg), (400 mcg + 12 mcg)**,
Fostair®	Inhaler	***Beclomethasone + Formoterol***	100 mcg + 6 mcg
Clenil Comp®	Inhaler	Beclomethasone + Salbutamol	200 mcg + 50 mcg
Dulera® , ***Zenhale®***	Inhaler	Mometasone + Formoterol	(100 mcg + 5 mcg), (200 mcg + 5 mcg)
Flutiform®	Inhaler	Fluticasone + Formoterol	(125 mcg + 5 mcg), (250 mcg + 10 mcg)
Seretide Diskus®, Brequal® Advair Diskus®	Inhalation powder	***Fluticasone + Salmeterol***	(100 mcg + 50 mcg), (250 mcg + 50 mcg), (500 mcg + 50 mcg)
Seretide Evohaler®, ***Rheoran®***	Inhaler	Fluticasone + Salmeterol	(50 mcg + 25 mcg), **(125 mcg + 25 mcg) (250 mcg + 25 mcg)**
Breo Ellipta®	Inh. powder	Fluticasone + Vilanterol	100 mcg + 25 mcg

*** Ciclesonide** is prodrug activated only in the lung, thus may cause **less local or systemic side effects.**
** Note that **20-40% of administered dose of the inhaled steroid is systemically absorbed**, so you may see systemic steroid effects if used in high doses and/or long-term.

1.1.3 – Anti-Muscarinic bronchodilators (Ipratropium, and Tiotropium)

1. They are used by inhalation as a bronchodilator in the treatment of asthma and chronic obstructive pulmonary disease (COPD).
2. **They Inhibit action of acetylcholine** on bronchial smooth muscle causing bronchodilation.
   - They cause this by **interfering with nerve signals** passed to the muscles through the autonomic nervous system.
   - Because they can stimulate a branch of the autonomic nervous system that controls the heart rate, they **may sometimes cause palpitations and trembling**.
3. Inhaled **Ipratropium is indicated (as needed);** due it has **short duration of action 3-5 hours**; or as an adjunctive therapy in severe acute asthma, for short-term relief in mild COPD, and for COPD exacerbations not completely responsive to β2-agonists alone.
   - **Ipratropium exhibits anti-secretory properties** when applied locally and provides symptomatic relief of rhinorrhea associated with allergic and other forms of chronic rhinitis.
4. **Tiotropium** has the advantage of having longer duration of action **(24hr)** than **Ipratropium**.
5. They **improve lung function and reduces the risk of exacerbation** in people with symptomatic asthma, However, it will not stop an asthma attack already in progress; Because it has no effect on asthma symptoms when used alone, it is most often paired with a short-acting β2-adrenergic agonist.
   - The use of anticholinergics in combination with short-acting β2-adrenergic agonists has been shown to reduce hospital admissions in children and adults with acute asthma exacerbations.
6. **Adverse Effects:** dry mouth, blurred vision, taste disturbance, Urinary retention, difficulty in passing urine [2]; Antimuscarinic bronchodilators should be **used with caution in patients with** prostatic hyperplasia, bladder outflow obstruction, and those with angle-closure glaucoma.
7. **Revefenacin**, a long-acting muscarinic antagonist; that has the advantage of **used once daily**; it's the first and currently the only once-daily, nebulized bronchodilator to be approved by FDA for the treatment of chronic obstructive pulmonary disease (COPD)

Scientific name	Dosage form	Trade name	concentration
Ipratropium	Inhaler	Atrovent® , Atroaldo®, Ipravent®	20 mcg
	Nebulizing Solu.		
Tiotropium	Cap (inhale powder)	Spiriva® , Tiohaler®	18 mcg
Oxitropium	Inhaler	Oxivent®	1.5 mg/ml
Aclidinium	Inhaler	Tudorza Pressair®	400 mcg
Glycopyrronium *	Cap (inhale powder)	Seebri Breezhaler®	50 mcg
Revefenacin	Nebulizing Solu.	Yupelri®	175 mcg/3 ml

** **Glycopyrronium** is also used (orally and by injection) **to suppress gastric acid secretion**, and has been used topically and orally **to treat hyperhidrosis** (condition characterized by abnormally increased sweating/perspiration); Since it reduces the body's sweating ability, it can even cause fever, heat stroke in hot environments.

Note1: Combination products for Anti-Muscarinic bronchodilators:

Scientific name	Dosage form	Trade name	concentration
Ipratropium + Salbutamol	Inhaler	***Combivent® , Duoneb®***	20 mcg + 100 mcg
	Nebulizing Solu.		
Ipratropium + Fenoterol	Inhaler	***Berodual N®***	20 mcg + 100 mcg
Umeclidinium + Vilanterol	Inhale powder	Anoro Ellipta®	62.5 mcg + 25 mcg
Glycopyrronium+ Indacaterol	Inhale powder	Ultibro Breezhaler®	50 mcg + 110 mcg
Glycopyrrolate + Formoterol	Inhaler	Bevespi Aerosphere®	9 mcg + 4.8 mcg
Tiotropium + Olodaterol	Inhaler	Stiolto Respimat®	2.5 mcg + 2.5 mcg

Note2: Triple products

1. These usually contain a long acting Anti-Muscarinic bronchodilator (LAMA), and a long acting beta2 agonists (LABA) and an Inhaled corticosteroid (ICS).
2. Triple inhalers have the advantage of convenience and may improve adherence, but there are risks that the three components may interact chemically in the device, and the fixed doses may require several dose combinations.
3. They are intended for patients with COPD, including chronic bronchitis and/or emphysema.
4. These combinations improve lung function, health status and reduce exacerbations compared with ICS/LABA or LAMA monotherapy.
5. Some are taken Once daily; some are taken twice daily.

Triple Products			
Scientific name(s)	D. Form	Trade name	Concentrations
Umeclidinium + Vilanterol + Fluticasone	Inhale powder	Trelegy Ellipta®	62.5 mcg + 25 mcg + 100 mcg
Tiotropium + Formoterol + Ciclesonide	Inhaler	Triohale®	9 mcg + 6 mcg + 200 mcg
	Cap (for inhale)	Triohale Rotacaps®	18 mcg + 12 mcg + 400 mcg
Glycopyrronium + Formoterol + Beclometasone	Inhaler	Trimbow®	10 mcg + 6 mcg + 100 mcg
Glycopyrronium + Formoterol + Budesonide	Pending FDA approval (by Novartis)		
Glycopyrronium + Indacaterol + Mometasone	Pending FDA approval (by AstraZeneca)		

Note: Nobel Prize in Physiology or Medicine 2019

The 2019 Nobel Prize in Physiology or Medicine awarded to William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza "for their discoveries of **how cells sense and adapt to oxygen availability**". The ability of organisms to respond to changes in oxygen availability is of fundamental importance to life on earth. Work by the prize-winning scientists has shown that in animal cells, oxygen availability affects gene expression through oxygen-sensitive post-translational modification and the subsequent proteasomal degradation of Hypoxia Inducible Factors. This research laid the foundation for understanding the mechanistic basis for the cellular response to hypoxia and paved the way for the therapeutic targeting of the response pathway.

1.1.4 - Theophylline (and Xanthine's derivatives)

1. There are 3 important Xanthine derivatives: (**Theophylline**, **Theobromine** and **Caffeine**).
2. **Theophylline** is a bronchodilator used in asthma and chronic obstructive pulmonary disease.
   - Xanthine drugs are thought to **relax the muscle in the bronchioles** by a direct effect on the muscle fibers, their precise action is hypnotized as:
     - ☒ Inhibit phosphodiesterase enzyme thus increasing cAMP; which leads to relaxation of the smooth muscles and contraction of the cardiac muscle.
     - ☒ Blocking Adenosine receptors; causing increased heart rate, and stimulant effect in brain.
3. Theophylline is given by injection as **Aminophylline**; Aminophylline injection **must be given by very slow intravenous injection** (over at least 20 minutes).
4. The use of **sustained release formulation of theophylline** (Phyllocontine®) is **preferred** over ordinary tablet (immediate release tablet) and it is usually **given twice daily** and the sustained release tablet **should not be splinted or crushed**.
   - Modified-release theophylline tablet should be taken with or just after food.
5. **Adverse Effects: tachycardia, palpitations, insomnia, restlessness, tremor**.
   - Smoking tobacco and drinking alcohol increase excretion of Xanthines from the body, reducing their effects, thus Stopping smoking after being stabilized on a xanthine may result in a rise in blood concentration, and an increased risk of side effects. It is advisable to stop smoking before starting treatment, also the effects of theophylline may last longer if you have a viral infection, heart failure, or liver cirrhosis.
6. **Have a high Drug-Drug interaction profile.**

Scientific name	Dosage form	Trade name	concentration
Theophylline	Tab	Asmasam®	120 mg
	Tab SR	Phyllocontine®	225 mg
	Cap SR	TeoCap®	300 mg
Aminophylline	Amp	Phyllocontine®	250 mg/10 ml
Dyphylline	Tab	Lufyllin® , Dilor®	200 mg , 400 mg
Diprophylline	Syrup	Euphillin®	57 mg/5 ml
Acefylline	Tab , Amp	Sureptil®	50 mg (tab) , 500 mg (amp)

1.1.5 - Leukotriene Receptor Antagonists

1. **Leukotrienes** occur naturally in the body, they are chemically related to the prostaglandins, but are much more potent in producing an inflammatory reaction; they are also much more potent than histamine at causing bronchoconstriction, thus **Leukotrienes** seem to play an important part in asthma; Drugs have been developed that block their receptors **(leukotriene receptor antagonists)** and **therefore reduce the inflammation** and **bronchoconstriction** of asthma.
2. They are given **orally** mainly for **prophylaxis of asthma.** (Not useful in acute asthma).
   - **Montelukast** is Also indicated in **exercise-induced bronchospasm** and in **perennial allergic rhinitis** in children as young as 6 months and for **seasonal allergic rhinitis** in children as young as 2 years.
   - must be **taken on a regular basis, even during symptom-free periods.**
3. In addition to ordinary tablet, Montelukast also formulated as Chewable tablet which contain a lower dose (4 mg) and intended mainly for children.
   - The **chewable tablet is taken on an empty stomach**; this means an hour before food or 2 hours after food.
   - Granules may be swallowed or mixed with cold, soft food (or liquid) and taken immediately.
4. **Adverse effects:** Elevations in serum hepatic enzymes, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the normal limit.

5. **Montelukast** and **Zafirlukast** are Leukotriene receptor antagonists, they block the binding of leukotriene to its receptors, thus prevent the inflammation process (Leukotriene (LT) B4 and the cysteinyl leukotrienes, LTC4, LTD4, and LTE4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade).
6. **Zileuton** is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB4 and the cysteinyl leukotrienes.
7. A study was recently published shows a link between **leukotriene receptor antagonists and neuropsychiatric adverse drug reactions** (depression, aggression, hyperactivity and nightmares); especially in pediatrics. (10)

Scientific name	Dosage form	Trade name	concentration
Montelukast	Tab	Singulair® , Monax® , Singomed®	5 mg , 10 mg
	Tab Chew.		5 mg , 4 mg
	Oral Granules		4 mg
Pranlukast	Oral Granules , Tab	Azlaire®	50 mg , 70 mg , 100 mg
Zafirlukast	Tab	Accolate®	20 mg
Zileuton	Tab ER	Zyflo® , Filmtab®	600 mg

Note: Combination products:

Scientific name	D. form	Trade name	concentration
Montelukast + Cetirizine	Tab	Broncho-Vokast®	(10 mg + 5 mg)
Montelukast + Desloratidine	Tab	Aircomb®	(10 mg + 5 mg)
Montelukast + Levocetirizine	Tab	OnceAir Plus®, Bronchorest® Fixdual®	(10 mg + 5 mg)
Montelukast + Fexofenadine	Tab	Lukafen®	(10 mg + 120 mg)
Montelukast + Ebastine	Tab	Ebamont® , Ebast-M®	(10 mg + 10 mg)

** **Desloratidine, Levocetirizine** and **Ebastine** are a 2nd generation antihistamine (see below).

1.1.6 – Cromoglicate and Nedocromil

1. The mode of action of **Sodium Cromoglicate (Cromoglycate)** and **Nedocromil** is not completely understood, but **they may be of value in asthma with an allergic basis.**
   - **Cromoglicate** and **Nedocromil** thought to **act by stabilizing mast cells in the lungs**, preventing them from releasing histamine, leukotrienes, and other inflammation-causing chemicals; Indicated for **prophylaxis of mild persistent asthma** in children and adults.
2. **Cromoglicate** is also called (**Cromoglicic acid**, **Cromolyn** and **Cromoglycate**).
   - **Cromoglicate** and **Nedocromil** may also have a role in allergic conjunctivitis; sodium Cromoglicate is used also in allergic rhinitis.
   - **Cromoglicate** is also used (orally as a capsule) for allergy-related diarrhea; food allergy (in conjunction with dietary restriction).
   - **Cromoglicate** Capsules maybe swallowed whole or the contents dissolved in hot water and diluted with cold water before taking, to be taken 30 to 60 minutes before food.
3. Dose frequency is adjusted according to response but is usually 3 to 4 times a day.
4. **Side effects include** throat irritation, cough, bronchospasm (including paradoxical bronchospasm), and headache.

Scientific name	Dosage form	Trade name	concentration
Cromoglicate	Inhaler	Intal®	5 mg per Puff
	Cap	Gastrocrom®	200 mg
Nedocromil	Inhaler	Tilade®	2 mg per Puff

1.1.7 – Other Asthma therapies

This section covers all the remaining therapies used in asthma; they are used rarely but still important because they are the last choice in poor responsive patient to traditional medications.

Scientific name	Dosage form	Trade name	concentration
Roflumilast	Tab	Daxas® , Daliresp®	500 mcg
Omalizumab	Amp (S.C inj.)	Xolair®	150 mg/ml
Mepolizumab	Amp (S.C inj.)	Nucala®	100 mg/ml
Reslizumab	Vial (infusion)	Cinqair®	100 mg/10 ml
Benralizumab	Prefilled Inj.	Fasenra®	30 mg/ml
Dupilumab	Amp (S.C inj.)	Dupixent®	300 mg/2 ml
Mg+ Sulphate	Amp	----------	40 mg/ml , 80 mg/ml
	Infusion Solu.	----------	1 gm/100 ml , 2 gm/100 ml

Notes:

1. **Roflumilast** is a drug that acts as a selective **long-acting inhibitor of the enzyme PDE-4** with anti-inflammatory properties; (it was developed from trails on Xanthines)
   - It's **approved for severe COPD** associated with chronic bronchitis, also approved for **reducing COPD exacerbations**, it **improves lung functions**.
   - It's C.I. in severe immunological disease; severe acute infectious disease; co-administration with immunosuppressive drugs (except short-term systemic corticosteroids).
2. **Omalizumab** is a monoclonal antibody that **binds to immunoglobulin E (IgE)**, decreasing its binding ability to receptors on mast cells and basophils; it is used as additional therapy in individuals with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high dose inhaled corticosteroid together with a long-acting beta2 agonist.
   - **Omalizumab** should be initiated by physicians in specialist centers experienced in the treatment of severe persistent asthma. **(Given S.C. twice a month),** and should be **used only in severe asthma with concurrent allergies.**
   - **Also indicated for chronic idiopathic urticarial.**
   - Approved only to Use in those ≥ 12 years, Half-life: 26 days.
   - In September 2014: FDA Drug Safety Communication announced that Omalizumab Slightly increased risk of cardiovascular and cerebrovascular serious adverse events, including MI, unstable angina, TIA, PE/DVT, pulmonary HTN; but no increase in risk of stroke or CV death.
3. **Mepolizumab, Reslizumab** and **Benralizumab** are indicated for **severe asthma with an eosinophilic phenotype** as add-on maintenance treatment in those above 12 years old.
   - It's an IgG1 Monoclonal antibody, specific for IL-5, it binds IL-5 and thus preventing it for binding with eosinophils, thus it **reduces the eosinophils** in blood, tissues and sputum.
   - Reduces rate of asthma exacerbations by > 50%.
   - Reduces corticosteroid dose by 50%.
4. **Magnesium sulfate** (administered I.V.) may be useful in some patients because of its modest ability to cause bronchodilation, it also improves the respiratory muscle strength in hypomagnesemia patients. It's also used:
   - As an **Anti-arrhythmic** for the treatment of **Torsade's De Pointes.**
   - As a **Tocolytic** to stop preterm labor in Obs/Gyne.
   - To **prevent seizers** associated with pre-eclampsia, and to control seizers with eclampsia.

Note1:

- There are several medications available for the treatment of Asthma; are they all the same? Well; the answer to that question is a little complex; since the choice of drugs depends on the stage of Asthma or COPD, and wither it's for acute relief or long-term symptoms control.

Note2: The table below shows a simple guide for choosing anti-asthmatics:

Category	Purpose	Types
Long-term asthma control medications	Taken regularly to control chronic symptoms and prevent asthma attacks; the most important type of treatment for most people with asthma	• Inhaled corticosteroids • Leukotriene modifiers • Long-acting beta agonists (LABAs) • Theophylline • Combination inhalers
Quick-relief medications (rescue medications)	Taken as needed for rapid, short-term relief of symptoms used to prevent or treat an asthma attack	• Short-acting beta agonists • Ipratropium • Oral and intravenous corticosteroids (for serious asthma attacks)
Medications for allergy-induced asthma	Taken regularly or as needed to reduce the body's sensitivity to a particular allergy-causing substance (allergen)	• Allergy shots (immunotherapy) • Allergy medications (antihistamines)
Biologics	Taken with control group to stop underlying biological responses causing inflammation in the lungs (for Sever Asthma)	• Omalizumab • Mepolizumab • Benralizumab • Reslizumab

Note3:

Inhaled corticosteroids differ in their potencies, anti-inflammatory effect, and side effects.

- The highest inhaled corticosteroid with Relative glucocorticoid receptor binding affinity (or the highest anti-inflammatory potency) is **Fluticasone Furoate**, the second in place is **Mometasone,** then in third place is **Budesonide.**
- The longest lung retention is with **Fluticasone Furoate.** (the longest half-life and duration).
- **Fluticasone Furoate** and **Mometasone** inhalers is given once daily; while other is given twice.
- The lowest systemic absorption inhaled corticosteroid is **Budesonide**.
- The lowest side effects profile is **Ciclesonide**, (it's a prodrug; activated only in the lungs).

Note4: Salmeterol or Formoterol?

1. The pharmacological evidence for a **rapid onset** of action of **Formoterol** (5 min), yet **long duration** of effect (12 hours), is supported by several clinical studies; The fast onset of bronchodilation and **high intrinsic activity** of **Formoterol** therefore suggest that it can be used for relief treatment in patients with asthma if they are concomitantly treated with inhaled glucocorticoids. [7] (i.e. Formoterol can be used also for acute attack relief).
2. **Salmeterol** has slightly **more prolonged activity** (13-14 hours); but **slower onset of action** (about 20 minutes); it's also a partial agonist; which means it **causes less side effects** than Formoterol; and has a **lower tolerance** on the β2-receptors with prolonged use. [8]
3. The real question is **Symbicort®** or **Seretide®**?
   - Well; it's for you to decide dear reader; corticosteroid potency or safety; the higher effect or the least systemic side effects.

Note5: Again; Salmeterol or Formoterol or Tiotropium?

1. In patients with moderate-to-very-severe COPD, **Tiotropium** is more effective than **Salmeterol** in preventing exacerbations. [11]
2. Currently, there is no documentation that **Tiotropium** is superior to **Formoterol** or the contrary, but a combination of them both is more effective than single drugs alone in inducing bronchodilation and a bronchodilator-mediated symptom benefit in patients suffering from COPD; although **Formoterol** has a fast onset and a bronchodilator effect of approximately 12 h, while **Tiotropium** has a 24-h bronchodilator effect and is given once daily. [12]

1.2-Antihistamines

1. Their main action is to **counter the effects of histamine**, one of the chemicals released in the body when there is an allergic reaction.
2. **Histamine** is also involved in other body functions, **including blood vessel dilation and constriction, contraction of muscles in the respiratory and gastrointestinal tracts, and the release of digestive juices in the stomach.**
3. The antihistamine drugs described here are also known as **H1 blockers** because they block the action of histamine only on certain receptors, known as H1 receptors. Another group of antihistamines, known as **H2 blockers**, is used in the treatment of peptic ulcers.
4. **Some antihistamines have a significant anticholinergic action; This is used to advantage in a variety of conditions, but it also accounts for certain undesired side effects.**
5. Histamine H1-receptor antagonists bind to H1 receptors without activating them, preventing histamine binding and action; **They are more effective in preventing the histamine response than in reversing it** (4).
   - Antihistamines block the action of histamine on H1 receptors; These are found in various body tissues, particularly the small blood vessels in the skin, nose, and eyes. **This helps prevent the dilation of the vessels, thus reducing the redness, watering, and swelling.**
   - the **anticholinergic action** of these drugs contributes to this effect **by reducing the secretions from tear glands and nasal passages**.
   - Antihistamine drugs pass from the blood into the brain. In the brain, the blocking action of the antihistamines on histamine activity may **produce general sedation and depression of various brain functions, including the vomiting and coughing mechanisms.**
6. Antihistamines are used in the treatment of **allergies, nasal allergies** (they **reduce rhinorrhea and sneezing**), also used to **treat urticarial rashes, pruritus, and insect bites and stings**.
   - Antihistamines are also prescribed for the **itching, swelling, and redness** of allergic reactions involving the skin such as **dermatitis**, and **Irritation from chickenpox.**
   - Antihistamines are often **included as an ingredient in cough and cold preparations,** when the anticholinergic effect of drying mucus secretions and their sedative effect on the coughing mechanism may be helpful.
   - Because most antihistamines have a depressant effect on the brain, **they are sometimes used to promote sleep**, especially when discomfort from itching is disturbing sleep, the depressant effect of antihistamines on the brain also extends to the centers that control nausea and vomiting; thus, **effective for preventing and controlling these symptoms** (see Anti-emetics).

The antihistamines may be classified into:

a) **Sedating antihistamines**: also referred as **1st generation antihistamines** older antihistamines that are associated with troublesome **sedative** and Antimuscarinic effects. Examples are (Chlorpheniramine, Clemastine, Cyproheptadine, Ketotifen, diphenhydramine, and Dimetindene maleate), Drowsiness is a major problem with the sedating antihistamines and those affected should **not drive or operate machinery**.

b) **Non-sedating antihistamines**: also referred **as 2nd**, are newer antihistamines, **they generally cause little or no drowsiness**; Examples are (Cetirizine, Loratadine).
   - **A new classification divides the 2nd generation into a 3rd generation,** which consists only from the active metabolites of the 2nd gen. **(ex: Desloratidine, Levocetirizine, Fexofenadine),** which has more efficacy and less side effects.

7. **Adverse effects: constipation, dry mouth, Sweating, Blurred vision, Tachycardia**.
   - **In high doses,** or in children, some antihistamines **can cause excitement, agitation**, and even, in extreme cases, hallucinations and seizures.
8. Antihistamines should be used with caution in patients predisposed to urinary retention and in those with increased intraocular pressure, hyperthyroidism, and cardiovascular disease.

9. **Contraindicated in: Narrow angle Glaucoma, Prostate enlargement, BPH**.
10. A new study published on (PubMed) states that: **(combining H_1 and H_2 antagonists in patients with acute allergic syndromes results in faster improvement from allergy).**
    (For H_2 antagonists see chapter 2, section 3)

1st Generation Antihistamines:

Scientific name	D. form	Trade name	Conc.
Clemastine	Tab	Tavegyl®	1 mg
	Amp	Tavegyl® , Tavesta®	2 mg
Diphenhydramine	Tab	Brandyl® , Allermine®	25 mg
	Amp	Allermine®	10 mg
	Syr.	Allermine®	10 mg/5 ml
Chlorpheniramine	Tab	Histadin®	4 mg
	Amp	Allergal®	10 mg/2ml
	Syr.	Pirafene®	2 mg/5 ml
Pheniramine	Tab	Avil®	20 mg
	Amp	Avil®	45.5 mg/2 ml
Dexchlorpheniramine	Tab	Poloramine®	6 mg
Doxylamine	Tab	Unisom®, Sleep Well®	25 mg
Cyproheptadine	Tab	Periactin®, Ciptadine®, Cyprodad®, Nebor®	4 mg
	Syr.	Cyprodine® , Citadine®	2 mg/5 ml
Ketotifen	Tab	Zaditin® , Ketofen®	1 mg
	Syr.	Ketofen® , Zylofen®	1 mg / 5 ml
	Eye Drop	Zaditor ® , Zyrtec®	0.025%
Hydroxyzine	Tab	Atarax®	10 mg , 25 mg
Dimetindene	Drop	Fenistil®	0.1 gm
	Tab		4 mg
	Syr.		0.01%
Promethazine	Tab	Phenadoz®	25 mg
	Syr.		6.25 mg/5 ml
Triprolidine	(Found in Combinations Only, As Actifed®)		
Carbinoxamine	Tab	Palgic® , Arbinoxa®	4 mg
Brompheniramine	Tab	Dimetane® , Respa®	10 mg
Alimemazine	Tab	Nedeltran®, Panectyl®	10 mg
	Syr.		7.5 mg/5 ml
Oxomemazine	Syr.	Toplexil® , Toxil®	1.65 mg/5 ml
	Tab		24 mg

Notes:

1. **Diphenhydramine** has pronounced sedative properties and may be **used as a hypnotic in the short-term management of insomnia** (taken before bedtime).
2. **Doxylamine** is usually categorized as a **sedative/hypnotic agent.**
3. **Cyproheptadine** has been widely **used as an appetite stimulant**, but in the long-term appears to have little value in producing weight gain and such use is no longer recommended.
4. **Hydroxyzine** has **strong Anxiolytic effect**, with high sedating capacity, it can be abused. **Dimetindene** is usually used for pediatrics as antipyretic and sedative, and for allergies, it is safe for infants from one month and older; **(But it's not recommended to use as sedative).**
5. **Triprolidine should be given only to children above 6 years old**, as **approved** by the U.S. Food and Drug Administration **(FDA),** although some doctors prescribe it to children below 6 years. (educate them about this fact)

6. **Alimemazine** is also called **Trimeprazine** (they are the same drug).
7. **Oxomemazine is not approved** by the U.S.A **(FDA),** but it is still sold as over the counter medication in some countries, **Oxomemazine** has **a strong sedative effect – Which may explain why it's abused in our markets - (don't give by hand, ONLY by Rx).**

2nd and 3rd Generation Antihistamines:

Scientific name	Dosage form	Trade name	Concentration
Fexofenadine	Tab	Telfast® , Fexofast® , Fexon®	180 mg , 120 mg
	Oral Susp.	Allerga®	30 mg/5 ml
Loratadine	Tab	Claritin®, Tidilor® ,	10 mg
	Syrup	Loratidine® , Lortin®	5 mg/5 ml
Cetirizine*	Tab	Zyrtec® , Cetriz®	5 mg , 10 mg
	Syrup , Oral drop	Zyrtec®	5 mg/5 ml
Desloratidine	Tab	Areus® , Clarinex®	5 mg
	Syrup		2.5 mg/5 ml
Levocetirizine	Tab	Xyzal®	5 mg
	Oral Solu.		2.5 mg/5 ml
Acrivastine	Tab , Cap	Semprex®	8 mg
Ebastine	Tab	Evastin® , Aleva®	10 mg , 20 mg
	Syrup		5 mg/5 ml
Bilastine	Tab	ILaxten®	20 mg
Mizolastine	Tab	Mizollen®	10 mg
Rupatadine	Tab	Rupafin®	10 mg
Terfenadine *	Tab	Seldane®	60 mg

** The safety profile of **Fexofenadine** is quite favorable, **as no cardiovascular or sedative effects** have been shown to occur even when taking 10 times the recommended dose.

** although **Cetirizine** is a 2nd generation antihistamine; it produces a marked sedation.

**** Terfenadine was withdrawn from the markets** in the USA due to the risk of disruption of the electrical rhythms of the heart **(cardiac arrhythmia caused by QT interval prolongation).**

Comparison of Antihistamines

Drugs	COMMON USES: Allergic rhinitis	Skin allergy	Sedation	Premedication	Nausea/vomiting	Cough/cold remedies	ACTIONS AND EFFECTS	Drowsiness	Anticholinergic action	DURATION OF ACTION
Alimemazine		●	●	●				■	□	◮
Acrivastine	●	●						□	◪	△
Cetirizine	●	●						□	□	▲
Chlorphenamine	●	●	●			●		◪	◪	△
Cyclizine					●			◪	◪	△
Diphenhydramine			●		●	●		◪	◪	△
Hydroxyzine		●	●					■	◪	▲
Loratadine	●	●						□	□	▲
Promethazine	●	●	●	●		●		■	◪	◮

KEY

● Drug used ■ Strong ◪ Medium □ Minimal ▲ Long (over 12 hours) ◮ Medium (6–12 hours) △ Short (4–6 hours)

Note1: which antihistamine is the most potent for allergy?

- **Levocetirizine** and **Fexofenadine** are the most potent antihistamines in humans in vivo; **Fexofenadine** also has the lowest side effects profile in antihistamines group. [9]

Note2: Topical Antihistamine

- These are useful for relieving itching that is often associated with sunburns, allergic reactions, eczema, psoriasis … etc. (for more information see chapter 14, section 9)

Scientific name	Dosage form	Trade name	concentration
Crotamiton	Cream/Lotion	Eurax®	10%
Calamine	Lotion	Calamine®	10%
Diphenhydramine	Gel	Banophen®	1% , 2%

Note3: Other Antihistamines (As Nasal Sprays & Eye drops)

Scientific name	Dosage form	Trade name	concentration
Azelastine	Nasal Spray	Astelin® , Allergodil® , Rhinolast®	0.1%
	Eye Drop	Optivar®, Allergodil®	0.05%
Olopatadine	Nasal Spray	Patanase®	6%
	Eye Drop	Pataday® , Patanot® , Olopat®	0.1% , 0.2%
Alcaftadine	Eye Drop	Lastacaft®	0.25%
Bepotastine	Eye Drop	Bepreve®	1.5%
Emedastine	Eye Drop	Emadine®	0.05%
Epinastine	Eye Drop	Elestat®	0.05%
Levocabastine	Eye Drop	Livostin®	0.05% (0.5 mg/ml)
	Nasal Spray		50 mcg/spray

Notes:

1. **Intranasal antihistamine** rapidly relieves symptoms of seasonal allergic rhinitis. However, patients should be cautioned about its potential for drowsiness because **systemic availability is ~40%**. Patients may also experience drying effects, headache, and diminished effectiveness over time. [4-5].
2. **Ophthalmic antihistamines** that can be used for allergic conjunctivitis that is often associated with allergic rhinitis.

1.3 - Cough preparations, Common Cold and Flu

1. Commonly, cough preparations contain a combination of antitussive or expectorants, antihistamine, and/or sympathomimetic (for congestion).
2. **Lozenges** may also be used for cough especially for pregnant women.
3. Some usually contain a combination of **Sympathomimetics** like **pseudoephedrine** and **phenylephrine** (they reduce nasal congestion) and **antihistamine** (like Triprolidine) (they reduce rhinorrhea and sneezing).
   - **Pseudoephedrine** in some countries are not available as an OTC; and only given by a prescription; that is due **Pseudoephedrine can be converted** chemically (by reduction) to **Methamphetamine**.
4. **Topical and systemic decongestants** are sympathomimetic agents that act on adrenergic receptors in the nasal mucosa to produce vasoconstriction, shrink swollen mucosa, and improve ventilation.
5. **Prolonged use of topical Sympathomimetics agents** (>3–5 days) can result in rhinitis medicamentosa (which is rebound vasodilation with congestion); Patients with this condition use more spray more often with less response. Abrupt cessation is an effective treatment, but rebound congestion may last for several days or weeks; Generally **recommended duration for usage of the topical Sympathomimetics is 3 days**.
6. Systemic decongestants should be used with caution in **hypertension**, **hyperthyroidism**, and **ischemic heart diseases**.

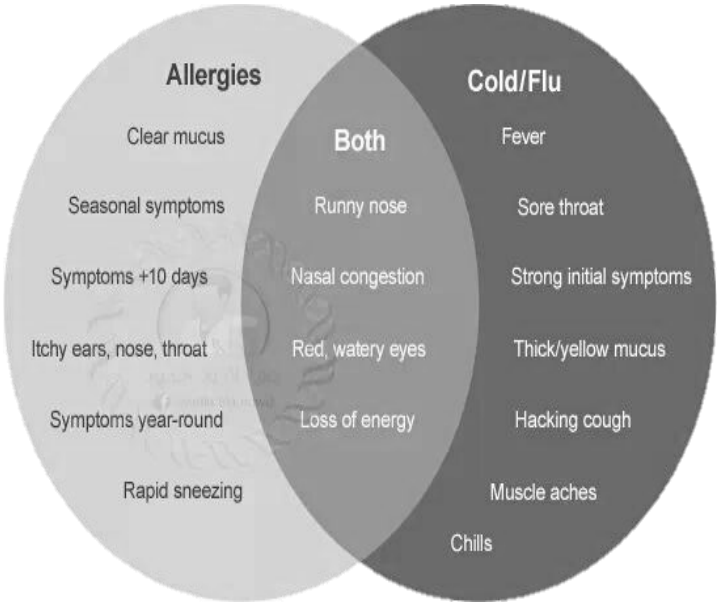
A) Topical Sympathomimetics:

Scientific name	Dosage form	Trade name	concentration
Xylometazoline *[4]	Nasal Drop / Nasal Spray	Otrivin Adult®, Triaminic®, Xylo-mepha®	0.1%
	Nasal Drop/Spray	Otrivin Child®	0.05%
Oxymetazoline	Nasal Drop	Afrin®, Dristan®, Nasordine®	0.05%
Phenylephrine	Nasal Spray/Drop	NeoSynephrine®, Nazafrine®	0.25% , 0.5%
Naphazoline	Nasal Spray/Drop	Privine®	0.05%
Tetrahydrozoline	Nasal Drop	Visine®, Burnil®	0.05% , 0.1%
Propylhexedrine	Nasal Spray	Benzedrex®	250 mg

Notes:

1. **All topical Sympathomimetics are <u>not recommended</u> to use in children below 6 years**, Except for **Xylometazoline 0.05% which can be used in children above 2 years old**.
2. Younger children (below 2 years) are to use **NaCl nasal drops** for treatment of decongestion.
3. **Adverse effects** of topical decongestants are burning, stinging, sneezing, and dryness of the nasal mucosa.
4. **Xylometazoline** is also available as a **topical cream 1%**, indicated for the topical treatment of persistent **facial erythema associated with rosacea in adults.**
   - **Xylometazoline** can be **abused** by addicts to obtain the **psychoactive effects** of inhaled Xylometazoline; which include excitation and feeling of strength.
5. **Topical Sympathomimetics** differ in their duration of action as shown in the Table below:

Medication	Duration (Hours)
Short-acting	
Phenylephrine hydrochloride	Up to 4
Intermediate-acting	
Naphazoline hydrochloride	4–6
Tetrahydrozoline hydrochloride	4–6
Long-acting	
Oxymetazoline hydrochloride	Up to 12
Xylometazoline hydrochloride	Up to 12



B) Common Cold and Flu:

1. Generally Common Cold and Flu are **viral in origin** and **self-limiting** (thus antibiotics have no role), usually patient will recover within 1 week**, Few Cases are due bacterial infection.**
2. **Mechanism of infection:** Once the virus is exposed to the mucosa, it invades the nasal and bronchial epithelia, causing damage to the ciliated cells. This results in the release of inflammatory mediators, which in turn leads to inflammation of the tissues lining the nose. Permeability of capillary cell walls increases, resulting in edema, which is experienced by the patient as nasal congestion and sneezing. Fluid might drip down the back of the throat, spreading the virus to the throat and upper chest causing cough and sore throat.
3. **All the treatment is given for symptomatic relief ONLY**.

Trade name	D. form	Scientific name(s)	Concentration
Actifed®	Tab	Triprolidine Pseudoephedrine	2.5 mg 60 mg
Actifed®, ***Samafed®***	Syrup (yellow)	Triprolidine Pseudoephedrine	1.25 mg/5ml 30 mg/5ml
Actifed® (red)	Syrup (red)	Triprolidine + Pseudoephedrine Dextromethorphan	1.25 mg + 30 mg 10 mg
Actifed® (green)	Syrup (green)	Triprolidine + Pseudoephedrine Guaifenesin	1.25 mg + 30 mg 100 mg
Panadol® Night	Tab	Paracetamol + Diphenhydramine	325 mg + 25 mg
Panadol® Sinus	Tab	Paracetamol + Pseudoephedrine	500 mg + 30 mg
Panadol® Extra	Tab	Paracetamol + Caffeine	500 mg + 65 mg
Panadol® ***Cold-Flu***	Tab	Paracetamol + Pseudoephedrine Chlorpheniramine	500 mg + 30 mg 2 mg
Panadol® ***Cold-Flu Lemon***	Tab, Sachet	Paracetamol + Phenylephrine + Vitamin C	600 mg + 10 mg + 40 mg
Panadol® ***Cold-Flu Day***	Tab	Paracetamol + Phenylephrine + caffeine	500 mg + 5 mg + 25 mg
Panadol® ***All in one***	Tab	Paracetamol + Phenylephrine + Guaifenesin	250 mg + 5 mg + 100 mg
Coldin® SDI	Tab	Paracetamol + Promethazine Phenylephrine	450 mg + 5 mg 5 mg
	Syrup	Paracetamol + Pseudoephedrine Chlorpheniramine Vitamin C	120 mg + 15 mg 2 mg 50 mg
Coldin® Mediphar	Cap	Paracetamol + Pseudoephedrine + Pyrilamine + Noscapine + Caffeine	300 mg + 30 mg + 15 mg + 10 mg + 30 mg
	Syrup	Paracetamol + Pseudoephedrine + Pyrilamine + Glyceryl Guaiacolate	120 mg + 15 mg 6.25 mg 15 mg
Flu-out®	Tab	Paracetamol + Chlorpheniramine + Vitamin C	350 mg + 2 mg + 100 mg
Flu-cure ® ***Stop-cold®***	Tab	Paracetamol + Chlorpheniramine	400 mg + 2 mg
Flu Stop®	Elixir	Paracetamol + Chlorpheniramine	120 mg + 2 mg
Semprex D®	Cap	Acrivastine + Pseudoephedrine	8 mg + 60 mg
Grippe stop®	Tab	Paracetamol + Pseudoephedrine + Dextromethorphan	325 mg + 30 mg + 15 mg
Tullin-D® (red), ***Congestal®***	Cap (red), Tab	Paracetamol + Pseudoephedrine + Dextromethorphan + Chlorpheniramine	325 mg + 30 mg + 10 mg + 2 mg
Tullin-D® (red), ***Congestal®***	Syrup	Paracetamol + Pseudoephedrine + Dextromethorphan + Chlorpheniramine	160 mg + 15 mg + 7.5 mg + 1 mg
Tullin® ***(blue)***	Cap (blue)	Guaifenesin + Pseudoephedrine + Dextromethorphan + Paracetamol	100 mg + 30 mg + 10 mg + 250 mg

Dolo-Cold® **	Tab	Paracetamol + Chlorpheniramine + Phenylpropanolamine ** + Caffeine + Pseudoephedrine	500 mg + 2 mg + 12.5 mg + 25 mg + 30 mg
Triaminic®	Syrup	Pseudoephedrine Dextromethorphan Chlorpheniramine	15 mg 5 mg 1 mg
Aspirin-C®, Cevamol®	Eff. Tab.	Aspirin + Vitamin C	400 mg + 250 mg
Hayanil®	Tab	Dexchlorpheniramine + Vit. C + Dexamethasone	2 mg + 75 mg + 0.25 mg
Co-Aleva®	Tab	Ebastine + Betamethasone.	10 mg + 500 mcg
Snip®	Tab	Paracetamol + Pseudoephedrine	325 mg + 15 mg
Salzone®	Cap	Paracetamol + Phenylephrine	500 mg + 6.1 mg
Clarinase®	Tab	Loratadine + Pseudoephedrine	5 mg + 120 mg
Xinase®, Clearest®	Tab	Cetirizine + Pseudoephedrine	5 mg + 120 mg
Orofar®	Lozenges	Benzoxonium Chloratum Lidocaine + Sorbitol	1 mg 1 mg + 1 gm
Bebe Col®	Syrup	Paracetamol + Diphenhydramine	(150 mg +1200 mg)/100 ml
Apidon®, Phenadone Histamed-F®	Syrup	Dexamethasone + Chlorpheniramine	10 mg + 40 mg

** **Phenylpropanolamine** has been **withdrawn from the markets in USA and Europe**, but unfortunately, it's still prescribed in our market, it was withdrawn due to the **risk of hemorrhagic stroke;** spread this fact

C) Expectorants & Antitussive

About Cough:

- The cough is a normal reflex to protect the airways, but sometime cough is a symptom of a pathological disease or a sign for something wrong. **To distinguish between the normal cough and the pathological one you must notice:**

1. **Sputum color:**
   a) **Mucoid (clear and white)** is normally of little consequence and suggests that no infection is present.
   b) **Yellow, green or brown sputum** normally indicates infection.
   c) **Mucopurulent sputum** is generally caused by a viral infection.
   d) **Hemoptysis** can either be **rust colored** (pneumonia), **pink tinged** (left ventricular failure) or **dark red** (carcinoma).
2. **Nature of sputum:**
   a) **Thin and frothy** suggests left ventricular failure.
   b) **Thick, Mucoid to yellow** can suggest asthma.
   c) **Offensive foul-smelling** sputum suggests either bronchiectasis or lung abscess.

- **It's Very important to ask about the nature of the cough** (wet or dry), since each type has its own type of medication: (5).
  - Wet cough (with sputum) → expectorants and mucolytic.
  - Dry cough (without sputum) → Cough suppressants (antitussive) + Antihistamines.
- **If you used an Antitussive for a wet cough → cause congestion → worsen the cough, so be sure of what you give to your patient.**

Note:

A. **Expectorants include:** (Glyceryl Guaiacolate **or** Guaifenesin (they are the same drug), Ammonium Chloride, Carbocysteine, potassium iodide, potassium guaiacolsulfonate).
B. **Mucolytics include:** (Bromhexine, Ambroxol, Carbocysteine, Acetyl cysteine, Erdosteine)
C. **Antitussive include:** (Codeine, Dextromethorphan, Butamirate, Benzonatate, Pipazethate, Pholcodine, Clobutinol, Cloperastine, Oxeladin, Benproperine, Noscapine and Carbetapentane).

Isilin®	Syrup	Diphenhydramine Ammonium chloride Sodium Citrate Menthol	0.270 gm/100 ml 2.630 gm/100 ml 0.9 gm/100 ml 0.020 gm/100 ml
Histalix®	Syrup	Diphenhydramine Ammonium chloride Menthol	14 mg 135 mg 1.1 mg
Tussilet®, ***Soolan®,*** ***Decopect®***	Syrup	Glyceryl Guaiacolate Chlorpheniramine Phenylephrine	50 mg 1 mg 2.5 mg
Tussiram®	Syrup	Ephedrine Phenylephrine Chlorpheniramine Codeine	15 mg/10 ml 5 mg/10 ml 2 mg/10 ml 8 mg/10 ml
Tussivan®	Syrup	Ephedrine Phenylephrine Chlorpheniramine Codeine	5 mg/10 ml 5 mg/10 ml 2 mg/10 ml 8 mg/10 ml
Sedilar®, Tussilar®	Tab	Dextromethorphan	15 mg
	Oral Drop		
Sedo-pect®	Syrup (children)	Diphenhydramine Sodium Citrate Menthol	7 mg/5 ml 28.5 mg/5 ml 0.55 mg/5 ml
Rhinathiol®	Syrup	Carbocysteine	5 gm/100 ml (Adult) 2 gm/100 ml (Child)
Rhinathiol Plus®	Syrup	Carbocysteine + Promethazine	(5 gm +0.05 gm)/100 ml
Sedo-pect®	Syrup (adult)	Diphenhydramine + Codeine + Sodium Citrate + Menthol	14 mg + 5.7 mg + 57 mg + 1.1 mg (per 5 ml)
Cemo®	Syrup (green)	Carbinoxamine + Ephedrine HCI + Codeine	2 mg + 4 mg + 10 mg (per 5 ml)
Cemo®	Syrup (red)	Carbinoxamine Ephedrine HCI Ammonium chloride	2 mg/5 ml 4 mg/5ml 100 mg/5ml
Samilin®	Syrup	Diphenhydramine Ammonium chloride Sodium Citrate Menthol	13.5 mg/5 ml 131.5 mg/5 ml 55 mg/5 ml 1 mg/5 ml
Sedafen®	Syrup	Ephedrine Dextromethorphan Chlorpheniramine	5 mg/5ml 10mg/5ml 2mg/5 ml
Toxil®	Syrup	Dextromethorphan Oxomemazine	10 mg/5 ml 1.5 mg/5 ml
Solvodin®	Syrup	Bromhexine HCI	4 mg/5 ml
Bisolvon®	Tab	Bromhexine	8 mg
	Amp	Bromhexine	8 mg/2 ml
Mucobrox®	Tab	Ambroxol	30 mg
MucoFree®, Mucol®	Syrup	Ambroxol	15 mg/5 ml , 30 mg/5 ml
Mucinex®	Tab	Guaifenesin	600 mg

Tusscapine®	Syrup	Noscapine	15 mg/5 ml
Selgon®	Tab	Pipazethate	20 mg
	Drop		40 mg/ml
Paxeladine®	Cap, Syrup	Oxeladine citrate	40 mg (cap) 2 mg/5 ml (syrup)
Mucosolvan®, Mucomyst®	Tab, Cap Susp.	Acetyl cysteine *	----------
Mucotec®	Cap, Susp.	Erdosteine	150 mg, 300 mg (cap) 175 mg/5 ml (Susp.)
Transpulmin®	Syrup	Pipazethate + Glyceryl Guaiacolate + Isothipendyl + Liquorice extract	10 mg + 25 mg + 2 mg + 50 mg
Codilar®	Syrup	Phenylephrine + Dextromethorphan + Chlorpheniramine	4 mg + 10 mg + 2 mg
Bronkovet®	Syrup	Salbutamol Bromhexine HCI + Guaifenesin	2 mg 4 mg + 50 mg
All-Vent®, Bro-zedex®	Syrup	Terbutaline + Bromhexine + Guaifenesin + Menthol	1.25 mg + 4 mg + 50 mg + 2.5 mg (per 5 ml)
Brovensin®	Syrup	Terbutaline + Bromhexine + Guaifenesin	2.5 mg + 8 mg + 100 mg (per 10 ml)
Farcosolvin® , Trisolvin®	Cap, Syrup	Ambroxol + Theophylline + Guaifenesin	(30mg+100mg+60mg) Cap (15mg+30mg+50mg)/5 ml
Ultrasolv®	Tab, Syrup	Guaiphenesin + Carbocysteine + Oxomemazine	(225mg+375mg+5mg) Tab (100mg+125mg+2mg)/5 ml
Bronchophane®	Syrup	Guaifenesin + Ephedrine + Diphenhydramine + Dextromethorphan	50 mg + 7.5 mg + 5 mg + 4.58 mg (per 5 ml)
Mucovent®	Cap	Acetyl cysteine + Ambroxol	200 mg + 30 mg
Mucophylline®	Syrup	Bromhexine + Acefylline	(4 mg + 100 mg)/5 ml
Octovent®	Syrup	Guaifenesin + Salbutamol	(50 mg + 2 mg)/5 ml
Achee®	Tab	Paracetamol + Bromhexine Chlorpheniramine + Guaifenesin	450 mg + 8 mg 2 mg + 100 mg
Bronquium®, Exidil®	Elixir	Glyceryl Guaiacolate Theophylline	0.6 gm/100 ml 1 gm/100 ml
Noradran®	Syrup	Guaifenesin + Diphenhydramine + Dihydroxypropyltheophylline + Ephedrine	25 mg + 5 mg + 50 mg + 7.5 mg (per 5 ml)
Sinecode®, Dricod®	Tab, Syrup, Oral Drops	Butamirate	50 mg (tab) 0.15% (syrup) 5 mg/ml (drop)

Antitussive Notes:

1. **Codeine** is also used as an **analgesic;** it suppresses cough for about 6 hours.
2. **Dextromethorphan** is best to be **avoided in asthma,** as it causes release of histamine, thus worsening the asthmatic attack.
   - It's free from addictive properties; but at high doses it may **cause hallucinations**.
3. **Butamirate** has the advantage of causing **bronchodilation;** so, it can be used in asthmatics.
   - Can be used safely in infants as drops.
4. **Noscapine** (an alkaloid); has a mild analgesic effect.

5. **Clobutinol** can prolong the QT interval; thus, was withdrawn from several markets.
6. **Cloperastine** has both **antitussive** and **antihistamine** properties.
7. **Oxeladin** is the most **potent antitussive** available, and has a high selectivity for cough center.
8. **Pipazethate** also has a **bronchodilation** effect.

Mucolytic Notes:

1. All Mucolytic agents should be **used with caution it patients with peptic ulcer**.
2. **Acetyl Cysteine** or N-acetylcysteine (NAC), a mucolytic with an **anti-inflammatory** and **anti-oxidant** effect; it decreases thickness (viscosity) of the mucus secretion in the lungs.
   - It's also used I.V. or orally to **treat Paracetamol overdose** and toxicity.
   - it's also given to **treat infertility** (decreasing sperm viscosity thus enhancing its motility).
3. **Ambroxol** Improve mucous flow and transport (Muco-kinetic effect); it's the active metabolite of **Bromhexine**.
4. **Erdosteine** has an anti-oxidant effect.
5. **Carbocysteine** has both Mucolytic and Expectorant effect; also has an **anti-oxidant** effect and **anti-inflammatory** effect; with mucoregulator properties.

Expectorants Notes:

1. **Guaifenesin** has a **muscle relaxant** effect and **anticonvulsant** properties.
2. **Guaifenesin** increases the analgesic effect of paracetamol and NSAIDs; and also increases the sedative effect of alcohol, Hypnotics and Anxiolytics.

Note: American College of Chest Physicians (ACCP) Recommendations

Drugs recommended in the 2016 ACCP guidelines for the treatment of acute and subacute cough

Drug or Drug class	Cough associated with common cold	Acute bronchitis	Post infectious cough	Pertussis (whooping cough)
Central-acting antitussives (prescription)	Not recommended	**Recommended**	Recommended if both inhaled ipratropium and inhaled corticosteroids are ineffective	Not recommended
Antihistamine/ Decongestants	**Recommended**	Not recommended	Not recommended	Not recommended
Inhaled Ipratropium	**Recommended**	Not recommended	First-line therapy	Not recommended
Naproxen *	**Recommended**	Not recommended	Not recommended	Not recommended
Inhaled corticosteroids	Not recommended	Not recommended	Recommended if inhaled ipratropium is not effective	Not recommended
β_2 Agonist bronchodilators	Not recommended	Recommended only when wheezing accompanies the cough	Not recommended	Not recommended
Antibiotics	Not recommended	Not recommended	Recommended only if associated with bacterial sinusitis	Macrolide antibiotics recommended early in the course of infection (first few weeks)

* **Naproxen** was the only NSAID recommended in the guidelines for treatment of cough associated with colds because it was the only NSAID studied in this setting.

D) Cough medications as Suppositories

These are usually given for infants and Childs.

Trade name	Dosage form	Scientific name(s)	concentration
Selgon®	Supp.	Pipazethate	10 mg
Eucaphol®	Supp.	Guaifenesin + Pholcodine + Camphor + Eucalyptus	30 mg + 5 mg + 50 mg + 100 mg
Rectoplexil®	Supp.	Oxomemazine + Paracetamol + Guaifenesin + Na^+ benzoate	3.3 mg + 66.6 mg + 66.6 mg + 66.6 mg
Prosban® , Liblab®	Supp.	Dried Ivy leaf extract	----------
Minophylline®	Supp.	Theophylline	125 mg , 250 mg

E) Herbal mixtures for Cough

Herbal preparation usually contains one or more of these herbs: Guava, Tilia, Thyme, Fennel, Licorice, Anise oil, Peppermint, Ginger, Honey, Ivy Leaves and Camphor.

- **Zexuf®** Syrup contains (**Glycyrrhiza Glabra**) which **can raise the blood pressure**, so try avoiding that herbal mixture in the high-risk group (cardiac patients).
- **GeloMyrtol** is used for **acute and chronic bronchitis, and sinusitis.**

Trade name	D. form	Scientific name	concentration
Zecuf®	Syrup, Lozenges	Herbal preparation	----------
Melrosum®	Syrup	Thyme fluid extract	15gm/100 ml
Bronchicum®	Elixir	Thyme fluid extract Primula root fluid extract	5 gm/100 ml 2.5 gm/100 ml
GeloMyrtol Forte®	Cap	Eucalyptus oil + Lemon oil + Myrtle oil + sweet orange oil	300 mg per cap
Balsam®	Syrup	Herbal preparation	----------
Apdyl-H®	Syrup	Herbal preparation	----------
Mucosal®	Syrup	Thyme + Grindelia + Honey	130 ml
Ribosan®	Syrup	Ribwort herb soft extract	100 ml
Ivypect®	Syrup	Dried Ivy extract + Honey	100 ml
Thymepect®	Syrup	Thyme fluid extract + Honey + Elderberry juice	100 ml
Liblab®, Prosban®	Syrup, Lozenges	Dried Ivy leaf extract	35 mg/5 ml
Meritus®	Syrup	Honey, Lemon, Strawberry	----------

The difference between the **Expectorant** and **Mucolytic:**

- **Expectorant** works to increase the **Bronchial Glands Secretions**, this means more impulsively secretion of the **Watery Secretions** and therefore the intensity and extent of (phlegm) is decreased in the bronchial tubes; thus, it becomes easier exit through coughing.
- **Mucolytic** Work to dissolve the mucus by the fragmentation of the bonds that bind them and thus diminish their density and ensure easy exit of (phlegm) either by coughing or is absorbed through the body and take it out through the other body secretions.

1.4 – Respiratory Stimulants

1. They are used in intensive care settings to stimulate the respiratory rate in patients with respiratory failure. Also, may be useful for treating respiratory depression that caused by certain drugs.
2. Respiratory stimulants can also be harmful in respiratory failure since they stimulate non respiratory as well as respiratory muscles. They should only be given under expert supervision in hospital and must be combined with active physiotherapy.

Scientific name	Dosage form	Trade name	concentration
Doxapram	Vial (solu.)	Dopram®	20 mg/ml (400 mg/20 ml)
Caffeine	Vial (solu.)	Vivarin® , Cafcit®, Cafirate®	20 mg/ml (3 ml vial)
Almitrine	Tab	Duxil®	30 mg

1.5 – Pulmonary Surfactant

1. Pulmonary surfactants are used in the management of respiratory distress syndrome (hyaline membrane disease) in neonates and preterm neonates. They may also be given prophylactically to preterm neonates at risk of developing the syndrome; They act by reducing surface tension, thus act to increase pulmonary compliance and prevent atelectasis (collapse of the lung) at the end of expiration, and to facilitate recruitment of collapsed airways.
2. Pulmonary surfactants have been associated with intracranial hemorrhage. Bradycardia, pulmonary hemorrhage.

Scientific name	Dosage form	Trade name	concentration
Beractant	Intra-tracheal Susp.	Survanta® , Alveofact®	25 mg/ml
Calfactant	Intra-tracheal Susp.	Infasurf®	3 ml , 6 ml
Lucinactant	Intra-tracheal Susp.	Surfaxin®	8.5 ml/Vial
Poractant Alfa	Intra-tracheal Susp.	Curosurf®	8 mg/ml (1.5 ml , 3 ml)

1.6 – Drugs for Cystic Fibrosis

1. Cystic fibrosis (CF), also known as **mucoviscidosis**, is an autosomal recessive genetic disorder that affects mostly the lungs, Difficulty in breathing is the most serious symptom and results from frequent lung infections.
2. The main signs and symptoms of cystic fibrosis are salty tasting skin, poor growth and poor weight gain despite normal food intake, accumulation of thick sticky mucus, frequent chest infections, and coughing or shortness of breath.
3. **Treatment options include**: **Bronchodilators**, **Hypertonic saline** (It hydrates the airway mucus secretions and facilitates mucociliary function), **Dornase Alfa** (Enzyme that cleaves extracellular DNA, which results in decreased viscosity of mucus), and **aerosolized antibiotics** such as Tobramycin (TOBI®)

Scientific name	Dosage form	Trade name	concentration
Dornase Alfa	Inhale Solu.	Pulmozyme®	1 mg/ml (2.5 ml)
Ivacaftor	Tab	Kalydeco®	150 mg
Nintedanib	Cap	Ofev®	100 mg , 150 mg
Pirfenidone	Cap	Esbriet®	267 mg
	Tab	Pirfenex®	200 mg
Combination Product			
Lumacaftor + Ivacaftor	Tab	Orkambi®	200 mg + 125 mg
Aerosolized Antibiotics			
Tobramycin	Inhale Solu.	TOBI®	300 mg/5 ml (amp)
Aztreonam	Inhale Solu.	Cayston®	75 mg/vial
Colistimethate	Inhale Powder	Colistin®	1 million IU

References

1- Sean C. Sweetman, Martindale: The Complete Drug Reference, 38th Edition
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Mary Anne koda-kimble, Applied Therapeutics: The clinical use of drugs, 11th Ed.
4- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Ed.
5- Comprehensive Pharmacy Review for NAPLEX 8th Ed.
6- Community Pharmacy: Symptoms, Diagnosis and Treatment, By Paul Rutter, 2017 4th ed.
7- https://www.ncbi.nlm.nih.gov/pubmed/11534896
8- https://www.atsjournals.org/doi/abs/10.1164/ajrccm.160.1.9901063
9- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3667286/
10- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5625152/
11- https://www.nejm.org/doi/full/10.1056/NEJMoa1008378
12- https://www.ncbi.nlm.nih.gov/pubmed/19863370

GASTROINTESTINAL SYSTEM

Chapter 2: Gastrointestinal System

Part One: Introduction

Part Two:

2.1 – Antacids

2.2 – Anti-Ulcer (Acid suppression) drugs

A) Proton Pump Inhibitors

B) H_2 Receptor Antagonists

- Some combination products of PPIs and H_2Ras

C) Other agents that suppress gastric acid secretion

D) Other GI ulcers related drugs

2.3 – Laxatives

- **a.** Stimulant Laxative
- **b.** Bulk Forming Laxative
- **c.** Stool Softeners
- **d.** Osmotic Laxative
- **e.** Guanylate Cyclase-C agonists
- **f.** Peripheral acting μ-opioid antagonist
- **g.** Other drugs used for Constipation

2.4 – Bowel Cleansing Preparations

2.5 – Anti-Diarrheals

- **a.** Anti-Motility drugs
- **b.** Adsorbents
- **c.** Other agents used for diarrhea

2.6 – Antispasmodics

- **a.** Anticholinergics
- **b.** Other antispasmodics
- **c.** Combination products for IBS
- **d.** Herbal Combination products for IBS

2.7 - Anti-Emetics and Prokinetics

2.8 – Drugs for the treatment of Hiccups

2.9 - Drugs for Inflammatory bowel disease - (IBD) (ulcerative colitis and Crohn's disease)

- **a.** Amino-salicylates
- **b.** Some Corticosteroids
- **c.** Some Immunosuppressant's

2.10- Products for flatulence and abdominal gases

- **a.** For Adults
- **b.** For Infants and children

2.11 - Enzymes preparation for digestion support

2.12 – Gallstone solubilizing agents

2.13 – Drugs for Hepatic (liver) detoxification

2.14 – Drugs for food allergy

2.17 - Preparations for anal and rectal disorders (hemorrhoids)

Chapter Two: Gastro-intestinal System

Part One:

1. Introduction:

- The gastrointestinal tract, also known as the digestive or alimentary tract, is the pathway through which food passes as it is processed to enable the nutrients it contains to be absorbed for use by the body.
- It consists of the mouth, esophagus, stomach, duodenum, small intestine, large intestine (including the colon and rectum), and anus. In addition, a number of other organs are involved in the digestion of food: the salivary glands in the mouth, the liver, pancreas, and gallbladder. These organs, together with the gastrointestinal tract, form the digestive system.
- The digestive system breaks down the large, complex chemicals – proteins, carbohydrates, and fats – present in the food we eat into simpler molecules that can be used by the body.
  - **The stomach** holds food and passes it into the intestine. The lining of the stomach releases gastric juice that partly digests food. The stomach wall continuously produces thick mucus that forms a protective coating.
  - **The duodenum** is the tube that connects the stomach to the intestine. Its lining may be damaged by excess acid from the stomach.
  - **The pancreas** produces enzymes that digest proteins, fats, and carbohydrates into simpler substances; pancreatic juices neutralize the acidity of the food passing from the stomach.
  - **The gallbladder** stores bile, which is produced by the liver, and releases it into the duodenum. Bile assists the digestion of fats by reducing them to smaller units that are more easily acted upon by digestive enzymes.
  - **The small intestine** is a long tube in which food is broken down by digestive juices from the gallbladder and pancreas. The mucous lining of the small intestine consists of tiny, finger-like projections called villi that provide a large surface area through which the products of digestion are absorbed into the bloodstream.
  - **The large intestine** receives both undigested food and indigestible material from the small intestine. Water and mineral salts pass through the lining into the bloodstream. When a sufficient mass of undigested material, together with some of the body's waste products, has accumulated, it is expelled from the body as feces.

- Food is propelled through the gastrointestinal tract by rhythmic waves of muscular contraction called **peristalsis**; Muscle contraction in the gastrointestinal tract is controlled by the autonomic nervous system and is therefore easily disrupted by drugs that either stimulate or inhibit the activity of the autonomic nervous system; **Excessive peristaltic action may cause diarrhea, and constipation may result from slowed peristalsis.**

2. What Can go wrong in the Gastrointestinal tract?

- Inflammation of the lining of the stomach or intestine **(gastroenteritis)** is usually the result of an infection or parasitic infestation.
- Damage may also occur through the inappropriate production of digestive juices, leading to minor complaints like acidity and major disorders like **peptic ulcers**.
- The lining of the intestine can be damaged by abnormal functioning of the immune system **IBD** (**inflammatory bowel disease**).
- The rectum and anus can become painful and irritated by damage to the lining, tears in the skin at the opening of the anus (**anal fissure**), or enlarged veins (**hemorrhoids**).
- **Constipation, diarrhea**, and **irritable bowel syndrome (IBS)** are the most frequently experienced gastrointestinal complaints, and they usually occur when something disrupts the normal muscle contractions that propel food residue through the bowel.

3. Medications Range and Types:

- Many drugs for gastrointestinal disorders are **taken by mouth and act directly on the digestive tract without first entering the bloodstream**; Such drugs include certain antibiotics and other drugs used to treat infestations.
- Some antacids for peptic ulcers and excess stomach acidity, and the bulk-forming agents for constipation and diarrhea, also **pass through the system unabsorbed.**
- However, for many disorders, drugs with a systemic effect are required, including antiulcer drugs, opioid antidiarrheal drugs, and some of the drugs for inflammatory bowel disease.

- **Medications available include**:

Drug classification		Examples
Antacids		Aluminium hydroxide, Calcium carbonate
Antifoaming agents (anti flatulence)		Dimeticone, Simethicone
Anti-ulcer drugs	**Proton pump inhibitors**	Esomeprazole, Lansoprazole, Omeprazole
	H_2 blockers	Cimetidine, Famotidine
	Others	Sucralfate, Misoprostol
Antidiarrheal drugs	**Opioid related**	Co-phenotrope, Loperamide
	Adsorbents	Kaolin
Laxatives	**Stimulant laxative**	Bisacodyl
	Bulk-forming laxative	Ispaghula
	Lubricants	Liquid paraffin
	Osmotic laxative	Lactulose
Antispasmodic drugs		Hyoscine, Otilonium
Drugs for irritable bowel syndrome		Mebeverine
Anti-Emetics and Prokinetics		Metoclopramide, Domperidone
Drugs for inflammatory bowel disease		Mesalamine, Sulfasalazine
Drug treatment for gallstones		Ursodeoxycholic acid
Drugs for Hepatic detoxification		Milk Thistle
Drug treatment for pancreatic disorders		Amylase, Lipase, Pancreatin, Protease
Drugs for rectal and anal disorders		Combination products (cream, Oint. , gel)

Part Two:

2.1 Antacids

- Digestive juices in the stomach contain acid and enzymes that break down food before it passes into the intestine. The wall of the stomach is normally protected from the action of digestive acid by a layer of mucus that is constantly secreted by the stomach lining. Problems arise when the stomach lining is damaged or too much acid is produced and eats away at the mucous layer.
- Excess acid that leads to discomfort, commonly referred to as **indigestion, may result from anxiety, overeating or eating certain foods, coffee, alcohol, or smoking**; Some drugs, (aspirin and non-steroidal anti-inflammatory drugs), can irritate the stomach lining and cause ulcers.

1. **Antacids** are basic compounds that neutralize hydrochloric acid in the gastric secretions; and thus, relieve pain; They are simple chemical compounds that are mildly alkaline and some also act as chemical buffers. Their chalky taste is often disguised with flavorings.
   - They are used in the symptomatic management of gastrointestinal disorders associated with gastric hyperacidity such as **dyspepsia**, **gastro-esophageal reflux disease (GERD)**, and **peptic ulcer disease**.
   - By neutralizing stomach acid, **antacids prevent inflammation, relieve pain, and allow the mucous layer and lining to mend.** When used in the treatment of ulcers, they prevent acid from attacking damaged stomach lining and so allow the ulcer to heal.
2. Antacids are best given when **symptoms occur (when required**) or are expected, usually between meals and at bedtime, their duration of action is short (about 30 minutes on an empty stomach), but duration of action can be extended to 3 hours when given with or within 1 hour after a meal.
3. **Types of antacids:** they are divided according to their base component as:
   - **Aluminium compounds:** These drugs have a prolonged action and are widely used, especially for indigestion and dyspepsia. **They may cause constipation, but this is often countered by combining this type of antacid with one containing magnesium**. Aluminium **compounds can interfere with the absorption of phosphate from the diet, causing muscle weakness** and bone damage if taken in high doses over a long period. A high blood level of Aluminium in people with kidney failure, may **cause a dementia-like illness.**
   - **Magnesium compounds** Like the Aluminium compounds, these have a prolonged action. In large doses **magnesium compounds can cause diarrhea**, and in people who have impaired kidney function, **a high blood magnesium level may build up, causing weakness, lethargy, and drowsiness.**
   - **Sodium bicarbonate:** This antacid act quickly, but its effect soon passes. It reacts with stomach acids to produce gas, which may cause bloating and belching. Sodium bicarbonate is **not advised for people with heart or kidney disease, because it can lead to accumulation of water (edema) in the legs and lungs** or serious changes in the acid-base balance of the blood.
   - **Combined preparations Antacids** may be combined with other substances called alginates and antifoaming agents. **Alginates are intended to float on the contents of the stomach and produce a neutralizing layer to subdue acid that can otherwise rise into the esophagus, causing heartburn.** Antifoaming agents are used to relieve flatulence. In some preparations, a local anesthetic is combined with the antacid to relieve discomfort in esophagitis; but the value of these additives is not proved.
4. Antacid **suspensions** are more effective and work more quickly than tablets (of the same type and quantity) the suspension is better due it acts faster and covers more area.
5. Patient should be instructed **to chew the tablets** thoroughly followed by a full glass of water to ensure maximum therapeutic effect.
6. It might be appropriate for the patient to have both; **tablet antacid may be taken during a day at the work while suspension is taken at home.**

7. **Interactions:** Antacids can affect the **absorption of a number of drugs** (via chelation and adsorption) and the majority of these interactions are easily overcome **by leaving a minimum gap of (1-2) hours between the doses of each drug**; Also, Antacids increase the PH of the stomach, thus cause a **premature release of enteric coated tablets** or granules in the stomach rather than the intestine.

8. **Side effects of antacids**
   - **A. AL-containing antacids tend to be constipating, Mg-containing antacids tend to cause osmotic diarrhea** and are useful in patients who are slightly constipated. Thus, **combination** products of AL and Mg salts cause minimum bowel disturbances.
   - **B.** Antacids containing sod. Bicarbonate **should be avoided in patients if sodium intake should be restricted (**e.g. in patient with CHF, hypertension).

9. Other drugs that may be combined with antacid formulations include **Simethicone**, which acts as a defoaming agent to reduce **excess gas in the stomach**, and **alginates**, which form a gel or foam on the surface of the stomach contents thereby impeding reflux and **protecting the esophageal mucosa from acid attack**.

Trade name	Dosage form	Scientific name	Concentration
Rennie®	Tab	Ca^+ carbonate , Mg^+ carbonate	680 mg + 80 mg
	Syrup	Ca^+ carbonate , Mg^+ carbonate	(680 mg + 80 mg)/5 ml
Citrogram®	Susp.	Tartaric acid Citric acid Na bicarbonate	26.5% 14.5% 59%
Stomacol®	Susp.	$AL(OH)_3$, $Mg(OH)_2$	(225mg + 195mg)/5ml
Maalus®, Malox® Moxal®	Tab , Susp.	$AL(OH)_3$ $Mg(OH)_2$	400 mg/10 ml 200mg/10 ml
Moxal PLus®, Acilox Plus®	Tab , Susp.	$AL(OH)_3$ + $Mg(OH)_2$ + Simethicone	(225mg+200mg+25mg)
Gaviscon®	Tab , Susp.	Na alginate, Ca^+ Carbonate Sodium hydrogen carbonate	----------
Actonorm®	Powder, (Susp.)	Atropine , Peppermint Oil , Mg Carbonate, Mg Trisilicate, Ca^+ Carbonate, Na Bicarbonate, $AL(OH)_3$	0.1 mg + 0.5 mg, 381.4 mg + 50 mg 145 mg + 373 mg 50 mg
	Gel	$AL(OH)_3$ + $Mg(OH)_2$ + Dimeticone	220mg + 200mg + 25 mg

Extra Notes about Antacids:

1. Small amounts of **Aluminum** and **Magnesium** are absorbed systemically and have the potential to accumulate in patients with renal insufficiency and lead to toxicity, thus magnesium-containing antacids should be avoided in patients with a creatinine clearance less than 30mL/ minute, and chronic use of aluminum-containing antacids in patients with renal failure should be avoided.
2. High-dose regimens of Ca^+ (4–8 g/day) in combination with alkalinizing agents (Na bicarbonate) can produce the **milk-alkali syndrome** (i.e., hypercalcemic nephropathy with alkalosis).
3. **Na bicarbonate** should not be used for long periods of time (especially in the renal impaired patient) because systemic alkalosis can result from the accumulation of bicarbonate. Additionally, the high sodium content (274 mg sodium/g sodium bicarbonate) has been associated with sodium retention and may pose a problem in patients with hypertension, ascites, severe renal dysfunction, or heart failure.
4. Antacids may interfere with the absorption of many orally administered drugs (digoxin, phenytoin, isoniazid, ketoconazole, Itraconazole, iron preparations) that require an acidic environment for dissolution and absorption.

5. Antacids containing calcium, aluminum, or magnesium can bind to concomitantly administered drugs and interfere with the absorption of drugs that are susceptible to complexation.
   - **Tetracyclines** and the **fluoroquinolones** are susceptible to this interaction, as they bind to divalent and trivalent cations. The bioavailability of ciprofloxacin is reduced by more than 50% when concomitantly administered with an antacid, because aluminum and magnesium ions chelate with the antibiotic to form an insoluble and inactive complex. The administration of ciprofloxacin 2 hours before an antacid increases ciprofloxacin bioavailability more than when administered 2 hours after the antacid.

2.2- Anti-Ulcer (Acid suppression) drugs

- Normally, the linings of the esophagus, stomach, and duodenum are protected from the irritant action of stomach acids or bile by a thin covering layer of mucus. If this is damaged, or if large amounts of stomach acid are formed, the underlying tissue may become eroded, causing a **peptic ulcer** (break in the gut lining).
- **An ulcer often leads to abdominal pain, vomiting, and changes in appetite;** the most common type of ulcer occurs just beyond the stomach, in the duodenum.
- An organism found in almost all patients who have peptic ulcers, **Helicobacter pylori**, is believed to be the main causative agent of peptic ulcers.
- The symptoms caused by ulcers may be relieved by an antacid, but healing is slow. The usual treatment is with an anti-ulcer drug, such as a PPI, H2 blocker, sucralfate and bismuth.

A. Proton pump inhibitors (PPIs)

1. PPIs are the most potent inhibitors of gastric acid secretion and include **Omeprazole**, **Lansoprazole**, **Rabeprazole**, **Pantoprazole**, and **Esomeprazole**.
   - PPI suppresses gastric acid secretion by **inhibition of the H+/K+-ATPase** in the gastric parietal cell; they inhibit 90-98% of 24-hour acid secretion.
2. PPIs are used for the treatments of **gastric** and **duodenal ulcers**; they are also used in **combination with Antibacterials for the eradication of Helicobacter pylori** (a bacterium that is common cause of ulcer); PPIs can be used for the treatment of **dyspepsia** and **gastro-esophageal reflux disease (GERD),** they are also used for the **prevention and treatment of NSAID-associated ulcers**.
3. A PPI can be used to **reduce the degradation of pancreatic enzyme supplements** in patients with cystic fibrosis; They can also be used to **control excessive secretion of gastric acid in Zollinger–Ellison syndrome**; high doses are often required
4. They are most effective when **taken 30 to 60 minutes before meals**; The once daily dose usually given in the morning **before meals**, while twice daily dose given morning and night before meals.
5. Various PPI dosage forms and formulations exist and include the **enteric-coated granules contained in gelatin capsules** (omeprazole, esomeprazole, and lansoprazole), and delayed release **enteric-coated tablets** (Rabeprazole, Pantoprazole) the enteric coating **prevents degradation of the drug in stomach acid**.
6. **Adverse effects are usually few**, but may include nausea, abdominal pain, constipation, flatulence and diarrhea.
   a. **Hypergastrinemia** occurs in 5-10% of long-time omeprazole users, Development of hypergastrinemic state predisposes the patient to rebound hyper-secretion of gastric acid following discontinuation of therapy.
   b. **PPIs have been associated with an increased risk of infections** (pneumonias, enteric infections) possibly owing to the ability of the microorganism's ability to survive in a less acidic environment. However, data suggest that they rarely lead to illness.
   c. PPIs have been associated with interstitial nephritis, **but this is an extremely rare finding. (Only with high doses and long-term use > 3 years).**

7. Prolonged therapy with agents that suppress gastric acid, such as the PPIs and H_2 antagonists:
   a. May result in low vitamin B_{12}, because acid is required for its absorption in a complex with intrinsic factor .
   b. Also, will result in Low Iron Absorption → lead to Anemias.
   c. Also, will result in Hypomagnesemia.
   d. Another problem is the potential for incomplete absorption of calcium carbonate products. **An effective option would be to use calcium citrate as a source of calcium for patients taking prolonged acid-suppressing medications, because the absorption of the citrate salt is not affected by gastric pH.**
   e. Thus, long term therapies may Cause Neuropathies (Due to low vitamin B_{12}) and increase risk of fractures (Due ↓ in Ca+), to avoid → give supplements of B_{12} and Ca^{+}.
8. A dosage reduction is not required in patients with renal insufficiency, but is recommended for patients with severe hepatic impairment.
9. The US Food and Drug Administration **(FDA)** issued a labeling change for Clopidogrel and a safety warning recommending providers to **avoid the co-administration of (omeprazole, omeprazole/sodium bicarbonate, or esomeprazole) with Clopidogrel.**
   a. This is because of the hypothesis that states: PPIs attenuates (decrease) the antiplatelet effects of Clopidogrel and potentially increases the risk of cardiovascular effects.
   b. **Solutions include: (double Clopidogrel dose to 150 mg, separate the two drugs by at least 8-12 hours, and switching to Pantoprazole).**
   c. There is no strong evidence to suggest switching from one PPI to another or that separating the timing of doses has any clear benefit on reducing the effect of interaction.
   d. **FDA and AGA then published a statement** notifying that **this interaction is of a LOW SIGNIFICANCE,** and there is no need to alter or change the medications accordingly. (8)
10. A study was published stated that long term **PPI is associated with Cancer**, below some explanations and available data:
    a. **There is no clinical evidence to suggest that long-term (>10 years) therapy progresses to a higher grade of hyperplasia or gastric ECL carcinoid.**
    b. There is evidence to suggest a relationship between elevated serum gastrin concentrations and ECL hyperplasia as a result of the PPIs' profound ability to inhibit gastric acid secretion. It has been hypothesized that this can progress to gastric carcinoid tumors (a precursor of gastric cancer).
    c. Bacterial overgrowth (secondary to PPI treatment) has been hypothesized to increase the risk of gastric cancer, because bacteria in the stomach responsible for conversion of dietary nitrates to nitrites can flourish at a higher pH and increase the development of N-nitrosamines (a carcinogenic by-product).
11. **Co-administration of other acid-suppressing agent with PPIs** (such as H_2-receptor antagonists or Anticholinergics) **will diminish the efficacy of the PPIs**
    a. Some patients when treated with PPIs will have nocturnal acid breakthrough, those patients will benefit from the addition of H_2-receptor antagonists at night to PPI regimen
    b. (Nocturnal acid breakthrough is Presence of at least 60 continuous minutes of intragastric pH less than 4 during the night, in patients taking a PPI twice daily before meals.
12. **Some says all PPIs are the same;** well that's not quite true, **they differ** in their onset of action, and in their safety profile regarding drug-drug interactions.
    - **The fastest acting PPI is Rabeprazole**, it acts within few minutes (about 5 to 8 min), and hence its named Rapi-prazole (from Rapid).
    - **The safest PPI regarding D-D interactions is Pantoprazole.**
    - The only PPIs that can be **takin without regarding the food** are **Rabeprazole** and **Pantoprazole,** (can be taken before or after meal); **Nexium®** dosage form formulation does so.
    - **The highest affinity for H+/K+-ATPase pump PPI is Esomeprazole.**
    - **The highest PPI with relative potency** is **Rabeprazole,** then in 2nd place **Esomeprazole.**

13. **PPIs** (especially Rabeprazole), **lowers serum TSH levels**; thus, may be beneficial in patients with hyperthyroidism, but PPIs should be added to the list of medications affecting the level of thyroid hormone in patients with hypothyroidism treated with Levothyroxine replacement; those Patients may need adjustment of their Levothyroxine dose. [7]

14. Regimen for the eradication of **Helicobacter Pylori** usually composed of **proton pump inhibitor (PPI), Clarithromycin, and either Amoxicillin or Metronidazole for 10–14 days**; this regimen is called (triple therapy) [4], other regimens are mentioned below.
    - In penicillin-allergic patients, metronidazole is substituted for amoxicillin.
    - Some Guidelines switch **Metronidazole** in H. Pylori eradication therapy with **Levofloxacin**.

Available H. Pylori Eradication Regimens [8]	
Regimen	**Drugs and doses**
Clarithromycin Triple	PPI (standard or double dose) BID + amoxicillin 1000 mg BID or metronidazole 500 mg TID + clarithromycin 500 mg BID for 10-14 days
Bismuth Quadruple	PPI (standard dose) BID + Bismuth subsalicylate 300 mg QID or Bismuth subcitrate 120-300 mg QID + metronidazole 250 QID or 500 mg TID-QID + tetracycline 500 mg QID d + PPI BID x 10-14 days
Concomitant	PPI (standard dose) BID + clarithromycin 500 mg BID + amoxicillin 1000 mg BID + metronidazole or Tinidazole 500 mg BID for 10-14 days
Sequential	PPI (standard dose) BID + amoxicillin 1000 mg BID for 5–7 days; then PPI BID + clarithromycin 500 mg BID + metronidazole or Tinidazole 500 mg BID for 5–7 days
Hybrid	PPI (standard dose) BID + amoxicillin 1000 mg BID for 7 days; then PPI BID + amoxicillin 1 g BID + clarithromycin 500 mg BID + metronidazole or Tinidazole 500 mg BID for 7 days
Levofloxacin triple	PPI (standard dose) BID + levofloxacin 500 mg daily + amoxicillin 1000 mg BID for 10–14 days
Levofloxacin sequential	PPI (standard or double dose) BID + amoxicillin 1000 mg BID for 5-7 days; then PPI BID + amoxicillin 1000 mg BID + levofloxacin 500 mg daily + metronidazole or Tinidazole 500 mg BID for 5-7 days
LOAD	PPI (double dose) daily + levofloxacin 250 mg daily + metronidazole or Tinidazole 500 mg BID + doxycycline 100 mg daily

15. Available **Diagnostic tests for H. pylori infection** include:
    a) **Serologic tests:** Detect immunoglobulin (Ig) G to H. pylori in the serum by enzyme-linked immunosorbent assay; it Cannot distinguish between active infection and past exposure. Because antibodies persist for long periods after eradication, **cannot use to test for eradication after treatment.**
    b) **Urea breath test:** detects the exhalation of radiolabeled CO2 after the ingestion of 13C- or 14C-radiolabeled urea. H. pylori hydrolysis of the radiolabeled urea results in CO2 production; **It is used to make a diagnosis and to test for eradication**.
    Recent use of antibiotics or PPIs can cause false-negative results in up to 40% of patients. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before UBT testing or wait 4 weeks after treatment has ended before having the UBT performed.
    c) **Stool antigen tests**: are polyclonal or monoclonal antibody tests that detect the presence of H. pylori in stool; **They can be used to make a diagnosis and to confirm eradication.**
    Recent use of bismuth, antibiotics, or PPIs can also cause false-negative results. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before stool antigen testing or wait 4 weeks after treatment has ended before having the stool antigen test performed.
    d) **Rapid urease tests:** detect the presence of ammonia (NH3) in a sample generated by H. pylori urease activity, False-negative results can be caused by a partly treated infection, GI bleeding, achlorhydria, or use of PPIs, H2RAs, or bismuth. Patients should discontinue antisecretory agents for at least 1 week before the test is performed.

PPIs products			
Scientific name	D. form	Trade name	Concentration
Esomeprazole	Cap	Nexium® , Es-omperal®	20 mg , 40 mg
	Vial	Nexium®	40 mg
	Sachet	Nexium®	10 mg
	Tab	Esofag®	20 mg
Lansoprazole	Cap	Lanzor® , Lancid®, Monolitum®	15 mg , 30 mg
	Oro Disp. Tab		15 mg
	Sachet		15 mg
Dexlansoprazole	Cap	Dexilant® , Kapidex®	30 mg , 60 mg
	Tab EC Retard	Delaxise®	30 mg
Omeprazole	Cap , Vial	Losec® , Gasic®, Asiloc® Aprazole® , Lomac® , Emilok®	20 mg , 40 mg
Rabeprazole	Tab	Aciphex® , Pariete® , Rabezole®	10 mg , 20 mg
	Tab	Ozo®	20 mg
Pantoprazole	Tab	Counterlac® , Protonix® , Pantium®	20 mg , 40 mg
	Vial	Protofix®	40 mg
Tenatoprazole	Cap	Acidlock®	20 mg , 40 mg
ILaprazole	Cap , Tab	Noltec® , Adiza®	5 mg , 10 mg , 20 mg

B. Histamine-2 Receptor Antagonists (H_2RAs)

1. H_2RAs include **Cimetidine**, **Ranitidine**, **Famotidine**, and **Nizatidine**.
2. H_2RAs are **competitive antagonists** of histamine at the parietal cell's H_2 receptor; they suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid, they accomplish this **by two mechanisms:**
   - Histamine released by ECL cells in the stomach is blocked from binding on parietal cell H_2 receptors, which stimulate acid secretion.
   - Other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H_2 receptors are blocked.
3. H_2RAs are used for the treatments of **gastric** and **duodenal ulcers**. They can be used for the treatment of **dyspepsia** and **gastro-esophageal reflux disease.**
   - **Ranitidine** when given by I.V. route **should be diluted with 10 ml DW and given over at least 10 minutes**, because **rapid I.V. injection may cause tachycardia or bradycardia** and can be complicated to **cause even cardiac arrest and death**, this is due to H2 antagonism in coronary smooth muscles and cholinesterase inhibition.
4. **Tolerance to the anti-secretory effect 0f H_2RAs may develop** after several days of regularly scheduled (continuous) use but can be avoided by taking the H_2RA only when needed.
5. Bioavailability is lower for **Cimetidine**, **Famotidine**, and **Ranitidine** because they are absorbed incompletely and undergo first-pass metabolism resulting in 40% to 65% bioavailability; but the bioavailability of **Nizatidine** is considered near 100% because this agent does not undergo first-pass metabolism.
6. Hepatic metabolism is the principal pathway for the elimination of cimetidine, famotidine, and ranitidine, whereas renal excretion is the major route for elimination of Nizatidine.
7. **Cimetidine inhibits several CYP450 isoenzymes**, resulting in **numerous drug interactions** (e.g., theophylline, warfarin, and Clopidogrel); Avoidance of the combination or a reduction in the dosage of these drugs may be required; Also switching to PPI would be reasonable, **Ranitidine has less potential for hepatic CYP450 drug interactions**, while famotidine and Nizatidine do not interact with drugs metabolized by the hepatic CYP450 pathway.

8. **Cimetidine** has a **weak anti-androgenic effect**, it also increases prolactin levels and may cause **Gynecomastia** and **Impotence** in men; these effects are usually **reversible**.
   - **Cimetidine** also can **cause confusion** in the elderly.
   - Some Dermatologists uses **Cimetidine for Hormonal Acne** Due its Anti-Androgenic effect.
9. They are rarely used these days, **most physicians and pharmacists prefer PPIs**, because PPIs are superior to H_2RAs in reducing gastric acid secretion and mucosal healing, **although Ranitidine can be used as on need basis (due it acts within few minutes).**
   - People who suffer from infrequent heartburn may take either antacids or H_2RAs for treatment. The latter offer several advantages over antacids, including longer duration of action (6–10 hrs. vs 1–2 hrs. for antacids), greater efficacy, and **ability to be used prophylactically before meals to reduce the chance of heartburn occurring.**
10. **Lafutidine,** a new type of H_2RAs, has a **unique mechanism of action**:
    a) **Activates calcitonin gene-related peptide,** resulting in the stimulation of nitric oxide (NO) and regulation of gastric mucosal blood flow.
    b) **Increases somatostatin levels**; thus, resulting in less gastric acid secretion.
    c) **Causes the stomach lining to generate more mucin.**
    d) **Inhibits neutrophil activation**; thus, preventing injury from inflammation.
    e) **blocks the attachment of Helicobacter pylori to gastric cells.**
11. **A 31-study review found that overall risk of pneumonia is about 1 in 4 higher among H_2RAs users;** named (Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis) and published on pubmed.

H_2RAs products

Scientific name	D. form	Trade name	Concentration
Cimetidine	Tab	Tagmet®	200 mg , 400 mg
	Amp	Tagmet® , Tagadin®	200 mg
Ranitidine	Tab	Zantac® , Peptacid® , Histac®	150 mg , 300 mg
	Sachet	Rani® , Aciloc®	75 mg , 150 mg
	Amp	Rantidine®	150 mg
Famotidine	Tab	Ulceran® , Famosam®	20 mg , 40 mg
	Tab	Pepcid®	20 mg
Nizatidine	Cap	Axid®	150 mg , 300 mg
Roxatidine	Cap	Roxit® , Roxane® , Roxagen®	75 mg , 150 mg
Lafutidine	Tab	Stogar® , Lafaxid®	10 mg

Combination products of some PPIs and H_2RAs

Scientific name(s)	D. form	Trade name	concentration
Omeprazole + Na Bicarbonate	Cap	Zegerid®, Aprazole pls®	20 mg + 100 mg
Omeprazole + Aspirin *	Cap	Asp Plus®	20 mg + 81 mg
Omeprazole + Ketoprofen *	Cap	Axorid®	(20 mg + 100 or 200 mg)
Esomeprazole + Naproxen *	Tab	Vimovo®	20 mg + 500 mg
Esomeprazole + Meloxicam *	Tab	Rumonal Pro®	20 mg + 15 mg
Omeprazole + Domperidone	Tab	Aprazole D®	40 mg + 10 mg
Rabeprazole + Domperidone	Tab	Dorafem®	20 mg + 10 mg
Pantoprazole + Domperidone	Tab	Ripane®	40 mg + 30 mg
Pantoprazole + Ranitidine	Tab	RaniPan®	40 mg + 150 mg
Famotidine + Ibuprofen *	Tab	Duexis®	26.6 mg + 800 mg
Famotidine + $Mg(OH)_2$ + Ca^+ Carbonate	Chew. Tab	Gastroprotect®	10 mg + 165 mg + 800 mg

* Those are NSAIDs (anti-inflammatory) for more info see chapter 9.

** **Domperidone** is an anti-emetic and prokinetic (see below section 8).

C. Other agents that suppress gastric acid secretion:

These are anticholinergics, works by blocking the activity of (acetylcholine) in the body, which decreases secretions of gastric acid. (They are also used to treat extra salivation and doodling; some is used as pre-anesthetic medication to dry up the mucosal secretions).

Scientific name	Dosage form	Trade name	concentration
Glycopyrrolate *	Tab	Cuvposa® , Robinul®	1 mg , 2 mg
	Inj. Solu	Glycopyrronium®	0.2 mg/ml
Mepenzolate	Tab	Cantil®	25 mg
Pirenzepine **	Tab	Gastrozepin	25 mg
Methscopolamine	Tab	Pamine®	2.5 mg , 5 mg

Notes:

1. **Glycopyrrolate** has been used topically and orally to **treat hyperhidrosis** (condition characterized by abnormally increased sweating/perspiration)**.** Since it reduces the body's sweating ability, **it can even cause fever and heat stroke in hot environments.**
   - It's also called **(Glycopyrronium)** as a scientific name; It's also used as an inhaler for the **treatment of Asthma** (see chapter 1, section 1.3).
2. **Pirenzepine** is an M1 selective antagonist, is used in the treatment of peptic ulcers, as it reduces gastric acid secretion and reduces muscle spasm.

D. Other GI ulcers related drugs:

Scientific name	D. form	Trade name	Concentration
***Bismuth subcitrate** *	Tab	Bismul®, Bismuth Arya®	120 mg
Bismuth subcitrate + Tetracycline + Metronidazole	Cap	Pylera®	140 mg + 125 mg + 125 mg
Omeprazole + Amoxicillin + Rifabutin	Cap DR	Talicia®	10 mg + 250 mg + 12.5 mg
Rebamipide	Tab	Mucosta® , Rebagen®	100 mg
Charcoal (antidote)	Tab	Eucarbon®	250 mg
Sucralfate	Tab	Ulcifat®, Antepsin®	1 gm
Misoprostol	Tab	Cytotec®	200 mcg

Notes:

1. **Bismuth subcitrate** is a chelating agent, has an **antibacterial effect** and an **anti-inflammatory effect**; with possible **antidiarrheal effect** (due to chelating).
   - May cause black discoloration of the tongue and stool.
2. **Pylera®** is mainly given for H. Pylori eradication; and usually with a PPI.
   - Taken as 3 capsules every 6 hours (12 cap/day) for 10 days with PPI twice a day.
3. **Talicia®** is specifically indicated for the treatment of H. pylori infection in adults.
   - Taken as 4 capsules every 8 hours (12 cap/day) for 14 days
4. **Rebamipide** is used for mucosal protection, healing of gastroduodenal ulcers, and treatment of gastritis; It works by enhancing mucosal defense, scavenging free radicals, and temporarily activating genes encoding cyclooxygenase-2 (act by increasing effects of gastric mucosal prostaglandin E2 and protective effect of gastric mucosa; It also increases gastric mucus and blood flow in gastric mucosa).
5. **Sucralfate** provides a direct mucosal barrier; modulates pepsin, mucus activity, bicarbonate secretion, and tissue growth repair, also it forms ulcer-adherent complex, thus protect the ulcer from acids, bile salts and allows it to heal.
   - It requires an acidic pH for activation; thus, PPIs and H_2RAs may reduce its effect.
   - Useful in the prevention of stress ulcers; but it does not prevent NSAIDs induced ulcers.
6. **Misoprostol** is a **prostaglandin analogue,** which is used to inhibit gastric acid secretion and protect gastric mucosa**, it is also used for pregnancy termination** and may be abused to induce illegal abortions, its effects are dose dependent including **Cervical dilation**.

2.3- Laxatives (Constipation drugs)

1. **Constipation** refers to bowel movements that are **infrequent or hard to pass**, the stool is often hard and dry; Other symptoms may include **abdominal pain**, **bloating**, and feeling as if one has not completely passed the bowel movement.
   - Another definition is a symptom-based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both.
2. **Complications from constipation** may include **Hemorrhoids**, **anal fissure** or **fecal impaction**, the normal frequency of bowel movements in adults is between three per day and three per week; Babies often have three to four bowel movements per day while young children typically have two to three per day.
   - **Certain drugs may be constipating**: for example, opioid analgesics, tricyclic antidepressants, and antacids containing aluminium.
   - **Some diseases, such as hypothyroidism** (an underactive thyroid gland), and **Parkinson disease** can also **lead to constipation.**
   - **Reduced fiber and water intake also causes constipation.**

Notes:

1. Laxatives promote defecation and are used in the treatment of **constipation** and for bowel **evacuation before investigational procedures such as endoscopy**.

2. Before prescribing laxatives, it is important to be sure that the patient is constipated and that **the constipation is not secondary to an underlying undiagnosed complaint.**
   - **Danger signs include:** Symptoms for more than 1–2 weeks despite treatment, Considerable pain or cramping, Presence of fever, Blood in the stool, Sudden Weight loss, Paraplegia, quadriplegia **(if one of those signs is present directly refer to a doctor).**

3. **Non pharmacological treatment of constipation** includes:
   a) Increasing **fluid intake** to 6–8 glasses of water per day, although minimal evidence to support efficacy if dehydration is not present,
   b) Increase **dietary fiber** to 20–30 g/day.
   c) Incorporate or increase **exercise** to 3–5 days/week.

4. **Type of laxative:**

Type of laxative	Example(s)	Approximate onset of action
1-Stimulant laxative	Senna , Bisacodyl , Sodium Picosulfate, and Glycerin (supp.) , Castor Oil	Oral: 6-12 hr. Rectal: 0.5-1 hr.
2-Bulk-forming laxative	Methylcellulose , Bran , Sterculia and Ispaghula Husk (Metamucil®)	1-3 days
3-Lubricant (stool softeners)	Liquid paraffin	6-8 hours
4-Osmotic laxative	Lactulose , Sorbitol	1-2 days
5-Saline Osmotic laxatives	Magnesium citrate, magnesium hydroxide, sodium phosphate	15 min to 3 hrs.
6-Guanylate Cyclase-C agonist	Linaclotide, Plecanatide	1 – 6 days
7-Peripheral acting μ-opioid antagonist (PAMORAs)	Methylnaltrexone, Naloxegol, Alvimopan	Within 4 hrs.

5. **Product selection guidelines**

Patient	Preferred laxative
1- Pregnant women	Bulk-forming laxative or Lactulose may be used.
2- Breast-feeding mother	Bulk-forming laxative
3- Children and infants	Glycerin(supp.) , Lactulose
4- Advanced age (elderly)	Bulk-forming laxative, Also Lactulose, Glycerin (supp.) are safe.

A- Stimulant laxatives:

1. Stimulants **cause the bowel muscles to contract**, increasing the speed at which fecal matter goes through the intestine.
2. Prolonged use may result in loss of colonic smooth muscle tone; Stimulant laxatives **should therefore be used for only short periods of a few days**.
3. Bisacodyl tablet is **enteric-coated**; therefore, it should be **swallowed whole** and should **not be taken within one hour of antacid or milk** as this will lead to dissolution of the coating and release of the drug into the stomach and cause gastric irritation.
4. **Usual Doses: Senna tab and Bisacodyl 5 mg tab: Adult dose**: usually 2 tablets (usually take at night to produce the effect next morning). While the dose of supp. Is one supp. (**usually in the morning**), **Glycerin suppositories**: The patient should expect to have bowel movement quickly (within one hour).
5. **Senna** may **color the urine** yellowish-brown at acid pH, and red at alkaline pH
6. **Castor Oil** is also given to ease the delivery of pregnant women. (C.I in early Pregnancy due it causes uterine contractions → dislodging of the fetus)

B- Bulk-forming laxative:

1. Bulk-forming laxatives relieve constipation by **increasing stool mass** which stimulates peristalsis; the laxative effect can **take several days to develop**.
2. Bulk-forming laxative preparations **should not be taken immediately before going to bed**, because there may be a **risk of esophageal blockage** if the patient lies down directly after taking them, also **they can cause gas and bloating**
3. When recommending the use of a bulk laxative, the pharmacist should advise that **an increase in fluid intake would be necessary**; (they require water to be effective).
4. **Methylcellulose, Ispaghula, and Sterculia** are useful in patients who cannot tolerate **bran**. Also, **Methylcellulose** also acts as a Stool softener.

C- Stool Softener (Liquid paraffin): its use declined nowadays due to many disadvantages.
these preparations make bowel movements softer and easier to pass without increasing their bulk, but prolonged use can interfere with the absorption of some essential vitamins.

D- Osmotic laxatives: [3] these include **Lactulose, Macrogols and Magnesium Salts**
they act by **keeping water in the bowel**, and thereby make the bowel movements softer; This also increases the bulk of the feces and enables them to be passed more easily.

1. **About lactulose:**
   a. It can be **taken by all age groups**, and can be **safely used in pregnancy**.
   b. It is intensely **sweet in taste** (but it is safe for diabetic patients).
   c. Adult laxative dose: **15 ml twice daily,** Child dose: **2.5 – 5 ml twice daily.**
   d. It discourages the proliferation of ammonia-producing organisms. It is therefore useful in the **treatment of hepatic encephalopathy** (in patients with liver cirrhosis).
2. **About Macrogols (Movicol®):**
   a. Adult and Child dose **1-3 sachets daily**
   b. **Safe in pregnancy**

E- Guanylate Cyclase-C agonists: This type of laxative changes stool consistency.
by **increasing the amount of water** into the GI lumen and **increases gastrointestinal movement,** they include **(Linaclotide, Plecanatide)**; which are **both C.I. in children below 6 years old**, and best to be avoided in patients below 17 years old.

   a. **Linaclotide** is indicated for the treatment of irritable bowel syndrome with constipation **(IBS-C)** and chronic idiopathic constipation **(CIC)**.
   b. **Plecanatide** is approved for chronic idiopathic constipation **(CIC)** only.

F- Peripheral acting μ-opioid antagonist (PAMORAs):

1. These are **used to reverse adverse effects caused by chronic use of opioids;** interacting with receptors outside the central nervous system (CNS), **mainly those located in the gastrointestinal tract**; PAMORAs are designed to specifically inhibit certain opioid receptors in the gastrointestinal tract and with limited ability to cross the blood-brain barrier; thus PAMORAs do not affect the analgesic effects of opioids within the central nervous system.
   - **PAMORAs are used in the treatment of opioid-induced bowel dysfunction (OIBD) or opioid-induced constipation (OIC)**, a potential adverse effect caused by chronic opioid use. PAMORAs act on the three pathophysiological mechanisms of this adverse effect: **They act on gut motility, gut secretion and sphincter function.**
2. They include:
   a. **Methylnaltrexone:** approved for **Opioid Induced Constipation (IOC)** in palliative care patients and for OIC in adult patients with non-cancer pain, when response to laxatives has not been sufficient.
   b. **Naloxegol**: indicated for **(IOC)** in adults with chronic non-cancer pain, contraindicated with use of strong CYP3A4 inhibitors or in patients with obstruction.
   c. **Alvimopan**: indicated for **postoperative ileus after bowel resection** with primary anastomosis; long-term use **associated with myocardial infarction.**
   d. **Naldemedine**: Opioid antagonist with **binding affinities for mu-, delta-, and kappa-opioid receptors**; it is a **derivative of naltrexone** to which a side chain has been added that increases the molecular weight and the polar surface area, thereby reducing its ability to cross the blood-brain barrier. It is indicated for **(OIC)** in adults with non-cancer pain.

General Notes:

- Tap water enemas may be used to treat simple constipation. The administration of 200 mL of water by enema to an adult often results in a bowel movement within 1.5 hours.
- Soapsuds are no longer recommended in enemas because their use may result in proctitis or colitis.
- Whole-bowel irrigation with PEG–electrolyte lavage solution has become popular for colon cleansing before diagnostic procedures or colorectal operations.
- Saline cathartics are composed of relatively poorly absorbed ions such as magnesium, sulfate, phosphate, and citrate, which produce their effects primarily by osmotic action to retain fluid in the GI tract. These agents may be given orally or rectally.

A) Stimulant laxative

Scientific name	Dosage form	Trade name	Concentration
Bisacodyl	EC Tab	Dulcolax®	5 mg
	Supp.	Dulcolax®, Laxamid®	5 mg, 10 mg
Glycerin (or) Glycerol	Supp.	Glycerol®	400 mg, 700 mg
	Enema	Baby Enema®	2.25 gm
Glycerin + Gelatin	Supp.	Glycerin®	(1.4 gm + 0.32 gm), (0.7 gm + 0.32 gm)
Senna Extract	Tab	Senade®	13.5 mg
Sennosides	Chocolated Tab	Exlax®	15 mg
Na+ Picosulfate	Cap	Dulco-lax Pico®	2.5 mg
	Drops	PicoLax®	7.5 mg/ml (15 ml)
	Elixir		5 mg/5 ml
Docusate Na+	Cap	Dioctyl®	100 mg
	Enema	Norgalax®	120 mg
Castor oil	Emulsion	Castor oil®	60 ml

B) Bulk-forming laxative drug

Scientific name	Dosage form	Trade name	Concentration
Methylcellulose	Powder, Tab	***Methylcellulose®,*** Celevac®	500 mg
Ispaghula husk	Powder (Sachets)	***Fybogel®,*** Ispagel®	3.5 gm/sachet
Sterculia	Granules	***Normacol®***	62%
Sterculia + Frangula	Granules	***Normacol Plus®***	62% + 8%

*** Bulk Laxatives** are useful in controlling diarrhea associated with diverticular disease.

Combination products: Stimulant Laxative + Bulk Laxative			
Scientific name	Dosage form	Trade name	concentration
Ispaghula husk + Plantago ovate + Senna	Granules	***Agiolax®***	----------
Ispaghula husk + Senna	Granules	Manevac®	54.2% +
Castor Oil + Glycerol + Gelatin	Cap	***Castolax®***	1000 mg cap

* **Ispaghula** is a Bulk Laxative,
* **Senna** is a stimulant Laxative.

C) Stool Softeners (No Longer Recommended)

D) Osmotic laxative drugs

Scientific name	Dosage form	Trade name	Concentration
Lactulose	Oral Solu. , Rectal Solu.	***Duphalac®***	10 gm/15 ml
Lactulose + Inulin + Fructo-oligosaccharide *	Oral Solu.	***Peristil®***	200 ml solu.
Lactitol + Fiber	Oral Solu.	***Lactofibre®***	(2.5 gm + 3 gm) Per 10 ml
Macrogol (PEG) + ***Na Chloride +*** ***Na Bicarbonate +*** ***K Chloride***	Powder for oral Solution	***Movicol®***	13.125 gm + 350.7 mg + 178.5 mg + 46.6 mg
Sorbitol	Solu.	Irragate®	3 gm/100 ml (3%)

* **Fructo-oligosaccharides** and **Inulin** promote the natural balance of the intestinal bacterial flora.

E) Guanylate Cyclase-C agonists:

Scientific name	Dosage form	Trade name	Concentration
Linaclotide	Cap	Linzess®, Constella®	145 mcg , 290 mcg
Plecanatide	Tab	Trulance®	3 mg

F) Peripheral acting μ-opioid antagonist (PAMORAs):

Scientific name	Dosage form	Trade name	Concentration
Alvimopan	Cap	Entereg®	12 mg
Naloxegol	Tab	Movantik®	12.5 mg , 25 mg
Naldemedine	Tab	Symproic®	0.2 mg
Methylnaltrexone	Inj. Solu.	Relistor®	8 mg/0.4 ml
	Tab		150 mg

G) Other drugs used for constipation (2)

Scientific name	Dosage form	Trade name	concentration
Lubiprostone	Cap	Amitiza®	8 mcg , 24 mcg
Tegaserod (Tegaseride)	Cap , Inj. Solu.	Zelnorm®	----------
Renzapride	Tab	Renzapride®	1 mg , 2 mg , 4 mg
Prucalopride	Tab	Resolor®, Resotran®	1 mg , 2 mg
Tenapanor	Tab	Ibsrela®	50 mg

Notes:

1. **Lubiprostone** is a **chloride channel activator** that acts locally on the gut to accelerate genitourinary transit time and delay gastric emptying. It is approved for chronic idiopathic constipation and constipation predominant IBS in adults.
    a. results in intestinal fluid secretion; **can reduce bloating and abdominal pain.**
    b. dose is 24 mcg twice daily for constipation and 8 mcg twice daily for IBS-C.
    c. **need negative pregnancy test before use.**
2. **Tegaseride (or Tegaserod)** is used for treatment of women who have irritable bowel syndrome (IBS) with constipation, **But it was withdrawn from the U.S. market on 2007**, due to a higher chance of heart attack, stroke, and worsening chest pain that can become a heart attack.
3. **Renzapride** is a **gastroprokinetic agent and antiemetic** which acts as a full 5-HT4 full agonist and 5-HT3 antagonist, it's used for the treatment of constipation-predominant irritable bowel syndrome **(IBS-C)**. It is also potentially effective for irritable bowel syndrome with alternating stool pattern **(IBS-A)**.
4. **Prucalopride** is a **selective, high affinity 5-HT4 receptor agonist,** which targets the impaired motility associated with chronic constipation, thus normalizing bowel movements.
    a. Elicits **GI prokinetic actions** that stimulates colonic peristalsis.
    b. **indicated for chronic constipation only when other Rx fails.**

2.4– Bowel Cleansing Preparations

1. Bowel cleansing preparations are used before colonic surgery, colonoscopy, or radiological examination to ensure the bowel is free of solid contents, **they are not treatments for constipation.**
2. Bowel cleansing preparations should be used with caution in patients with fluid and electrolyte disturbances. Renal function should be measured before starting treatment in patients at risk of fluid and electrolyte disturbances; Bowel cleansing preparations should be used with caution in colitis (avoid if acute severe colitis), in children, in the elderly, or in those who are debilitated.
3. **To use Bowel Cleansers:** Empty the content of the sachet into 1 Liter of water and stir until the powder is completely dissolved, then drink 1 glassful of the solution every 10 minutes until all the solution has been consumed. Repeat the step with each sachet as instructed.

Scientific name	D. form	Trade name	concentration
Macrogol + Na Sulfate + Na^+ Bicarbonate + NaCL + KCL	Sachets	Klean-Prep®, ***Coloclean®, Fortrans®***	59 gm + 5.685 gm +1.68 gm +1.46 gm + 743 mg
Macrogol + Na Sulfate + NaCL + KCL	Sachets	Moviprep®	100 gm + 7.5 gm 2.691 gm + 1.015 gm
Mg^+ Carbonate + Citric acid	Sachets	Citramag®	11.57 gm + 17.79 gm
Na^+ Picosulfate + Mg^+ Citrate	Sachets	Picolax®, CitraFleet®	10 mg/sachet
Na^+ Picosulfate + Mg^+ Oxide + Citric acid	Sachets	**Picoprep®**	10 mg + 3.5 gm + 12 gm
Monosodium phosphate + Anhydrous disodium phosphate	Tab	Colokit®	1102 mg + 398 mg

2.5- Anti-Diarrheals

1. Diarrhea is an **increase in the fluidity and frequency (more than 3 per day)** of bowel movements. In some cases, diarrhea protects the body from harmful substances in the intestine by hastening their removal.
   - The most common causes of diarrhea are **viral infection**, **food poisoning**, and parasites, but it also occurs as a symptom of other illnesses; also, it can be a side effect of some drugs.
   - Diarrhea may also be **caused by anxiety**.
   - **Danger signs include:** Immunocompromised, Presence of fever, Blood in the stool, Sudden Weight loss, suspected invasive infection.
     - **if one of those signs is present directly refer to a doctor.**

2. The main aim in the management of acute diarrhea is **the correction of fluid and electrolyte depletion with rehydration therapy**; this is especially important **in infants and young children and anti-Diarrheals are not generally recommended for this age group.**
   - **Zinc supplements** have been shown to **reduce the incidence, intensity, or duration of acute diarrhea in children**, the WHO/UNICEF recommend that children with acute diarrhea also receive zinc (10 mg of elemental zinc/day for infants younger than 6 months; 20 mg of elemental zinc/day for older infants and children) for 10 to 14 days.
   - **Probiotics (Lactobacillus species)** have been shown to **decrease the duration** of infectious and **antibiotic-induced diarrhea (AAD)** in adults and children; these actions due to Competition with pathogenic organisms, production of antimicrobial substances, and enhancement of immune response.

1- Anti-motility drugs (opioid related) [Loperamide, (Diphenoxylate + Atropine)]

These **decrease the intestinal muscles propulsive activity** so that fecal matter passes more slowly through the bowel, avoid if suspected invasive infection.

- **Loperamide is pregnancy category B.**

A) **Anti-motility drugs** are not recommended for acute diarrhea in young children, in the UK, both **Diphenoxylate** and **Loperamide** are **not licensed for children under 4 years of age**, in the USA, **Loperamide** is not recommended for children under the age of 2 years.

Adult doses: *** Loperamide**: initially 2 tablets followed by 1 tablet after each loose stool;
(16 mg/day maximum).
*** Diphenoxylate** + **Atropine**: 4 tablets initially followed by 2 tablets every 6 hours.

B) **Codeine** is used as an **anti-motility** drug for the treatment of acute diarrhea, it's given as 30 mg 3-4 times per day. (**Codeine** is also an **analgesic** and an **antitussive**).

2- Adsorbents (pectin + kaolin)

These **absorb water and irritants in the bowel**, resulting in larger, firmer stools at less frequent intervals.

- **Kaolin is a clay-like powder believed to work by attracting and holding onto the bacteria or germ that may be causing the diarrhea.**
- **Kaolin** has been used for years in combination with **pectin** for diarrhea**;** However, in April 2003, the **U.S. (FDA) found that there wasn't enough scientific support for kaolin's use in treating diarrhea.** Since April 2004, drug manufacturers have not been allowed to put kaolin in diarrhea medicine.
- Adsorbents such as **kaolin are not recommended for acute diarrheas**.
- **Kaolin** can form insoluble complexes with some drugs in the gastrointestinal tract and reduce their absorption; **oral doses should not be taken at the same time**.
- **Bulk-forming Laxatives**, such as **Ispaghula, methylcellulose, and Sterculia** (section 3) are useful in controlling diarrhea associated with diverticular disease.

3- Oral rehydration solution (ORS)

1. A **premixed solution** or **sachets of powder** for reconstitution are available; these contain sodium as chloride and bicarbonate, glucose and potassium
2. Only **water should be used to make the solution** and that **boiled and cooled water should be used for children < 1 year.**
3. **Stability of the ORS after reconstitution:** After reconstitution, any unused solution should be discarded after 1 hour of preparation unless it stored in refrigerator where it may be kept for 24 hours.
4. **Dose of ORS**: See table →

Table Amount of rehydration solution to be offered to patients.

Age	Quantity of solution (per watery stool)
Under 1 year	50 mL (quarter of a glass)
1–5 years	100 mL (half a glass)
6–12 years	200 mL (one glass)
Adult	400 mL (two glasses)

A) Anti-Motility drugs

Scientific name	D. form	Trade name	Concentration
Diphenoxylate + Atropine [1]	Tab	Lomotil® , Entero stop®	2.5 mg/0.025 mg
Loperamide [2]	Tab	Vacontil® , Diarrhea stop®	2 mg
	Cap	Imodium®	2 mg
	Syrup	Imodium®	1 mg/5 ml
Loperamide + Simethicone [3]	Caplet	Imodium plus®	2 mg + 125 mg
Difenoxin + Atropine	Tab	Motofen®	1 mg/0.025 mg
Opium tincture	Oral Liquid	Paregoric®	2 mg/5 mL

Notes:

1. **Atropine** is added in sub-therapeutic quantity to discourage deliberate overdose of Diphenoxylate, Difenoxin **(opioids)**
2. The FDA issued a **warning** about **Loperamide** in 2016 = (in high doses, it can cause serious heart problems – including abnormal heart rhythm - that can lead to death).
3. **Simethicone** is an anti-Flatulence.
4. **Opium tincture** contain morphine → inhibit GI motility, **used in** Acute diarrhea, Chronic orphan diarrhea, **it should not be used in diarrhea due to poisoning**

B) Adsorbents

Scientific name	Dosage form	Trade name	Concentration
Kaolin + pectin	Susp.	Pectokal® , Pecta®	1 gm + 0.02 gm
Polycarbophil *	Tab	Mitrolan® , Equalactin®	625 mg
	Chewable Tab		625 mg
Diosmectite **	Sachets	Smecta®	3 gm
Tannate Gelatin **	Cap	Tasectan®	500 mg
	Sachets		250 mg
Attapulgite	Tab	Diasorb®	600 mg
	Oral Liquid	K-Pek®	750 mg/15 ml

*** Polycarbophil** is also a bulk producing laxative that restores normal moisture levels in intestine

** **Tannate** acts mechanically by protecting inflamed intestinal mucosa, due its ability to form a protective, protein-based mucoadhesive film which forms a complex with the mucoproteins responsible for local inflammation and promotes their precipitation and elimination in the feces.

**** Diosmectite** is an activated natural **Aluminosilicate** clay consisting of a double **Aluminium** and **Magnesium** silicate.

C) Other drugs used for Diarrhea

Scientific name	D. form	Trade name	concentration
Bismuth subsalicylate	Tab	Kaopectate® , Pepto B®	262 mg , 525 mg
	Oral Susp.		262 mg/15 ml , 525 mg/15 ml
Lactase	Oral drops	Lactaid®	1,250 units/4 drops
Lactobacillus acidophilus + Lactobacillus bulgaricus	Tab, cap Drops	Vitalatic B®, Lactol® Enterolactis®	----------
Lactobacillus Species + Zinc Sulphate + **Inulin**	Sachet	Biolact®	5 billion unit + 10 mg zinc
Octreotide	Inj. Solu.	Sandostatin®	0.1 mg/ml , 0.5/ml , 1mg/ml
Alosetron	Tab	Lotronex®	0.5 mg , 1 mg
Racecadotril	Cap	Hidrasec®	100 mg
	Granules		10 mg/sachet , 30 mg/sachet
Crofelemer	Tab	Fulyzaq®	125 mg
Eluxadoline	Tab	Viberzi®	75 mg , 100 mg
Telotristat	Tab	Xermelo®	250 mg

Notes:

1. **Bismuth** has Antimicrobial + anti-inflammatory effect, while **subsalicylate** has the anti-secretory effect, generally it's **used in the treatment of diarrhea associated with H. pylori** infections, and often used **for treatment or prevention of (traveler's diarrhea).**
   - It also **binds toxins** in the intestinal tract, may cause **Stool discoloration.**
   - avoid in salicylate allergy, age <12 years, and in pregnancy.
2. **Lactase** is an enzyme that **digests lactose** (the naturally occurring sugar in milk), **used for Diarrhea due to the Lactose Intolerance.**
3. **Lactobacillus** preparation is **intended to replace colonic micro normal flora**; This supposedly restores intestinal functions and suppresses the growth of pathogenic microorganisms, generally used to normalize GIT in Irritable Bowel Syndrome (IBS).
4. **Octreotide**, a synthetic octapeptide analogue of endogenous somatostatin, it blocks the release of serotonin and other active peptides and is effective in controlling diarrhea and flushing.
   - Used for managing **diarrhea associated with carcinoid tumors.**
   - Used in **HIV-associated diarrhea.**
   - Also is given as an infusion for **management of acute hemorrhage** from esophageal varices in liver cirrhosis on the basis that **it reduces portal venous pressure.**
   - Used in the **treatment of refractory hypoglycemia** in neonates and sulphonyl urea induced hypoglycemia in adults.
   - associated with adverse effects such as Hyperglycemia, gallstone formation **(cholelithiasis)**, nausea, and abdominal pain.
5. **Alosetron** is a **5-HT_3 antagonist** used for the management of severe diarrhea-predominant irritable bowel syndrome (IBS) in women only, **it was withdrawn from the market in 2000** owing to the occurrence of serious life-threatening gastrointestinal adverse effects (colonic ischemia), **but was reintroduced in 2002 with availability and use restricted.**
6. **Racecadotril** reduce intestinal motility and has **an anti-secretory effect.**
   - It is an **oral enkephalinase inhibitor** for use in the treatment of acute diarrhea; it acts by preventing the degradation of endogenous enkephalins.
   - **Racecadotril reduces hypersecretion of water and electrolytes** into the intestinal lumen; thus, reducing the incidence and duration of acute diarrhea and reduces diarrhea-associated symptoms, also results in significant reductions in stool output.
7. **Crofelemer** is indicated for non-infectious diarrhea in adult patients with HIV, AIDS who are receiving antiretroviral therapy.
8. **Eluxadoline** is **μ-opioid receptor agonist,** it is indicated for diarrhea-predominant irritable bowel syndrome (IBS-D).

2.6- Antispasmodics

1. Used for smooth muscle contraction, especially in tubular organs of the gastrointestinal tract, the effect is to **prevent spasms of the stomach, intestine** or **urinary bladder.**
2. **Anticholinergic/antispasmodic agents inhibit the action of acetylcholine**; they stop the transmission of parasympathetic nerve impulses → lessens the spasms of smooth muscle.

A) Antimuscarinics (Hyoscine butyl-bromide)

1. Used for symptomatic relief of gastro-intestinal disorders due to smooth muscle spasm.
2. Antimuscarinics are **contraindicated in patients with prostatic enlargement, glaucoma.**
3. **They should be used with caution in the elderly.**

B) Other antispasmodics **(Mebeverine, Alverine, Drotaverine**) are used to relieve pain in **irritable bowel syndrome**; They **have no anticholinergic side effects.**

A) Antimuscarinics/Anticholinergics:

Scientific name	D. form	Trade name	Concentration
Atropine	Tab	Atreza®	0.4 mg , 0.6 mg
Hyoscine butyl bromide	Amp	Buscopan® , Scopinal®	10 mg/2 ml
	Tab	Buscopan®, Spasmosam®	10 mg
Scopolamine Metho-nitrate	Syr.	Kimidal®	0.12 gm/5 ml
Prifinium Bromide	Tab	Riabal®	30 mg
	Amp	Riabal®	15 mg/2 ml
	Syrup	Riabal®	7.5 mg/5 ml
Otilonium Bromide	Tab	Spasmomen®	40 mg
Tiemonium methyl-sulfate	Tab , Supp.	Visceralgine®	50 mg (tab) , 20 mg (supp)
	Oral Syrup	Spasmofree®	10 mg/5 ml
	Amp		5 mg/2 ml
Propantheline bromide	Tab	Pro-Banthine®	15 mg
Dicyclomine*	Tab , Cap	Bentyl® , Spasmorest®	20 mg (Tab) , 10 mg (Cap)

*** Dicyclomine = Dicycloverine, they are the same drug.**

B) Other antispasmodics

Scientific name	D. form	Trade name	Concentration
Mebeverine HCL	Tab	Duspatalin®, Colospasmine® Meva® , Antispasmin® , Mevir®	135 mg
	Cap	Duspatalin Retard® , ColoFac MR®	200 mg
Alverine	Cap	Spasmonal®	60 mg
	Cap	Spasmonal Forte®	120 mg
Peppermint Oil	Cap	Mintec® , Colpermin®	0.2 ml/Cap , 200mg
Pinaverium	Tab	Dicetel® , Eldicet®	50 mg , 100 mg
Drotaverine	Tab	Dot®, Dotarin®, Dover®, Doverin®	40 mg , 80 mg
Trimebutine	Tab , Susp.	Debridat®	100 mg
Phloroglucinol + Trimethylphloroglucinol	Tab	Spasfon®	80 mg + 80 mg

1. **Peppermint Oil** causes heartburn, it can worsen GERD, but can improve symptoms in IBS.
2. **Drotaverine** is also prescribed for patients with renal colic as a muscle relaxant, as well as for pregnant women to accelerate labor.
3. **Trimebutine** is a regulator of digestive motility, it has a spasmolytic effect.
4. **Spasfon®** is used in treatment of spasmodic pain of the intestines, biliary tract, bladder or uterus.
   a. It Provide relief from irritable bowel syndrome; preventing or treating bladder spasm after transurethral resection of the prostate.
   b. **Phloroglucinol** is not widely used because it also used in making explosives.

Combination Products of Mebeverine			
Scientific name	D. form	Trade name	concentration
Mebeverine + Sulpiride*	Coated Tab	Colona®	100 mg + 25 mg
Mebeverine + Sulpiride + Simethicone	Tab	Coloprid® , IB-Lax®	135 mg + 25 mg + 180 mg
Mebeverine + Simethicone + Escitalopram*	Tab	PrXicol®	135 mg + 40 mg + 10 mg
Mebeverine + Dimethicone	Tab	Coloverin D®	135 mg + 40 mg
Mebeverine + Ispaghula	Granules	Fybogel Plus®	(135 mg + 3.5 gm)/sachet

1. **Sulpiride** is an **anti-psychotic**; it has a sedative effect, **it may have a role in IBS**, but it causes extrapyramidal side effects (involuntary movements of the face lips and tongue)**; thus its use is unjustified and not preferred for long term use;** (For more info see chapter 4, section 2).
2. **Simethicone, Dimethicone** are an anti-flatulence drug.
3. **Escitalopram** is an antidepressant (SSRIs), see chapter 4 for more info.
4. **Ispaghula** is a bulk forming Laxative.

Notes for Irritable Bowel Syndrome (IBS):

1. Antispasmodics may be combined with benzodiazepine (Librax®) or a phenothiazine (Stelabid®) and **used for gastrointestinal disorders associated with or due to anxiety;** and for **irritable bowel syndrome (IBS);** Also, they may be combined with analgesics.
2. Tricyclic antidepressants (TCAs) as (**Amitriptyline**) and Selective serotonin reuptake inhibitors (SSRIs) as (**Fluoxetine, Escitalopram**) are used for IBS (used at sub-therapeutic doses); they increase pain threshold in the guts and delay gastric emptying time, and decrease stool frequency.
   - TCAs have anti-pain and gut-slowing qualities, and seem to do this by acting on the neurotransmitter's serotonin and norepinephrine; This slowing down of gut motility makes the TCAs better suited for the treatment of diarrhea-predominant IBS (IBS-D); while the lack of a constipating effect makes the SSRIs a better choice for those who suffer from constipation predominant IBS (IBS-C); For more info on antidepressants see chapter 4.
3. Some guidelines support the use of **Probiotics** for the treatment of IBS.

Combination products for IBS			
Trade names	**Scientific name**	**D. form**	**Concentration**
Librax®	Chlordiazepoxide + Clidinum bromide	Tab	5 mg + 2.5 mg
Coloverin A®	Chlordiazepoxide + Mebeverine	Tab	5 mg + 135 mg
Stelabid®	Trifluoperazine + Isopropamide	Tab	1 mg + 5 mg
Meteospasmyl®	Alverine + Simethicone	Cap	60 mg + 300 mg
Dicetel Duo®	Pinaverium + Dimethicone	Tab	100 mg + 300 mg
Colo-Tri®	Trimebutine + Simethicone	Tab	200 mg + 80 mg
Buscopan Plus®, **Spazmotek Plus®**	Hyoscine butyl bromide + Paracetamol	Tab	10 mg + 500 mg
Riabal-Co®	Clidinum bromide + Paracetamol	Tab	5 mg + 325 mg
Panvoxan®	Pantoprazole + Simethicone + Levosulpiride	Tab	40mg+ 80mg + 25mg
Donnatal®	Atropine + Hyoscyamine + Scopolamine + Phenobarbital	Tab, Cap	----------
Bellamine® *	Belladonna + Ergotamine + Phenobarbital	Tab	----------

* **Bellamine®** is also used to treat symptoms of menopause including hot flashes, sweating, anxiety, and trouble sleeping. **(It's contraindicated in pregnancy).**

Herbal Combinations for IBS			
Trade names	**Scientific name**	**D. form**	**Concentration**
ProIBS®	Fructose + Aloe Barbadensis extract + Vit. C + Vit. B_2 + Inulin	Sachet	----------
Biocolin®	Curcumin + Fennel oil	Cap	42 mg + 25 mg

2.7– Anti-Emetics and Prokinetics

A) Vomiting is a reflex action for getting rid of harmful substances, but it may also be a symptom of disease; Vomiting and nausea are often **caused by a digestive tract infection, travel sickness, pregnancy, or vertigo** (a balance disorder involving the inner ear), they can also **occur as a side effect of some drugs**, especially those used for cancer, radiation therapy, or general anesthesia.

B) Nausea and vomiting occur when the **vomiting center** in the brain is stimulated by signals from three places in the body: the digestive tract, the part of the inner ear controlling balance, and the brain itself via thoughts and emotions and via its **chemoreceptor trigger zone**, which responds to harmful substances in the blood.

- Anti-emetic drugs may act at one or more of these places.
- Some help the stomach to empty its contents into the intestine.
- A combination may be used that works at different sites and has an additive effect.

C) Stimuli for nausea are processed through several major anatomic areas, each of which has various receptors associated with input to the medullary vomiting center:

a) Visceral stimuli: Mediated through **dopamine** and **serotonin** receptors; Major stimuli include: Gastric irritants, Non-gastric stimuli (peritonitis, intestinal or biliary distension, pancreatitis, gastroparesis), Abdominal radiation, Chemotherapeutic agents, Pharyngeal stimulation.

b) Chemoreceptor trigger zone: Mediated by **dopamine** (D2), **serotonin**, and some **histamine** (H1) and **muscarinic** (M1) and **substance P/neurokinin** 1; major stimuli include: Medications (Opiates, dopamine agonists, digoxin, chemotherapeutic agents, macrolides, general anesthetics), Metabolic disturbances (uremia, diabetic ketoacidosis, hypercalcemia, hypoxemia), Bacterial toxins, Radiation therapy.

c) Vestibular labyrinths: Mediated through **H1 and M1**; Major stimuli include: Motion sickness, Labyrinth infection.

d) Cerebral cortex: Receptor involvement not well characterized; noxious odors, visions, and tastes.

1. Antiemetics **should be prescribed only when the cause of vomiting is known** because otherwise, they may delay diagnosis, particularly in children, they **are unnecessary and sometimes harmful** when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin or antiepileptic overdose.

2. They include: (**Prochlorperazine**, **Metoclopramide**, **Domperidone** and **Cinnarizine**), which all can be used to treat or prevent nausea and vomiting.

3. Cinnarizine is an antihistamine. Used to prevent **motion sickness** where the dose **is taken two hours before travel**, also used to relief the symptoms of inner ear disorders such as Meniere's disease (sensations of ringing or other noise in the ears).

- It acts by **preventing Ca^{+} ions from entering the cells**, thus preventing the smooth muscle of the arteries from contraction, thereby increasing the blood supply to the brain and extremities = relief Nausea and vertigo.

4. Metoclopramide sometimes **causes a seizure-like reaction (Tardive dyskinesia)** which is characterized by the eye lid blinking and muscle rigidity.

- So, in patients under 20 years: the dose of **Metoclopramide** should be determined on the **basis of body-weight** (0.1 mg/kg/dose) to avoid dystonic reaction.
- **Should not be given more than 5 days, and its C.I in children below 1 year.**
- Should be **used with caution** in patients with **heart disease** and **Liver cirrhosis,** because it may lead to **fluid accumulation** by causing an **increase in serum aldosterone.**
- Also, should be **used with caution in patients with epilepsy** (increase convulsions frequency).
- **Metoclopramide** is the only anti-emetic that has been specifically studied in the **treatment of renal colic**, in 2 double-blinded studies; **Metoclopramide provided pain relief equivalent to narcotic analgesics in addition to relieving nausea.**

5. **Prochlorperazine** is a **dopamine (D2) receptor antagonist** that belongs to the phenothiazine class of antipsychotic agents that are used for the antiemetic treatment of nausea and vertigo. It is also a **highly potent typical antipsychotic**, 10–20 times more potent than chlorpromazine. It is also **used to treat migraine headaches**.
   - May cause dry mouth, blurred vision, or difficulty in passing urine

6. **Domperidone has the advantage** over metoclopramide and the Prochlorperazine of being less likely to cause central effects such as **dystonic reactions** (**tetanus-like reaction**) because it does not readily cross the blood-brain barrier, it also **improves upper GIT motility**.
   - **Domperidone** is **not approved** by the **FDA**, it's approved in EMA and MHRA only.
   - **Domperidone I.V formulation** was **withdrawn** from the markets in 2006 due cases of **cardiac arrest, arrhythmias** and **sudden death**; oral formulation may cause the same cardiac problems in patient over 60 years old if given more than 30 mg/day.
   - **The max recommended dose is 30 mg per day for 7 days only.**
   - **With the recommendation of avoidance** in patients with **cardiac diseases.**
   - Avoid co-administration with drugs that prolong QT interval (Azithromycin, Ciprofloxacin) due increased risk of cardiovascular side effects.

a) Anti-emetics and also Gastric Motility Stimulant (Prokinetics)

Scientific name	Dosage form	Trade name	Concentration
Metoclopramide	Tab	Placil®, Meclodin®	5 mg , 10 mg
	Drop	Meclodin®	4 mg/1 ml
	Syrup	Meclopram®	5 mg/5ml
	Amp	Placil® , Metamide®	10 mg/2 ml
Domperidone *	Tab	Motilium® , Motinorm®	10 mg
	Supp.	Motilium®	10 mg , 30 mg , 60 mg
	Oral Susp.	Domby®	200 ml

b) Gastric Motility Stimulant (Prokinetics)

1. They enhance gastrointestinal motility by increasing the frequency of contractions in the small intestine or making them stronger, but without disrupting their rhythm.
2. They are used to relieve gastrointestinal symptoms such as abdominal discomfort, bloating, constipation, heart burn, nausea, and vomiting.

Scientific name	Dosage form	Trade name	concentration
Mosapride	Tab	Fluxopride®	5 mg
Cisapride	Tab	Prepulsid® , Propulsid®	10 mg , 20 mg
Itopride	Tab	Ganaton®	50 mg
Prucalopride	Tab	Resotran®	1 mg , 2 mg

c) Other Anti Emetics

Scientific name	Dosage form	Trade name	Conc.
Cinnarizine *	Tab , Cap	Stugeron®	25 mg , 75 mg
Prochlorperazine **	Tab	Stemetil® , Compazine®	5 mg , 10 mg
	Amp	Promotil®, Stemetil®	12.5 mg/1 ml
Meclizine *	Tab	Antivert®	25 mg , 50 mg
Vitamin B_6 (Pyridoxine)	Tab , Amp	----------	40 mg
Meclizine + B_6 *	Tab	Navidox® , Navidoxine®	25 mg + 50 mg
Cinnarizine + Domperidone	Tab	Vertigun®	20 mg + 15 mg

*** Safe in pregnancy, the most used antiemetic in pregnancy is (Meclizine + B_6).**

*** Note**: also see (Chapter 4, Section 6) **for more details on the Drugs that are used in nausea/vomiting and vertigo.**

2.8- Drugs for the treatment of Hiccups

1. **A hiccup** is an **involuntary contraction** (myoclonic jerk) **of the diaphragm** that may repeat several times per minute, in medicine, it is known as **synchronous diaphragmatic flutter (SDF)**, or **Singultus.**
2. Hiccups, in general, **resolves itself without intervention**, although many home remedies are often used to attempt to shorten the duration, Medical treatment is occasionally necessary in cases of chronic hiccups.
3. A simple treatment involves increasing the partial pressure of CO_2 and inhibiting diaphragm activity by holding one's breath or rebreathing into a paper bag, or by scaring the patient suddenly.
4. Various medications have been used to cure hiccups; **Chlorpromazine appears to be the drug of choice**, **Haloperidol** and **Metoclopramide** have been used successfully.
   - **Chlorpromazine** is an antipsychotic, used for intractable hiccups 25-50 mg orally every 8 hours, if the hiccups still persist after 3 days of oral treatment; administer 25 mg I.M. every 4 hours. (For more info see chapter 4, section 2 for more info).
   - **Haloperidol** is useful in treatment of irregular spasmodic movements of muscles, 2-5mg I.M. followed by 1-4 mg tid orally for two days may be equally effective with less potential for side effects. (For more info see chapter 4, section 2 for more info).
   - **Metoclopramide** 10 mg I.V. or I.M. followed by a maintenance regimen of 10 to 20 mg qid for 10 days. (See the previous section for more info).
5. Several anticonvulsant agents (**phenytoin**, **Valproic acid**, and **carbamazepine**) have effectively treated intractable hiccups in typical anticonvulsant doses. **Gabapentin** has been effective in patients with central nervous system (CNS) lesions and in some other groups.
6. Of the anesthetic agents, **ketamine** has been the most successful; **Baclofen** is particularly useful in patients for whom other agents are contraindicated, Other reportedly beneficial agents include muscle relaxants **(Orphenadrine)**.

Scientific name	D. form	Trade name	Concentration
Chlorpromazine	Tab	Largactil®, Thorazine®	50 mg , 100 mg , 200 mg
	Amp		25 mg/5 ml , 25 mg/ml
Haloperidol	Tab	Haldol®, Peridol®	0.5 mg , 1 mg , 2 mg , 5 mg
	Amp	Haldol Lactate®	5 mg/ml

2.9- Drugs for Inflammatory bowel disease IBD (ulcerative colitis and Crohn's disease)

1. **Inflammatory bowel disease (IBD)** is the term used for disorders in which inflammation of the intestinal wall causes recurrent attacks of abdominal pain, general feelings of ill-health, and frequently diarrhea, with blood and mucus present in the feces, Loss of appetite and poor absorption of food may often result in weight loss.
2. **There are two main types** of IBD: **Crohn's disease** and **ulcerative colitis**.
   - In **Crohn's disease** (also called regional enteritis), any part of the digestive tract may become inflamed, although the small intestine is the most commonly affected site.
   - In **ulcerative colitis**, it is the large intestine (colon) that becomes inflamed and ulcerated, often producing blood-stained diarrhea.
3. The exact cause of these disorders is not known, although stress-related, dietary, infectious, and genetic factors may all be important.
   - The exact cause of continuing inflammation of the GI mucosa is unknown, but it is thought that the **inflammation is secondary to an antigen-driven response**; Contributing factors include: **Defects in the intestinal epithelial barrier and immune system.**

4. Establishing a proper diet and a less stressful lifestyle may help to alleviate these conditions, Bed rest during attacks is also advisable, However, these simple measures alone do not usually relieve or prevent attacks, and drug treatment is often necessary.
   - Note: **Smoking worsens Crohn's disease**; but **Smoking is associated with improvement in Ulcerative Colitis symptoms,** (who says smoking has no advantages?).

5. **Clinical Features of Inflammatory Bowel Disease:**

Clinical Findings	Crohn Disease	Ulcerative Colitis
Bowel involvement	May be anywhere from mouth to anus (66% of cases located in ileum)	Confined to rectum and colon Terminal ileal involvement (backwash ileitis) in a minority of patients
Perianal involvement	Yes	Unlikely
Depth of ulceration	May extend to submucosa or deeper	Superficial
Continuous inflammation	Rarely, a patchy, "cobblestone" appearance	Very common
Histology	Transmural lesions, granulomas	Nontransmural, crypt abscesses
Fistula, perforation, or strictures	Yes	No
Development of toxic mega colon	No	Yes
Malabsorption or malnutrition	Yes, often vitamin deficiencies; possible growth retardation in children	Rare
Risk factor for colorectal cancer	Uncommon	Yes
Pseudo polyps	Fairly uncommon	Common

6. Three types of drug are used to treat IBD: **Aminosalicylates anti-inflammatory drugs** (**sulfasalazine**), **corticosteroids, Immunosuppresants** (including Monoclonal antibodies). Nutritional supplements (used especially for Crohn's disease) and antidiarrheal drugs may also be used. Surgery to remove damaged areas of the intestine may be needed in severe cases.
   - **Drugs cannot cure inflammatory bowel disease**, but treatment is needed, not only to control symptoms, but also to prevent complications, especially severe anemia and perforation of the intestinal wall.
   - Aminosalicylates are used to treat acute attacks of ulcerative colitis and Crohn's disease, and they may be continued as maintenance therapy.
   - People who have severe bowel inflammation are usually prescribed a course of corticosteroids, particularly during a sudden flare-up.
   - Once the disease is under control, an **immunosuppressant** may be given to prevent a relapse.

7. **Corticosteroids and sulfasalazine damp down the inflammatory process, allowing the damaged tissue to recover**; They act in different ways to prevent migration of white blood cells into the bowel wall, which may be responsible in part for the inflammation of the bowel.
   - Taken to treat attacks, **these drugs relieve symptoms within a few days**, and general health **improves gradually** over a period of a few weeks.
   - **Aminosalicylates** usually provide long term relief from the symptoms of IBD.
   - Treatment with an **immunosuppressant** drug may **take several months before the condition** improves; and regular blood tests to monitor possible drug side effects are often required.

A. Aminosalicylates (Mesalamine, and Sulfasalazine)

1. **Sulfasalazine** combines **Sulfapyridine** (antibiotic) and **Mesalamine** (5-aminosalicylic acid – an anti-inflammatory) in the same molecule, **Sulfasalazine** is given orally. **Sulfapyridine is believed to be responsible for many of the adverse reactions of sulfasalazine**; Mesalamine alone can be used.
   - **Sulfasalazine** is cleaved by colonic bacteria to the active portion (5-aminosalicylate) **Sulfapyridine; Avoid in patients with a sulfa allergy.**
   - Dosed 4–6 gm/day for induction and 2–4 gm/day for maintenance; titrated from 500 mg once or twice daily to avoid adverse effects.
   - **Sulfasalazine** is often associated with either dose-related or idiosyncratic adverse drug effects, or Dose-related side effects usually include GI disturbances such as nausea, vomiting, diarrhea, or anorexia, but they may also include headache and arthralgia.
2. **Patients receiving sulfasalazine should receive oral folic acid** supplementation, as sulfasalazine **inhibits folic acid absorption**.
   - Patient should **avoid direct sun light,** because it increases sun light sensitivity.
   - It may **cause urine discoloration** to brown orange color.
   - May **lead to temporary sperms malformation in men**, thus preventing conception.
3. **Mesalamine** can be used as an **enema or suppository** for the treatment of proctitis or given orally in **slow-release formulations** that deliver it to the small intestine and colon.
   - **Mesalamine** formulations are **coated tablets or granules**, they should not be crushed or chewed.
   - **Mesalamine** it safe to use **for patients with sulfonamide allergies.**
   - May impose a lower frequency of adverse effects compared with **sulfasalazine**.
4. **Enemas or suppositories should be administered in the evening**; They are given rectally, particularly when **disease affects the sigmoid colon and rectum**.
5. **Other Aminosalicylates available:**
   a) **Olsalazine**: The Dimer of 5-aminosalicylic acid, converted to Mesalamine by the intestinal flora, associated with secretory diarrhea in up to 25% of patients.
   b) **Balsalazide:** contains 2 molecules of Mesalamine attached together; link is broken by the intestinal flora to give 2 molecules.
6. **Sulfasalazine** is also used for rheumatoid arthritis (it is one of the Disease-Modifying Antirheumatic Drugs).

B. Other drugs may be used for the Inflammatory bowel disease (IBD) include **corticosteroids (see Chapter 11), immunosuppressant's (see Chapter 10)**

Scientific name	Dosage form	Trade name	Conc.
Sulfasalazine	EC Tab	Salazopyrin®	500 mg
	Supp.		500 mg
Mesalamine	EC Tab	Pentasa® , Mesacol®	500 mg
	EC Tab	Asacol®	400 mg , 800 mg
	Tab	Mezavant XL®	1.2 gm
	Supp.	Asacol®	1000 mg
	Enema	Pentasa® , Salofalk®	1 gm , 2 gm , 4 gm
Olsalazine *	Cap	Dipentum®	250 mg
Balsalazide *	Cap	Colazal® , Colazide®	750 mg
	Tab	Giazo®	1.1 gm

Some of the Corticosteroids that have a role in IBD:

- Corticosteroids work quickly to suppress inflammation during acute flares.
- They **have no role in maintenance therapy**; however, more than 50% of patients with severe disease may become steroid-dependent.

Scientific name	Dosage form	Trade name	concentration
Budesonide *	Cap	Budenofalk®	3 mg
	Granules		9 mg
	Enema	Entocort®	2 mg/100 ml
Hydrocortisone	Tab	Cortef®	10 mg
	Vial		100 mg
	Rectal Foam	Colifoam®	10%
Methylprednisolone	Tab	Medrol®	4 mg
	Vial	DepoMedrol®	40 mg , 80 mg
	Vial	SoluMedrol®	250 mg , 500 mg , 1000 mg
Prednisolone	Tab	Cortancyl®	5 mg , 20 mg
	Rectal Foam	Predsol®	20 mg
	Enema		20 mg/100 ml

*** Budesonide** is about 15-fold more potent than prednisone; with minimal systemic adverse effects compared with other corticosteroids.

Some FDA approved Immunosuppressant for IBD

- **Immunomodulators** such as **Mercaptopurine**, **azathioprine**, or **methotrexate** are Indicated only for maintenance therapy; because of long onset of action (3–15 months).
  - Use can result in a steroid-sparing effect.
- **Infliximab** (monoclonal antibody against TNFα), **is contraindicated in New York Heart Association (NYHA) class III/IV heart failure**; do not exceed 5-mg/kg dose in other patients with chronic heart failure.
  - Since it's a Chimeric monoclonal antibody; **it may cause Antibody induction,** up to 50% of patients may develop antinuclear antibodies; 19% may develop anti-double-stranded DNA antibodies.
  - **May cause reactivation of latent infections** (bacterial, including disseminated tuberculosis, fungal, sepsis and hepatitis); do not give to patients with active infections.
- **Adalimumab** (Fully humanized antibody to TNFα), therefore, theoretically, no development of antibodies as in with **Infliximab**.
  - **Higher efficacy compared to Infliximab**; with Complete remission rates at week 4 range from 21% to 54%; Efficacy rates for maintenance therapy are 56%–79% at week 4 and 36%–46% at week 56.
  - The adverse effect profile of **Adalimumab** is similar to that of **Infliximab**, except for the development of antibodies to **Adalimumab**.

Scientific name	Dosage form	Trade name	concentration
Methotrexate	Tab	Trexall®, MTX®	2.5 mg
	Vial (Solu.)		50 mg
Azathioprine	Tab	Imuran®	50 mg , 75 mg , 100 mg
	Inj. Powder		100 mg/Vial
Mercaptopurine	Tab	6-MP® , Puri-nethol®	50 mg
Cyclosporine	Cap	Sandimmune® , Gengraf®	25 mg , 50 mg , 100 mg
	Inj. Solu.		50 mg/ml
Infliximab	Inj. Powder	Remicade®	100 mg/vial
Adalimumab	Prefilled Inj.	Humira®	40 mg/0.8 ml
Certolizumab	Inj. Powder	Cimzia®	200 mg/vial
Natalizumab	Inj. Solu.	Tysabri®	300 mg/15 ml
Golimumab	Prefilled Inj.	Simponi®	50 mg/0.5 ml
Vedolizumab	Inj. Powder	Entyvio®	300 mg/vial

2.10- Products for flatulence and abdominal gases

A- Gas in the digestive system is part of the normal process of digestion. Getting rid of excess gas, either by **Burping** or passing gas (**farting**), also is normal; Gas pain may occur if gas is trapped or not moving well through the digestive system.
- An increase in gas or gas pain may result from eating foods that are more likely to produce gas; Often, relatively simple changes in eating habits can lessen bothersome gas.
- some digestive system disorders, such as irritable bowel syndrome or celiac disease, may cause (in addition to other signs and symptoms) an increase in gas or gas pain.

B- Also **Burping** is normal, particularly during or right after a meal; Most people pass gas up to 20 times a day. Therefore, while having gas may be inconvenient or embarrassing, **burping and passing gas are rarely by themselves a sign of a medical problem.**

C- Gas in the stomach is primarily caused by swallowing air during eating or drinking, also Gas forms in the large intestine (colon) when bacteria ferment carbohydrates — fiber, some starches and some sugars — that aren't digested in the small intestine. Bacteria also consume some of that gas, but the remaining gas is released when passing gas from the anus.

D- Several products are available for flatulence and abdominal gases; these products usually contain **Simethicone** (or **Dimethicone**), **Dill oil, Fennel Oil, Alpha-galactosidase, Lactase, Activated Charcoal** and **Probiotics.**

Notes:

1. **Simethicone** is an **anti-foaming** agent that **decreases the surface tension of gas bubbles**, causing them to combine into larger bubbles in the stomach that can be passed more easily.
   - **Simethicone does not reduce or prevent the formation of gas** in the digestive tract, rather, it increases the rate at which it exits the body**;**
   - **It is not absorbed by the body into the bloodstream,** and thus is considered safe.
2. **Fennel essential oil** can help to clear the bowels, relieve constipation, and get rid of gas and bloating, **Dill oil** (the essential ingredient for gripe water); is given to babies to relieve flatulence and colic.
3. **Alpha-galactosidase** is an enzyme used for the prevention of flatulence and bloating attributed to a variety of grains, cereals, nuts, and vegetables containing the sugars raffinose, stachyose, verbascose.
4. **Lactase** helps to digest the sugar in dairy products (lactose); this reduces gas symptoms if the patient is **lactose intolerant**.
5. **Probiotics** is used to help kill the bad bacteria and add good bacteria to the digestive tract, thus helping in normalizing the gas production rate.

a) For Adults

Trade name	Dosage form	Scientific name	Concentration
Dimicone®	Chew Tab, Cap	Dimethicone	40 mg
Disflatyl®	Tab	Simethicone + Silicon Dioxide	40 mg + 2 mg
Ovol®	Cap	Simethicone	180 mg
Mestil Forte®	Tab	Simethicone	80 mg
Gazclear®	Tab	Simethicone + Charcoal	50 mg + 300 mg
Meteospasmyl®	Cap	Simethicone + Alverine	300 mg + 60 mg
lactaid®	Tab , chew tab	Lactase enzyme	9,000 units
Gas enzyme®	Chew Tab	Alpha-galactosidase	300 units
Carminex®	Syrup	Herbal Preparation	----------
Eucarbon®	Tab	Senna + Rhubarb + Charcoal + Sulphur sublimated + Peppermint oil + Fennel oil	105 mg + 25 mg +180 mg + 50 + 20 mg
Flatulence®	Sachets	Simethicone + Anise extract + Mint extract	80 mg + 5 mg + 5 mg
Aeris®	Cap	Charcoal + Fennel oil + Lemon Balm + Green Aniseed	315 mg + 140 mg + 90 mg + 3.6 mg

b) For infants and Children

Trade name	Dosage form	Scientific name	Concentration
Disflatyl®	drop	Simethicone	40 mg / 30 ml
Infasooth®	drop	Simethicone	40 mg / 50 ml
Ovol®, Baby Cone®	drop	Simethicone	40 mg / 15 ml
Colic EZ®	drop	Simethicone + Dill oil + Fennel Oil	(40 mg + 0.005 ml + 0.0007 ml)/1 ml
Happy baby®	drop	Chamomile dry extract + Lemon balm + Fennel oil	50 mg + 10 mg + 0.2 mg
Spastal®, * ***Babytal®***	drop	Pipenzolate + Phenobarbitone	4 mg 6 mg
Stop Colic®	cream	Cumin oil + Vaseline	5% (50 ml cream)

Notes:

1. **Pipenzolate** is an **Antimuscarinic**; It binds to muscarinic acetylcholine receptors as an antagonist therefore preventing acetylcholine from binding to the receptors.
    - Inhibition of Acetylcholine produces relaxation of smooth muscles of gastrointestinal tract and genitourinary tract and reduces the painful spasm and cramp.
    - It does not produce CNS effects and free from atropine-like side effects.
2. **Spastal®** is not recommended anymore in any guideline; because **it contains phenobarbital,** which has been **associated with brain atrophy when used in infants** as the new studies have stated. [2-4]; **Phenobarbital** is added to potentiate the spasmolytic action of Pipenzolate, also to **sedate the child**, and to relieve anxiety which usually associates colic.
3. **Cumin oil** helps to facilitate digestion and elimination of gas pains; its applied by massage into the baby's abdomen 2-3 times a day, used for babies older than 5 weeks.

2.11- Drugs for pancreatic disorders (Enzymes for digestion support)

1. The pancreas releases certain enzymes into the small intestine that are necessary for digestion of a range of foods. If the release of pancreatic enzymes is impaired (by chronic pancreatitis or cystic fibrosis), enzyme replacement therapy may be necessary.
    - They **do not cure the underlying disorder**, but it restores normal digestion.
    - **should be taken just before or with meals**, and usually take effect immediately.
    - Sometimes, the doctor will probably advise patients to eat a diet that is high in protein and carbohydrates and low in fat.
    - **Pancreatin, is a protein composed of (amylase, Lipase and protease) –** enzymes in which they respectively digest carbohydrates, fats and proteins**.**
        - Pancreatin is extracted from pig pancreas
        - **Treatment must be continued indefinitely** as long as the pancreatic disorder persists.
    - Other products contain **Cellulase**, **Lactase**, **Maltase** and other lytic enzymes.

Trade name	Dosage form	Scientific name	Concentration
Creon®	Cap	Pancreatine	150 mg , 400 mg
Spasmo-Canulase®	Bitab (multi layers)	Digestive Enzymes	----------
Trizyme®	Tab	Digestive Enzymes	----------
Combizyme®	Tab	Digestive Enzymes	----------
Digest Support®	Tab	Digestive Enzymes	----------

2.12- Gallstone solubilizing agents

1. The formation of gallstones is the most common disorder of the gallbladder, which is the storage and concentrating unit for bile, a digestive juice produced by the liver.
   - During digestion, bile passes from the gallbladder via the bile duct into the small intestine, where it assists in the digestion of fats.
   - Bile is composed of several ingredients, including bile acids, bile salts, and bile pigments; It also has a significant amount of cholesterol, which is dissolved in bile acid.
   - If the amount of cholesterol in the bile increases, or if the amount of bile acid is reduced, a proportion of the cholesterol cannot remain dissolved, and under certain circumstances this excess accumulates in the gallbladder as gallstones.

2. **Gallstones may be present in the gallbladder for years without causing symptoms**; However, if they become lodged in the bile duct, they cause pain and block the flow of bile.
   - If the bile accumulates in the blood, it may cause an attack of jaundice, or the gallbladder may become infected and inflamed.

3. **Drug treatment with Ursodeoxycholic acid is only effective against stones made principally of cholesterol** (some contain other substances), and even these take many months to dissolve.
   - Therefore, surgery and ultrasound have become widely used, especially the use of laparoscopic (keyhole) surgery; Surgery and ultrasound treatments are always used to remove stones blocking the bile duct.

4. **Ursodeoxycholic acid** is a substance that is naturally present in bile; It acts on chemical processes in the liver **to regulate the amount of cholesterol in the blood by controlling the amount that passes into the bile.**
   - Once the cholesterol level in the bile is reduced, the bile acids are able to start dissolving the stones in the gallbladder.
   - To achieve maximum effect, **Ursodeoxycholic acid treatment usually needs to be accompanied by adherence to a low cholesterol, high-fiber diet.**
   - Even after successful treatment with drugs, gallstones often recur when the drug is stopped; In some cases, drug treatment and dietary restrictions may be continued even after the gallstones have dissolved, to prevent a recurrence.
   - Although **it reduces cholesterol in the gallbladder, it increases the level of cholesterol in the blood** because it reduces its excretion in the bile; thus, **caution should be advised in patients with cardiovascular risk or with atherosclerosis.**

5. **Ursodeoxycholic acid** is also used in **primary biliary cirrhosis; i**t slows disease progression, and usually combined with **Fenofibrate** for better results in cirrhosis.
   - Also indicated for **Cholestatic liver disease**, **Alcoholic and non-alcoholic fatty liver.**
   - Sometimes combined with **Silymarin** (antioxidant and liver detoxifying agent), for the management of some liver diseases.

6. Other drug options: **Terpene mixtures** (Rawachol®) are **used for prevention only.**

Scientific name	Dosage form	Trade name	concentration
Ursodiol	Cap	Urso® , Ursoflor® , Actigall®	300 mg
	Tab	Urso 250®	250 mg
	Tab	Urso Forte®	500 mg
Chenodiol	Tab	Chenodal®	250 mg
Terpene mixtures	Cap	Rawachol®	----------

*** Ursodiol = Ursodeoxycholic Acid,** they are the same drug.

* Chenodiol = Chenodeoxycholic Acid, they are the same drug.

2.13– Drugs for Hepatic (liver) detoxification

1. The liver represents the human body's primary filtration system, one of the largest and most important human organs; in addition to storing and releasing energy from foods, it acts by converting toxins into waste products, cleansing the blood, and metabolizing nutrients and medications to provide the body with some of its most important proteins.

2. There are a lot of products in our markets with names like "Liver Guard," "Liver Rescue," and "Liver Detox" that claims they can get the liver in top shape — and help patients to feel better in the process, but unfortunately; **few ingredients have been shown to have positive results in hepatic disease** in studies, these include:
   - **Milk Thistle:** has been shown to decrease liver inflammation.
   - **Turmeric Extract:** has been shown to protect against liver injury.
   - **Artichoke leaf:** antioxidant, it may help liver cells regenerate.
   - **Dandelion root:** used to treat liver ailments
   - **S-adenosyl-L-methionine** (SAMe): antioxidant, used in alcohol liver disease.
   - **Silymarin:** antioxidant – the active metabolite of milk thistle, works by reducing the turnover of membrane phospholipids and stabilizes the cell membranes of hepatocytes.

3. But also, there have not been adequate clinical trial data in humans to recommend the routine use of these natural compounds for prevention.

Trade name	D. form	Scientific names	concentration
Simal®	Tab	Milk Thistle + Curcuma Rhizomes + Artichoke + Liquorice	90 mg + 70 mg + 90 + 50 mg
Legalon Forte®	Cap	Milk Thistle extract	173 mg
Bilirel®	Tab	Artichoke + Milk Thistle + L-Methionine + Fumitory + L-Glutathione	900 mg Comb.
ElixirSame®	Tab	S-Adenosyl L-Methionine + Folic acid + Vitamin B_{12}	200 mg + 200 mcg + 2.5 mcg

2.14– Drugs for food allergy

1. Food allergy is an immune system reaction that occurs soon after eating a certain food, even a tiny amount of the allergy-causing food can trigger signs and symptoms such as digestive problems, hives or swollen airways. In some people, a food allergy can cause severe symptoms or even a life-threatening reaction known as anaphylaxis.
2. Allergy with classical symptoms of vomiting, colic and diarrhea caused by specific foods such as shellfish should be managed by strict avoidance.
3. The condition should be distinguished from symptoms of occasional food intolerance in those with irritable bowel syndrome.
4. **Sodium Cromoglicate may be helpful as an adjunct to dietary avoidance.**
5. For a minor allergic reaction, over-the-counter or prescribed antihistamines may help reduce symptoms. These drugs can be taken after exposure to an allergy-causing food to help relieve itching or hives. However, antihistamines can't treat a severe allergic reaction.
6. For a severe allergic reaction, you may need an emergency inj. of **epinephrine**, this device is a combined syringe and concealed needle that injects single dose of medication when pressed.

For antihistamines see chapter 1, section 2

Scientific name	Dosage form	Trade name	concentration
Na^+ Cromoglicate	Cap	Nalcrom®	100 mg
Epinephrine	Prefilled Inj.	EpiPen® , Twinject®	0.15 mg/0.15 ml
		Auvi-Q®	0.3 mg/0.3 ml

2.15- Preparations for anal and rectal disorders (Hemorrhoids)

1. The most common disorder of the rectum (the last part of the large intestine) and anus (the opening from the rectum) is **hemorrhoids**, commonly known as piles; **They occur when hemorrhoidal veins become swollen or irritated**, often due to prolonged local pressure such as that caused by a pregnancy or a job requiring long hours of sitting.
   - Hemorrhoids **may cause irritation and pain**, especially on defecation, and are aggravated by constipation and straining during defecation.
   - In some cases, **hemorrhoids may bleed**, and occasionally clots form in the swollen veins, leading to severe pain, a condition called thrombosed hemorrhoids.
   - Other common disorders include **anal fissure** (painful cracks in the anus) and **pruritus ani** (itching around the anus).
2. Preparations for relief of hemorrhoids and anal discomfort fall into three main groups:
   - Drugs **act locally to relieve inflammation and irritation.**
   - Drugs which **reduces pain by relieving anal pressure and increasing blood flow.**
   - Drugs that **relieve constipation**, which contributes to the formation and discomfort from hemorrhoids and anal fissures.
3. These products are usually formulated as **ointments and creams or suppositories**.
   - Ointments and creams can be used for **internal and external hemorrhoids** while **suppositories are used for internal hemorrhoids**, however both are **usually given twice daily** (morning and evening) and **after each bowel movement.**
   - When used intra-rectally, the ointment may be inserted using an applicator or finger but the **applicator is preferred** because it can reach an area where the finger cannot reach. The applicator should be **lubricated** by the ointment before insertion.
   - Locally acting treatments often contain a **soothing agent** with **antiseptic, astringent, or vasoconstrictor properties**, such ingredients include **zinc oxide, bismuth, hamamelis (witch hazel), and Peru balsam.**
   - Some of these also include a mild local **anesthetic** such as **lidocaine**.
   - Some contain a **corticosteroid to relieve inflammation around the anus.**
     - **Steroid-containing agents should not be used for more than 14 days**, as they may cause thinning of the skin
   - May include a **barrier substance** such as **Petroleum jelly** or **Zinc oxide** and a **vasoconstrictor** such as **Epinephrine**.
   - Some products contain Calcium Channel blockers (**Amlodipine** or **Nifedipine**) or **Glyceryl tri-nitrate**; these are **added due their topical effect as vasodilators**, although they are used off-label to treat hemorrhoids
4. There is a **new tech**. that uses **cryotherapy (ice therapy)** for immediate relief of pain, itching, inflammation, and bleeding of hemorrhoids, these devices usually contains a formulated cooling liquid which when dispensed cause a controlled degree of cold directly to the internal rectal tissue, this cooling action causes the blood vessels in the affected area to shrink, which in turn soothes the swollen tissue, reducing bleeding, pain and itching.
   - An example of such devices is **Anurex®**, usually used twice daily.
5. **Neither of these treatments above can shrink large hemorrhoids**, although they may provide relief while anal fissures heal naturally.
   - Severe, persistently painful hemorrhoids that continue to be troublesome in spite of these measures may need to be removed surgically or, more commonly, by banding. This is a procedure in which a small rubber band is applied tightly to a hemorrhoid, thereby blocking off its blood supply; the hemorrhoid will eventually wither away.

Trade name	Dosage form.	Scientific name	Concentration
Procto-Glyvenol®	Cream , Supp.	Tribenosid + Lidocaine	5 gm + 2 gm
Faktu®	Supp.	Policresulen* + Cinchocaine	100 mg + 2.5 mg
Hirudoid®	Cream , Oint.	Mucopolysaccharide + Heparinoid	0.3 gm 25,000 U
Proctoheal®	Oint. , cream, Supp.	Lidocaine + Fluocinolone	20 mg + 0.1 mg
H-Formula®	Cream , Supp.	Shark liver oil + Phenylephrine + Dibucaine	3% + 0.25% + 1%
Proctosedyl®	Oint.	Cinchocaine HCL + Hydrocortisone + Framycetin Sulphate + Aesculin	5 mg 5 mg 11.89 mg 10 mg
Proctosedyl bd®	Cream	Lignocaine + Phenylephrine + Beclomethasone	2.5% + 0.1% + 0.025%
Procto-Venart®	Oint.	Ruscogenins + Prednisolone + Cinchocaine + Menthol + Zinc oxide	0.8 gm + 0.15 gm + 0.5 gm + 0.2 gm +10 gm
Anugesic HC®, Anusol HC®	Cream , Supp.	Benzyl benzoate + Bismuth Oxide + Pramocaine Zinc Oxide + Hydrocortisone	1.2% + 0.86% + 1% 12.35% + 0.5%
Xyloproct®	Oint.	Lidocaine + Hydrocortisone + Zinc Oxide + Aluminum acetate	5% + 0.275% + 18% + 3.5%
Daflon®, Pelethrocin®	Tablet	(Diosmin + Hesperidin)**	500 mg
Pelethrocin®	Cream	(Diosmin + Hesperidin)**	2% (50 gm tube)
Pilex®	Cream , Tab	Herbal preparation	----------
Rectogesic®, Myovin®	Rectal Gel	Glyceryl tri-nitrate	4 mg/gm (2%)
ANO Bliss®	Cream	Nifedipine + Lidocaine	0.3% + 1.5%
CremaGel®	Gel	Diltiazem	2%

* **Policresulen** is a topical hemostatic and antiseptic.

** **Daflon®** and **Pelethrocin®** are a micronized purified flavonoid fraction containing **(90% Diosmin and 10% Flavonoids)** expressed as **Hesperidin**, it is a **veno-tonic** (it increases venous tone) and a **vasculoprotector** (it increases resistance in small blood vessels). It is recommended **for treating venous circulation disorders** (swollen legs, pain, restless legs) and for **treating acute hemorrhoid attack.**

References

1- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition
2- Lexi-comp, Drug information handbook, 2022Ed.
3- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition.
4- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th ed.
5- Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care, 17th Edition.
6- Comprehensive Pharmacy Review for NAPLEX 8th Ed.
7- https://www.ncbi.nlm.nih.gov/pubmed/17669709
8- ACCP Updates in Therapeutics® 2021: Pharmacotherapy Preparatory Review

CARDIOVASCULAR SYSTEM

Chapter Three: Cardiovascular System

Part One: Introduction

Part Two:

3.1 – Diuretics

a. Loop Diuretics
b. Thiazide Diuretics
c. K+ sparing Diuretics
d. Osmotic Diuretics
e. Carbonic anhydrase inhibitors
f. Combination Diuretics products

3.2 – Angiotensin converting enzyme inhibitors (ACEI)

3.3 - Angiotensin II receptor antagonists (A2RAs or ARBs)

3.4 – Direct Renin inhibitor

3.5 – Neprilysin inhibitors

3.6- Beta-adrenoceptor blocking drugs (Beta-Blockers)

3.7 - Calcium-channel blockers (CCBs)

3.8 - Fixed-dose Combination Products

a. Two fixed products
b. Three (triple) dose combination products

3.9 - Centrally acting (α) agonists Vasodilators

3.10 - α-adeno receptor antagonists

3.11 - Drugs for Pheochromocytoma

3.12 - Nitrates, Vasodilators and Anti-Anginal Drugs:

a. Nitrates
b. Other Anti-Anginal drugs
c. Other Central Vasodilators
d. Peripheral Vasodilators

3.13 - Emergency Antihypertensives

3.14 - Anti-Arrhythmic Drugs

3.15 - Lipid-regulating drugs (Anti-Lipemic agents)

a. Statins
b. Fibrates
c. Bile acid Sequestrants
d. Injectable Anti-Lipemic drugs
e. Other Anti-Lipemic drugs
f. Anti-Lipemic Combos

3.16 - Drugs used to prevent Abnormal Blood Clotting

a. Antiplatelet drugs
b. Anticoagulants
c. Thrombolytic drugs (Fibrinolytics)

3.17 – Drugs used to Prevent Bleeding (anti-Fibrinolytics)

3.18 – Drugs that raise low blood pressure (Anti-Hypotensive)

3.19 - Volume Expanders (I.V. Fluids)

a. Crystalloids
b. Colloids

3.20 – Positive Inotropics

3.21 – Drugs for Pulmonary Hypertension

3.22 - Miscellaneous cardiovascular drugs

Chapter Three: Cardiovascular System

Part One:

1. Introduction:

- The blood transports oxygen, nutrients, and heat, contains chemical messages in the form of drugs and hormones, and carries away waste products for excretion by the kidneys; Blood is pumped by the heart to and from the lungs, and then in a separate circuit to the rest of the body, including the brain, digestive organs, muscles, kidneys, and skin.
- The heart is a pump with four chambers – two atria and two ventricles. The atrium and ventricle on the left side pump oxygenated blood to the body, while those on the right pump deoxygenated blood to the lungs; Backflow of blood is stopped by one-way valves at the chamber exits.
- Arteries carry blood away from the heart; Their muscle walls are elastic, contracting and dilating in response to nerve signals.
- Veins carry blood back to the heart; Their walls are thinner and less elastic than those of arteries.

2. What Can go wrong in the Cardiovascular system

- The efficiency of the circulation may be impaired by weakening of the pumping action of the heart **(heart failure)** or by irregularity of the heart rate **(arrhythmia)**.
- The blood vessels may be narrowed and clogged by fatty deposits **(atherosclerosis).**
- reduced blood supply to the brain and the extremities **(peripheral vascular disease)**, or reduced to the heart muscle **(coronary heart disease)**, causing **(Angina)**.
- Cardiovascular disorders that can be complicated by the **formation of clots** that may block a blood vessel; a clot in the arteries supplying the heart muscle is known as **coronary thrombosis**; a clot in an artery inside the brain is the most frequent cause of **(stroke).**
- abnormal high blood pressure **(hypertension)**, in which the pressure of circulating blood on the vessel walls is increased for many reasons, or abnormal low blood pressure **(hypotension).**

3. Medications Range and Types:

Because people suffering from heart disease often have more than one problem, several drugs may be prescribed at once.

- Many drugs act directly on the heart to alter the rate and rhythm of the heartbeat; These are known as **anti-arrhythmics** and include **Beta blockers (BBs)**, **Calcium channel blockers (CCBs)**, and **Digoxin**.
- Other drugs affect the diameter of the blood vessels, either by dilating them **(vasodilators)**; such as **Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II receptor blockers (ARBs),** or other direct vasodilators - to improve blood flow and reduce blood pressure
- drugs affecting the diameter of the blood vessels by constricting them **(vasoconstrictors)**.
- **Diuretics** (used in the treatment of hypertension and heart failure) increase the body's excretion of salt and water.
- **Lipid-lowering drugs** reduce blood cholesterol levels, thereby minimizing the risk of atherosclerosis.
- **Drugs to reduce blood clotting** are administered if there is a risk of abnormal blood clots forming in the heart, veins, or arteries, **Drugs that increase clotting** are given when the body's natural clotting mechanism is defective.
- **Drugs that increase the heart rate and contractility (used in emergencies).**
- **Drugs for pulmonary hypertension.**
- **Drugs that increase the blood volume (IV solution - plasma expanders).**

4. What is Blood Pressure BP

1. Blood pressure is the force exerted by the blood against the artery walls. Two measurements are taken: one indicates force while the heart's ventricles are contracting **(systolic pressure);** This reading is a higher figure than the other one, which measures the blood pressure during ventricle relaxation **(diastolic pressure)**.
2. Blood pressure varies among individuals and normally increases with age. **If a person's blood pressure is higher than normal on at least three separate occasions**, a doctor may diagnose the condition as hypertension.
3. Although hypertension does not usually cause any symptoms, severely raised blood pressure may produce headaches, palpitations, and general feelings of ill-health; It is important to reduce high blood pressure because it **can have serious consequences, including stroke, heart attack, heart failure, and kidney damage.**
4. Certain groups are particularly at risk from high blood pressure; These risk groups include diabetics, smokers, people with pre-existing heart damage, and those whose blood contains a high level of fat.
5. Blood pressure depends not only on the force with which the heart pumps blood, but also on the diameter of blood vessels and volume of blood in circulation: **blood pressure is increased either if the vessels are narrow or the volume of blood is high.**
6. Antihypertensive drugs lower blood pressure either by dilating the blood vessels or by reducing blood volume; Each type of antihypertensive acts in a different way to lower blood pressure:
   - **Centrally acting drugs** act on the mechanism in the brain that controls the diameter of the blood vessels.
   - **Beta blockers** reduce the force of the heartbeat.
   - **Diuretics** act on the kidneys to reduce blood volume.
   - **ACE inhibitors** act on enzymes in the blood to dilate blood vessels.
   - **Vasodilators** and **calcium channel blockers** act on the arterial wall muscles to prevent constriction.
   - **Alpha blockers** block nerve signals that trigger constriction of blood vessels.

5. How Does the Body Control Blood Pressure

1. Changes in blood pressure are routinely made in order to direct appropriate amounts of oxygen and nutrients to specific parts of the body. For example, when exercise demands additional supplies of oxygen to skeletal muscles, blood delivery to these muscles increases, while blood delivery to the digestive organs decreases. Adjustments in blood pressure are also required when forces are applied to the body, such as when starting or stopping in an elevator.

A) Blood pressure can be adjusted by producing changes in the following variables:

1. **Cardiac output:** which can be altered by changing stroke volume or heart rate.
2. **Resistance to blood flow in the blood vessels:** it is most often altered by changing the diameter of the vessels **(vasodilation or vasoconstriction)**; Changes in **blood viscosity** (its ability to flow) or in the length of the blood vessels (which increases with weight gain) can also alter resistance to blood flow.

B) The following mechanisms help regulate blood pressure:

1. **The cardiovascular center** provides a rapid, neural mechanism for the regulation of blood pressure by managing cardiac output or by adjusting blood vessel diameter, Located in the medulla oblongata of the brain stem.
   - **The cardiac center stimulates cardiac output by increasing heart rate and contractility**; These nerve impulses are transmitted over **sympathetic cardiac nerves.**
   - **The cardiac center inhibits cardiac output by decreasing heart rate.** These nerve impulses are transmitted over **parasympathetic vagus nerves.**

- **The vasomotor center regulates blood vessel diameter;** Nerve impulses transmitted over sympathetic motor neurons called **vasomotor nerves** innervate smooth muscles in arterioles throughout the body to maintain vasomotor tone, a steady state of vasoconstriction appropriate to the region.

- The cardiovascular center receives information about the state of the body through the following sources:
  a. **Baroreceptors:** are sensory neurons that monitor arterial blood pressure, major baroreceptors are located in the carotid sinus (an enlarged area of the carotid artery just above its separation from the aorta), the aortic arch, and the right atrium.
  b. **Chemoreceptors**: are sensory neurons that monitor levels of (CO_2 and O_2); These neurons alert the cardiovascular center when levels of O_2 drop or levels of CO_2 rise (which result in a drop in pH), Chemoreceptors are found in carotid bodies and aortic bodies located near the carotid sinus and aortic arch.
  c. **Higher brain regions**, such as the cerebral cortex, hypothalamus, and limbic system, signal the cardiovascular center when conditions (stress, fight-or-flight response, hot or cold temperature) require adjustments to the blood pressure.

2. **The kidneys provide a hormonal mechanism for the regulation of blood pressure** by managing blood volume.
   - **The renin-angiotensin-aldosterone system** of the kidneys regulates blood volume; In response to rising blood pressure, the juxtaglomerular cells in the kidneys secrete **renin** into the blood; **Renin** converts the plasma protein **angiotensinogen** to **angiotensin I**, which in turn is converted to **angiotensin II** by enzymes from the lungs. **Angiotensin II** activates two mechanisms that raise blood pressure:
     a. **Angiotensin II constricts blood vessels throughout the body** (raising blood pressure by increasing resistance to blood flow). Constricted blood vessels reduce the amount of blood delivered to the kidneys, which decreases the kidneys' potential to excrete water (raising blood pressure by increasing blood volume).
     b. **Angiotensin II stimulates the adrenal cortex to secrete aldosterone**, a hormone that reduces urine output by increasing retention of H_2O and Na^+ by the kidneys (raising blood pressure by increasing blood volume).

C) Various substances influence blood pressure; Some important examples follow:

1) **Epinephrine and norepinephrine,** hormones secreted by the adrenal medulla, raise blood pressure by increasing heart rate and the contractility of the heart muscles and by causing vasoconstriction of arteries and veins. These hormones are secreted as part of the fight-or-flight response.
2) **Antidiuretic hormone (ADH),** a hormone produced by the hypothalamus and released by the posterior pituitary, raises blood pressure by stimulating the kidneys to retain H_2O (raising blood pressure by increasing blood volume).
3) **Atrial natriuretic peptide (ANP),** a hormone secreted by the atria of the heart, lowers blood pressure by causing vasodilation and by stimulating the kidneys to excrete more water and Na^+ (lowering blood pressure by reducing blood volume).
4) **Nitric oxide (NO),** secreted by endothelial cells, causes vasodilation.
5) **Nicotine** in tobacco raises blood pressure by stimulating sympathetic neurons to increase vasoconstriction and by stimulating the adrenal medulla to increase secretion of **epinephrine and norepinephrine.**
6) **Alcohol lowers blood pressure** by inhibiting the vasomotor center (causing vasodilation) and by inhibiting the release of **Antidiuretic hormone (ADH)**; (increasing H_2O output, which decreases blood volume).
   - Cheeeeeeeeeers!

Part Two:
3.1-Diuretics

- The kidney normal filtration process takes water, salts (mainly potassium and sodium), and waste products out of the bloodstream, most of the salts and water are returned to the bloodstream, but some are expelled from the body with the waste products in the urine.
  - Diuretics interfere with this filtration process by reducing the amounts of sodium and water taken back into the bloodstream, thus increasing the volume of urine produced.
  - Modifying the filtration process in this way means that the water content of the blood is reduced; less water in the blood causes excess water present in the tissues to be drawn out and eliminated in urine.
  - Thus; **Diuretic drugs help to turn excess body water into urine**, and as the urine is expelled, the tissues become less water-swollen (less edema) and the heart action improves because it has to pump a smaller volume of blood.

- There are several classes of diuretic, each of which has different uses, modes of action, and effects; But all diuretics act on the kidneys, the organs that govern the water in the body.

- **Diuretics are most commonly used in the treatment of high blood pressure (hypertension)**; By removing a larger amount of water than usual from the bloodstream, the kidneys reduce the total volume of blood circulating; This drop in volume causes a reduction of the pressure within the blood vessels, **Diuretics are also widely used to treat heart failure** in which the heart's pumping mechanism has become weak; they do that remove fluid that has accumulated in the tissues and lungs; The resulting drop in blood volume reduces the work of the heart.

- Other conditions for which diuretics are often prescribed include **nephrotic syndrome** (a kidney disorder that causes edema), **liver cirrhosis** (in which fluid may accumulate in the abdominal cavity), and **premenstrual syndrome** (when hormonal activity can lead to fluid retention and bloating), and Less commonly, diuretics are used to treat **glaucoma** and **Ménière's disease.**

1. **They are not the 1st line of therapy in Comorbid Hypertension;** so don't use them instantly for any HT case, they may increase the blood viscosity and lead to decrease perfusion and blood supply, which may lead to serious deteriorations.

2. The principal **groups of diuretics** are as follows.

Diuretic type	examples
Thiazide and related diuretics	Hydrochlorothiazide, Chlorthalidone
Loop Diuretics	Furosemide, Bumetanide
Potassium (K^+)-sparing diuretics	Amiloride
Aldosterone antagonist	Spironolactone
Carbonic anhydrase inhibitors	Acetazolamide **(mainly for glaucoma)**
Osmotic diuretics	Mannitol **(to ↓ intracranial pressure)**

3. Diuretics are effective in lowering BP by 10-15 mm Hg in most patients.
4. Diuretics ideally **should be dosed in the morning** if given once daily and in the **morning and afternoon** if dosed twice daily to minimize the risk of night-time diuresis.
5. **Thiazide and loop diuretics** can cause **hypokalemia** while **K-sparing diuretics** can cause **retention of potassium** and therefore, they are given with thiazide or loop diuretics to minimize hypokalemia.
   - **Hypokalemia can cause confusion, weakness, and trigger abnormal heart rhythms** (especially in people taking digitalis drugs).
   - Potassium supplements or a diet that is rich in potassium (containing plenty of fresh fruits and vegetables) may be helpful.

6. **Spironolactone** has an **anti-androgenic property**, therefore:
   - **A.** It causes side effects like **Gynecomastia** and **impotence** in men.
   - It has been used for its **anti-androgenic** properties in some cases of **Acne** and for women with **Hirsutism.**
7. **Loop and thiazide diuretic may cause Sulphur allergies** in some patients, so in Patient with Sulpha allergies **switch to (Ethacrynic acid),** which don't cause (S) allergies.
   - ➢ For a synergistic effect, combine Loop diuretic with **(Metolazone)**.
8. **Thiazide diuretic cause Hyperuricemia** (raise blood levels of uric acid), thus they **are not recommended in Patient with Gout**, they may trigger Acute Gout Attacks.
9. Loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease it.
10. Because **they do not alter disease progression or prolong survival in patients with heart failure,** diuretics are not required for HF patients without fluid retention.

a) Loop Diuretics

The loop diuretics are the **drugs of choice for reducing the acute pulmonary edema** of heart failure; Because of **their rapid onset of action**.

- ➢ Act at the ascending limb of the loop of Henle in the kidney.
- ➢ They are also useful in treating **hypercalcemia** and **hyperkalemia**.
- ➢ **a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension**, or in patients with impaired renal function or heart failure.
- ➢ Large doses given into a vein **may disturb hearing** or cause a temporary hear loss.
- ➢ Loop diuretics **produce a more potent diuresis**, but a smaller decrease in peripheral vascular resistance (PVR), and **less vasodilation** than thiazide diuretics.
- ➢ The loop diuretics **are more potent than thiazides**, and **retain their effectiveness in renal insufficiency**; Thus, in most patients with HF, loop diuretics are preferred.
  - Loop diuretics usually have a "**ceiling" effect** where there is a maximum level of dosage where **further increase in dosage will not increase the clinical effect** of the drug.
- ➢ **I.V Furosemide** doses greater than 50 mg given by intravenous infusion only. Give continuously in sodium chloride 0.9%; glucose solutions are unsuitable.
  - **Intravenous dose of furosemide is twice as potent as the oral route**.
- ➢ **Torsemide** has **longer half-life** (12-16 hours) when compared to Furosemide (6-8 hours); Also, **Torsemide** has a more **rapid oral absorption** (1 hour) than Furosemide (2-3 hours).
- ➢ A dose of 40 mg of **furosemide** is equivalent to 20 mg of **Torsemide** and 1 mg **bumetanide**.
  - Thus, **Bumetanide is 40 times more potent than Furosemide.**

Scientific name	Dosage form	Trade name	Conc.
Furosemide	Tab	Lasix® , Lasimex®	40 mg
	Tab		500 mg
	Amp	Lasix®	20 mg/2 ml
	Oral Solu.	Lasidex®	10 mg/ml
Bumetanide	Tab	Burinex®	1 mg
	Amp		500 mcg/ml
Torsemide	Tab	Torem® , Demadex® Toras-Denk®	5 mg , 10 mg , 20 mg
	Tab PR	Sutril Neo®	5 mg , 10 mg
	Solu. For Inj.		10 mg/ml
Ethacrynic acid	Tab	Edecrin®	25 mg
Azosemide	Tab , Amp	Azoselic® , Daitalic®	40 mg , 80 mg (amp = 20 mg)
Piretanide	Tab	Arelix® , Eurelix®	3 mg , 6 mg
Tripamide	Tab	Normonal®	15 mg

b) Thiazide Diuretics and Thiazide-Like Diuretics

1. Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule, **they act within 1 to 2 hours of oral administration and most have a duration of action of 12 to 24 hours;** they are usually administered early in the day so that the diuresis does not interfere with sleep.
   - **Thiazides lose their effectiveness** when creatinine clearance decreases to less than 30 mL/minute; thus, Not recommended for patients with a CrCl less than 30 mL/minute because of reduced efficacy.
   - **Metolazone** is an exception in that its activity may be preserved in these patients.
   - **Chlorthalidone**, a thiazide-related compound, has a longer duration of action than the thiazides and **may be given on alternate days** to control edema.
   - **Xipamide** and **Indapamide** are chemically related to Chlortalidone.

2. **Indapamide** is claimed to lower blood pressure with less metabolic disturbances, particularly less aggravation of diabetes mellitus; (thus its preferred by endocrinologists for the Rx of HT).
   - **Lowers systolic blood pressure 54% more than HCTZ.**
   - It has a **direct vasodilation effect** (Ca^{+2} channel blocker effect).
   - In a study pairing an **ACEI (perindopril)** with **Indapamide** as the diuretic in hypertensive diabetic persons, the relative risks of diabetic micro- and macro-vascular disease were reduced in the ACEI-Indapamide combination by 9%, cardiovascular mortality by 18%, and all-cause mortality by 14%. [8]

3. **Thiazides have the unique ability to produce hyperosmolar urine,** they can substitute for antidiuretic hormone in the **treatment of nephrogenic diabetes insipidus**; the urine volume of such individuals may drop from 11 L/day to about 3 L/day when treated with these drugs.
4. **Thiazides also lower urinary calcium excretion**, making them useful in **preventing calcium-oxalate containing kidney stones**; This effect is associated with positive calcium balance and is associated with an increase in bone mineral density and reductions in fracture rates attributable to osteoporosis.
5. By a poorly understood mechanism, **thiazides directly stimulate osteoblast differentiation and bone mineral formation**, further slowing the course of **osteoporosis**.

Scientific name	D. form	Trade name	Conc.
***Chlorthalidone** **	Tab	Hygroton® , Thalitone®	50 mg
Chlorothiazide	Tab	Diuril®	250 mg , 500 mg
	I.V. Solu.		500 mg/vial
Hydrochlorothiazide	Tab , Cap	HydroDiuril®, Microzide®, Esidrix®	12.5 mg , 25 mg
Indapamide	Tab	Natrilix®, Diurex®	1.25 mg , 2.5 mg
Xipamide	Tab	Diurexan®	20 mg
Clopamide	Tab	Hypoten®, Brinaldix®	20 mg
Metolazone	Tab	Zaroxolyn®, Metenix® , Mykrox®	2.5 mg , 5 mg
Cyclopenthiazide	Tab	Navidrex®	5 mg
Bendroflumethiazide **	Tab	Aprinox® , Urizide® , Naturetin®	2.5 mg , 5 mg
Hydroflumethiazide	Tab	Saluron®	50 mg
Methyclothiazide	Tab	Enduron®	5 mg
Polythiazide	Tab	Renese®	1 mg , 2 mg , 4 mg
Trichlormethiazide	Tab	Naqua®	2 mg , 4 mg
Quinethazone	Tab	Hydromox®	50 mg

*** Chlorthalidone = Chlortalidone,** they are the same drug.
**** Bendroflumethiazide = Bendrofluazide,** they are the same drug.

Comparison between Loop diuretics and Thiazides

Agent	Oral Bioavailability (%)	Initial Daily Dose	Maximal Total Daily Dose (mg)	Duration of Action (hr)
Loop Diuretics (inhibit 20%–25% of sodium reabsorption)				
Furosemide[b]	10–67	20–40 mg daily or BID	600	6–8
Bumetanide[b]	80–100	0.5–1 mg daily or BID	10	4–6
Torsemide	80–100	10–20 mg daily	200	12–16
Ethacrynic acid[b]	100	25–50 mg daily or BID	200	6–8
Thiazide Diuretics (inhibit 10%–15% of sodium reabsorption)				
Hydrochlorothiazide	65–75	25 mg daily or BID	100	6–12
Metolazone	40–65	2.5 mg daily	20	12–24
Chlorthalidone	64	12.5–25 mg daily	100	24–72
Chlorothiazide[b]	30–50	250–500 daily or BID	2000	6–12

c) K^+ sparing Diuretics

1. On their own are **weak diuretics**, they cause retention of potassium and are therefore given with thiazide or loop diuretics as a more effective alternative to potassium supplements.
2. Administration of a potassium sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalemia.
3. **Eplerenone and Spironolactone** are also an **Aldosterone Antagonists**, they are used in the **treatment of primary hyperaldosteronism**.
4. **Spironolactone** is also used in the treatment of **Ascites in cirrhosis of the liver,** it frequently causes gastric upsets and can cause peptic ulcers.
   - **Furosemide** can be used as an adjunct with **Spironolactone** in **Ascites.**
   - Low doses of **spironolactone** are beneficial in moderate to severe heart failure**.**
   - **It's also acts as anti-androgen** that is employed for reducing elevated or unwanted androgen activity in the body.
   - Thus, it's used off-label in the **treatment of Hirsutism in females,** and **hormonal Acne.**
   - **Also used to treat hyperandrogenism in polycystic ovary syndrome (PCOS).**
5. **Eplerenone** is a **selective aldosterone antagonist,** adverse effects such as **Gynecomastia** and vaginal bleeding seem to be less likely in patients who take **Eplerenone** than in those who take **spironolactone**.
   - Clinical trials demonstrated that **Eplerenone** has antihypertensive activity that is additive with that of either an **ACEIs** or **ARBs** alone.
   - In diabetic hypertensive patients with microalbuminuria, adding **Eplerenone** to ACEIs therapy reduces proteinuria more than using the ACRIs alone, independent of effects on Blood Pressure.

Scientific name	Dosage form	Trade name	Conc.
Non-Aldosterone Antagonists (epithelial channel blockers)			
Amiloride	Tab	Midamor®	5 mg
Triamterene	Cap	Dyrenium®	50 mg , 100 mg
Aldosterone Antagonists			
Eplerenone	Tab	Inspra®	25 mg , 50 mg
Spironolactone	Tab	Aldacton®	25 mg , 50 mg , 100 mg

d) Osmotic Diuretics

Mannitol is used to **decrease (↓) intraocular pressure**, and in the **treatment of cerebral edema**, it's also **used to force diuresis in Anuria/Oliguria.**

- Used for **Preservation of perioperative renal function** in patients undergoing major vascular and cardiac surgery and in those with jaundice.
- Used for **Promotion of urinary excretion of toxic materials.**
- Also used as **Mucolytic** by inhalation route for the treatment of **Bronchiectasis** in patient suffering from **Cystic Fibrosis**.
- **In concentrations of 15% or greater, mannitol may crystallize when exposed to low temperatures.** Do not use a mannitol solution containing crystals. If such crystallization occurs, the recommended procedure for resolubilization is to heat the mannitol in a dry heat cabinet to 70 °C for flexible plastic containers with the overwrap intact or to 80 °C for glass containers with vigorous shaking; the use of a water bath is not recommended.

Other Osmotic Diuretics include: **Glycerin**, **Isosorbide** and **Urea**. (Rarely used these days).

Scientific name	Dosage form	Trade Name	Conc.
Mannitol	Inj. Solu. (infusion)	Osmitrol®	5% , 10% , 20% , 25%
Isosorbide	Oral Solu.	Ismotic®	(45%) 100 gm/220 mL
Glycerin	Oral Solu.	Osmoglyn®	(50%) 0.6 mg/ml

e) Carbonic anhydrase inhibitors (CAIs)

1. **Carbonic anhydrase inhibitors** are **weak diuretics**; they are mainly used to treat **Glaucoma**; (See chapter 12)
2. **Acetazolamide inhibits carbonic anhydrase,** an enzyme which is responsible for the small amount of active Na+ reabsorption in the proximal tubule in exchange for H+ secretion into the tubule.
   - Used with other medications to **treat high pressure inside the eye** due to certain types of **Glaucoma**; It works by decreasing the production of fluid inside the eye.
   - It is also used as **an anticonvulsant** to control certain seizures in the treatment of epilepsy.
   - It is also sometimes used to **prevent or lessen some effects in mountain climbers who climb to high altitudes**; it can decrease headache, tiredness, nausea, dizziness, and shortness of breath that can occur when climbing quickly to high altitudes
   - Used **for urine alkalizing to enhance renal secretion of uric acid and cysteine.**

Oral CAIs				
Scientific name	D. form	Trade name	Conc.	Indication
Acetazolamide	Tab	Cidamex®	250 mg	Glaucoma, Drug-induced edema, CHF edema, Mountain Sickness
	Cap ER	Diamox Sequels®	500 mg	
Methazolamide	Tab	Neptazane®	25 mg , 50 mg	Glaucoma , Altitude Sickness
CAIs as Eye Drops				
Dorzolamide	Eye drop	Trusopt® , Xola®	2%	Ocular hypertension (only)
Brinzolamide	Eye drop	Azopt®	1%	Ocular hypertension + Open-angle Glaucoma
Dorzolamide + Timolol *	Eye drop	Cosopt® , Xolamol®	0.5/2%	Open-angle Glaucoma (only)

*** Timolol** is a Beta blocker, used topically to treat Glaucoma

**** For other combination products see chapter 12, section 1.**

F) Combination Diuretics products:

- These products usually contain a **Thiazide/Loop diuretic plus a Potassium sparing diuretic**, this combination cause a balance in potassium levels.
- It is preferable to prescribe thiazides and potassium-sparing diuretics separately, the use of fixed combinations may be justified if compliance is a problem.

Trade name	Dosage	Scientific name	concentration
Loop Diuretic + K sparing Diuretic			
Lasilacton®	Tab	Furosemide + Spironolactone	40 mg + 100 mg
Frusene®	Tab	Furosemide + Triamterene	40 mg + 50 mg
Frumil®	Tab	Furosemide + Amiloride	40 mg/5 mg , 80 mg/10 mg
Buriplus®	Tab	Bumetanide + Amiloride	1 mg + 5 mg
Thiazide Diuretic + K sparing Diuretic			
Navispare®	Tab	Cyclopenthiazide + Amiloride	2.5 mg + 2.5 mg
Moduretic®	Tab	Hydrochlorothiazide + Amiloride	50 mg + 5 mg
Aldactazide®	Tab	Hydrochlorothiazide + Spironolactone	25 mg/25 mg , 25 mg/50 mg
Dyazide®	Tab	Hydrochlorothiazide + Triamterene	50 mg + 25 mg
Maxzide®	Cap	Hydrochlorothiazide + Triamterene	50 mg + 75 mg
Kalspare®	Tab	Chlorthalidone + Triamterene	50 mg + 50 mg
Epitens®	Tab	Xipamide + Triamterene	10 mg + 30 mg

3.2-Angiotensin-converting enzyme inhibitors (ACEIs)

1. Examples include (**Captopril, Enalapril, Lisinopril and Ramipril**).
2. They Inhibit the **conversion of angiotensin I to angiotensin II** (a powerful vasoconstrictor), also **prevent the degradation of bradykinin** (a vasodilator) thus Causing vasodilatation, and they **decrease aldosterone secretion**; (thus inhibiting the reduction in urine volume and the raise in blood pressure due to increased blood volume).
   - The main uses of ACE inhibitors are in the management of **heart failure, hypertension, and myocardial infarction**, also they are used for the **prevention and treatment of diabetic nephropathy.**
   - Can **provide nephroprotection and reduced CV risk** when used in diabetic patients.
   - It may take several weeks before the full antihypertensive effects of ACEIs are seen.
   - In **Heart Failure; They Decreased mortality** (about 25%–50% relative risk reduction compared with placebo depending on severity of HF)
3. Pronounced **hypotension** may occur at the start of therapy with ACEIs **(first dose hypotension)** [1]. Therefore:
   A- The **first dose s**hould preferably be given at **bedtime**.
   B- Starting dose should be low then **increased gradually**.
4. **All ACEIs (except Captopril and Lisinopril) undergo hepatic conversion to active metabolites**, so these agents may be preferred in patients with severe hepatic impairment.
5. **Renal function and electrolytes should be checked before starting ACEIs** (or increasing the dose) and monitored during treatment; Patients with an increase in serum creatinine of greater than 30% should have their ACEI therapy temporarily discontinued.

6. Adverse effects include **persistent dry cough**, **Angioedema (swelling of the face, lips and tongue), and hyperkalemia.**
   a. If **dry cough** is **annoying** to the Patient → Switch to **ARBs**.
   b. A new study suggests that **iron supplementation** may be a simple solution to the persistent **dry cough associated with the use of ACEIs**
   c. **Angioedema** is treated with an **antihistamine**, if no response occurs then stop the **ACEI**.
      - Sever angioedema is treated with **norepinephrine** S.C. inj. (EpiPen®).
   d. They are **contraindicated in pregnancy (teratogenic).**

Scientific name	D. form	Trade name	Concentration
***Enalapril** *	Tab	Renitec® , Vasotec® , Korandil®	5 mg , 10 mg , 20 mg
***Lisinopril** *	Tab	Zestril®, Privinil®,Lisnop®, Omace®	5 mg , 10 mg , 20 mg
Captopril	Tab	Capoten®, Aceprotin®, Captophen®	25 mg , 50 mg
Ramipril	Tab , Cap	Altace® , Tritace®, Rampil®	2.5 mg , 5 mg , 10 mg
Imidapril	Tab	Tanatril® , Hipertene®	2.5 mg , 5 mg , 10 mg
Delapril	Tab	Delaket®	15 mg , 30 mg
Benazepril	Tab	Lotensin®	5 , 10 , 20 , 40 mg
Fosinopril **	Tab	Monopril®	10 , 20 , 40 mg
Cilazapril	Tab	Vascace®	5 mg
Moexipril	Tab	Perdix® , Univasc®	7.5 mg , 15 mg
Perindopril	Tab	Aceon®	2 mg , 4 mg , 8 mg
	Tab	Coversyl®	2.5 mg , 5 mg , 10 mg
Quinapril	Tab	Accupril®, Accupro®	5 mg , 10 mg , 20 mg
Trandolapril	Tab	Gopten® , Mavik®	1 mg , 2 mg , 4 mg
Zofenopril	Tab	Zofecard® , Zocardis®	15 mg

* **Enalapril** is a pro-drug which is converted into **Enalaprilat.**
*** Lisinopril** is given **once daily** without regard to meal (not effected by food).
** **Fosinopril** is the only ACEI that is eliminated from both kidney and liver.

Note:

- So many ACEIs are available in the markets; which one is better than others?
  Well; the answer to that question is complicated, as each drug has some advantages over others, and that's the beauty of pharmacology and pharmacotherapy. So; below some studies that shows some of the main differences in ACEIs.

A) Comparison of the Efficacy and Safety of Different ACEIs in Patients with Chronic Heart Failure; a meta-analysis of ACEIs in patients with heart failure showed that:

1) **Enalapril** might be the best option when considering factors such as increased ejection fraction, stroke volume, and decreased mean arterial pressure. However, Enalapril was associated with the highest incidence of cough, gastrointestinal discomfort, and greater deterioration in renal function.
2) **Trandolapril** ranked first in reducing systolic and diastolic blood pressure.
3) **Ramipril** was associated with the lowest incidence of all-cause mortality.
4) **Lisinopril** was the least effective in lowering systolic and diastolic blood pressure and was associated with the highest incidence of all-cause mortality.

B) Regarding **Perindopril**: has a sustained **24 h antihypertensive activity** with **once-daily dosing**, it was able to **reverse arterial remodeling** in hypertensive patients; also, trials have shown that **reversal of abnormal endothelial function**. [9]

- In a study pairing an ACEI **(Perindopril)** with **Indapamide** as the diuretic in hypertensive diabetic persons, the relative risks of diabetic micro- and macro-vascular disease were reduced in the ACEI-Indapamide combination by 9%, cardiovascular mortality by 18%, and all-cause mortality by 14%. [8]

3.3-Angiotensin II receptor antagonists (A_2RAs or ARBs)

1. Examples include (**Candesartan, Telmisartan, losartan and valsartan**), (**Sartans**).
2. They **act as vasodilators**; They **block the binding of angiotensin II to the AT1 receptor**, thereby inhibiting the effects of angiotensin II; Their main uses are in the management of **heart failure, hypertension, diabetic nephropathy and myocardial infarction.**
   - As ACEIs; they Decrease HF-related hospitalizations and decrease death from CV causes.
3. **Unlike ACE inhibitors they do not inhibit the breakdown of bradykinin**; thus, they are **less likely to cause the persistent dry cough** which can complicate ACEIs therapy; They are a useful alternative for patients who have to discontinue an ACEI because of persistent cough.
4. Contraindicated in pregnancy **(teratogenic).**
5. ARBs have differing potencies in relation to blood pressure control, with statistically differing effects at the maximal doses. When used in clinical practice, the particular agent used may vary based on the degree of response required.
6. Some of these drugs have a **Uricosuric Effect** (increase uric acid secretion in urine); such as **Losartan.**
7. **ARBs are slightly more effective than ACEIs** in preventing angiotensin II vasoconstriction due the last can be generated from angiotensin I by non-ACE enzyme (such as chymase); **Thus, ARBs are slightly better Antihypertensives than ACEIs.**

Scientific name	D. form	Trade name	concentration
Candesartan	Tab	Atacand®, Blopress®, Amias®	8 mg , 16 mg
Losartan	Tab	Cozaar® , Losanet® , Angizar®	25 mg , 50 mg
Telmisartan	Tab	Micardis®	20 mg , 40 mg , 80 mg
Valsartan	Cap	Diovan®, Tareg® , Univan® , Arbiten®	80 mg , 160 mg
Irbesartan	Tab	Avapro® , Approvel® , Gezlan®	75 mg , 150 mg , 300 mg
Olmesartan	Tab	Benicar® , Olmetec®	5 mg , 20 mg
Fimasartan	Tab	Kanarb®	60 mg , 120 mg
Eprosartan	Tab	Teveten®	400 mg , 600 mg
Azilsartan	Tab	Edarbi®	40 mg , 80 mg

Note1:

We all know that Antagonizing angiotensin II will lower the high blood pressure; but what if we triggered it and used Agonism instead??? The answer is below:

- **Recently the US (FDA) has approved angiotensin II injection for intravenous infusion to increase blood pressure** in adults with **septic shock** or other **distributive shock.**

Scientific name	D. form	Trade name	Concentration
synthetic human angiotensin II	Injectable Solu.	Giapreza®	2.5 mg/ml, 5 mg/2 ml

Note2:

Again; so many ARBs are available in the markets; are they all the same? Here some Key elements

- **Losartan: -** The only medicine in its class **proven to lower the chance of stroke**.
  - Only ARB that has been shown to **reduce serum uric acid levels**.
  - Only ARB approved by the FDA for treating nephropathy in patients with T_2DM.
- **Valsartan: -** First ARB to receive approval in Heart Failure
  - Reverses **ventricular remodeling and Improves survival outcome** in HF.
- **Telmisartan: -** Highly selective inhibition of the angiotensin II receptor 1 (AT1)
  - **Has the longest plasma half-life** and largest volume of distribution of any ARBs.
  - **Powerful 24-hour action**, curbing the morning surge in blood pressure
  - Has PPAR-gamma activity and hence **improves Insulin sensitivity**
- **Olmesartan: - Significant mean double-digit blood pressure (BP) reductions** vs baseline at the starting dose, only once daily dose.

Note3: Anti-inflammatory effects of Olmesartan

- EUTOPIA study, stated that Treatment with **Olmesartan** significantly **reduces biochemical markers of (vascular) inflammation** in patients with essential hypertension by as early as week 6 of therapy; These anti-inflammatory properties may have beneficial cardiovascular effects in addition to their BP lowering action.

Note4: AT 1 affinity

- The specific AT1 affinity relates to how specifically attracted the medicine is for the correct receptor, in which **Valsartan has the highest affinity** (20,000 folds), and **Losartan has the Lowest affinity** (1000-fold).
  Valsartan > Olmesartan (12,500) > Candesartan > Irbesartan (8500) > Telmisartan > Losartan
- Although; **Olmesartan** and **Telmisartan** are faster than older ARBs in Blood Pressure reduction at 1 and 2 weeks.

Note5: Monotherapy at Starting doses achieving goal BP*

Drug	Olmesartan	Telmisartan	Irbesartan	Losartan	Valsartan
Daily Dose	20 mg/d	40 mg/d	150 mg/d	50 mg/d	80 mg/d
BP reduction	33%	32%	26%	16%	14%

* a retrospective analysis; note also that combination products have the similar results.

Note6: ACEIs or ARBs in DM?

A) A recent meta-analysis (Cheng et al 2014) concluded that:
- ACEIs and ARBs differentially affect the risk of all-cause mortality, CV deaths and CV events patients with diabetes.
- **ACEIs reduce the risk of mortality, myocardial infarction and heart failure, while ARBs do not affect risk of mortality and major CV events**.
- **ARBs therapy did reduce the risk of heart failure.**
- No effect on stroke was seen with either treatment.
- Based on these data, **ACEIs should be considered first-line treatment in patients with diabetes mellitus**, to reduce mortality and morbidity, **and not ARBs**.
- This study questions the 'alternative' status of ARBs in diabetics**.**

B) Although; Telmisartan and **Olmesartan:** May increase insulin sensitivity (activate PPAR Gamma), May decrease systemic inflammation (decrease CRP).

C) The Spanish researchers found that taking (ARBs or ACEIs or BBs) at bedtime rather than waiting until morning may cut the risk of developing type 2 diabetes by **more than half**. [18]

Note7: FDA approvals

1) **Valsartan** and **Candesartan** - FDA approved for heart failure, to reduce cardiovascular mortality in clinically stable patients with left ventricular failure, left ventricular dysfunction following myocardial infarction.
2) **Irbesartan** - FDA approved for diabetic nephropathy.
3) **Losartan** - FDA approved for stroke prophylaxis

Note8: Bed time is the best time to take blood pressure medication

- People with high blood pressure who take all their ARBs or ACEIs or BBs at bedtime have better controlled blood pressure and a significantly lower risk of death or illness caused by heart or blood vessel problems, compared to those who take their medication in the morning. [17]

Note9: Combination Products of ACEIs and ARBs:

- Products incorporating an ACEIs/ARBs with a thiazide diuretic or a calcium-channel blocker are available for the management of hypertension. Use of these combination products should be reserved for patients whose blood pressure has not responded adequately to a single antihypertensive drug.
  - For combination with diuretics see next page.
  - For combination with other drugs see section 8 below (2 fixed products).

Diuretics and ACE inhibitors Combos:

- Hydrochlorothiazide—captopril (Capozide®)
- Hydrochlorothiazide—benazepril (Lotensin HCT®)
- Hydrochlorothiazide—Lisinopril (Prinzide)®, (Zestoretic)®
- Hydrochlorothiazide—Enalapril (Vaseretic®)
- Hydrochlorothiazide—Fosinopril
- Hydrochlorothiazide—Moexipril (Uniretic®)

Diuretics and ARBs Combos:

HCTZ—losartan (Hyzaar®), (Angizar-H)®
Hydrochlorothiazide—Irbesartan (Avalide)®
Hydrochlorothiazide—valsartan (Co-Diovan)®
Hydrochlorothiazide—Telmisartan (Micardis plus)®
Hydrochlorothiazide—candesartan (Atacand plus)®
Hydrochlorothiazide—Eprosartan (Teveten HCT)®
Hydrochlorothiazide—Olmesartan (Benicar HCT)®
Chlorthalidone—Azilsartan (Edarbyclor) ®

3.4- Direct Renin inhibitor

1. These drugs **inhibit the first and rate-limiting step of the renin–angiotensin–aldosterone system (RAAS)**, namely the conversion of angiotensinogen to angiotensin I; This leads to a totality in absence of Angiotensin II based on the rationale that renin only acts to inhibit this step unlike Angiotensin Converting Enzyme which is also involved in other biochemical reactions.
2. The first drug in this class was **Aliskiren**, which received a marketing approval in 2007; As of January 2012, it is the only renin inhibitor on the market.
   - It can also be combined other Antihypertensives.
   - **Aliskiren** is an alternative therapy because of lack of long-term studies evaluating CV event reduction and its significant cost.
   - **Aliskiren** can cause diarrhea, especially at higher doses.
   - **Aliskiren** can **also cause cough and angioedema,** but probably less often than ACEIs.
   - **Aliskiren is contraindicated during pregnancy**.

Scientific name	D. form	Trade name	concentration
Aliskiren	Tab	Rasilez® , Tekturna®	150 mg , 300 mg
Aliskiren + Amlodipine	Tab	Tekamlo®	150 mg/5mg , 150 mg/10mg
Aliskiren + Valsartan	Tab	Valturna®	150 mg/160 mg

3.5- Neprilysin inhibitors

1. **Neprilysin** is responsible for the **degradation of atrial and brain natriuretic peptide**, thus a **Neprilysin inhibitor** act by **increasing levels of natriuretic peptides;** resulting in varied effects including increased diuresis, natriuresis, and vasodilation.
2. **Sacubitril** is a **Neprilysin inhibitor**, it's indicated **in combination with Valsartan** for the treatment of **chronic Heart failure in patient with reduced ejection fraction** (reduce risk of Cardiovascular death by 20% and reduce hospitalization rate by 21%).
3. **Sacubitril/Valsartan** Combo decreased all-cause mortality (16% relative risk reduction) and CV death (20% relative risk reduction) compared with **Enalapril** monotherapy.
   - Although a study published recently; showed that **Sacubitril/valsartan did not result in a Significant lower rate of hospitalizations for heart failure and death** from cardiovascular causes among patients **with heart failure** and an **ejection fraction of 45% or higher.** [16]
   - This study shows that Sacubitril/Valsartan Combo is **useful only in heart failure with low ejection fraction.**
4. Because of the risk of **angioedema**, patients should not start taking **Sacubitril** within 36 hours of taking their last ACEI dose.
5. **Omapatrilat**: also, a **Neprilysin inhibitor** (as well as an **ACEI** and aminopeptidase P inhibitor), was studied in both hypertension and HF, but **terminated because of an unacceptable incidence of angioedema** (3-fold increased risk of angioedema as compared with Enalapril).

Scientific name	D. form	Trade name	concentration
Sacubitril + Valsartan	Tab	Entresto®	(24 mg + 26 mg), (49 mg + 51 mg), (97 mg + 103 mg)

3.6-Beta-adrenoceptor blocking drugs (Beta-Blockers)

a. Beta blockers are drugs that **interrupt the transmission of stimuli through beta receptors** of the body; and since the actions that they block originate in the adrenal glands they are called beta adrenergic blocking agents.

b. There are 3 types of beta receptor in the body: beta1, beta2, beta3; **Beta1 receptors are located mainly in the heart muscle**; **Beta2 receptors in the airways and blood vessels**; **Beta3 are located on adipocytes** and are thought to be involved with fatty acid metabolism, Cardioselective drugs act mainly on beta1 receptors: non-Cardioselective drugs on all types.

c. By occupying the beta receptors, in different parts of the body, **beta blockers nullify the stimulating action of norepinephrine (noradrenaline)**, the main "fight or flight" hormone; and as a result, **they reduce the force and speed of the heart beat** and **prevent the dilation of the blood vessels** surrounding the brain and leading to the extremities, as a summery:

- **In Heart:** Slowing of the heart rate and reduction of the force of the heart beat reduces the workload of the heart (means that less oxygen is required), thus helping to prevent angina and abnormal heart rhythms; This action may worsen heart failure, however.
- **In Lungs**: Constriction of the airways, thus may provoke breathlessness in asthmatic patients or those with chronic bronchitis.
- **In Brain:** Dilation of the blood vessels that surround the brain is inhibited, thereby preventing migraine.
- **In Blood vessels:** causing constriction, thus may cause coldness of the hands and feet and erectile dysfunction.
- **In Eye**: Beta blocker eye drops reduce fluid production, lowering pressure inside the eye.
- **In Muscles**: Muscle tremor caused by anxiety or over activity of the thyroid gland is reduced.

d. They **lower Blood pressure** due to **reduction in the rate and force** at which the heart pumps blood around the body.

1. Examples include **(Atenolol, Bisoprolol, Carvedilol, Metoprolol, and Propranolol).**

2. Beta blockers are used in the management of:

- **a.** Cardiovascular disorders such as **hypertension**, **angina pectoris**, **cardiac arrhythmias, myocardial infarction**, and some of them are used for **heart failure**.
- **b.** They are also given to control symptoms of **sympathetic over activity**, **anxiety states**, **hyperthyroidism** (in which all condition has a hypersecretion of **norepinephrine).**
- **c.** Used in the prophylaxis of migraine, **(Propranolol).**
- **d.** Some Beta blockers used as eye drops **(Timolol)** to reduce raised intra-ocular pressure in **Glaucoma**.

3. **Bisoprolol, Carvedilol, Metoprolol (Succinate)** and **Nebivolol** are the beta-blockers that are **used to treat heart failure** (**other beta- blockers are contraindicated in heart failure**). (4-5)

- When used in HF they **decrease mortality** (about 35%), and **decreased hospitalizations** (about 25%) compared with placebo.
- Should be initiated only when HF symptoms are stable and patients are euvolemic.
- **higher β-blocker doses are associated with greater mortality reduction**; Therefore, if hypotension alone is the problem, try reducing the ACEI (or another antihypertensive) first.

4. **Esmolol** is a relatively Cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of **supraventricular arrhythmias**.

5. **Sotalol** is a non-Cardioselective beta-blocker with additional class III **anti-arrhythmic activity**, that is used for **prophylaxis and treatment in ventricular & supraventricular arrhythmias**.

6. When used for heart failure or Hypertension, β-blockers should be started in very low doses with slow upward dose titration every one or two weeks (**start low, go slow**) example:

Carvedilol start with 3.125 mg ⟶ 6.25 mg ⟶ 12.5 mg ⟶ 25 mg

7. Beta-blockers can **precipitate bronchospasm** and should therefore usually be **avoided in patients with a history of asthma, or use Cardioselective Beta blockers**.

8. Beta-blockers **can affect carbohydrate metabolism**, causing hypoglycemia or hyperglycemia in patients with or without diabetes; **they can also interfere with metabolic and autonomic responses to hypoglycemia, thereby masking symptoms, such as tachycardia.**
9. Beta-blockers, especially when combined with a thiazide diuretic, **should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.**
10. **Abrupt cessation of β-blocker therapy should be avoided** (abrupt discontinuation of *β*-blockers may be associated with tachycardia, in addition to increased BP). For these reasons, it is always prudent to **taper the dose gradually** over 1 to 2 weeks before discontinuation.
11. **At higher doses, β1 selectivity is lost.**
12. **Some Beta Blockers Properties:**
    A. **Water solubility:** the major β-selective agents can be remembered by the mnemonic PAANTS = **(Pindolol, Atenolol, Acebutolol, Nadolol, Timolol, and Sotalol)**. Water soluble agents tend to be renal excreted **(thus C.I. in renal failure)**, have longer half-lives, are less able to cross the blood brain barrier and **are less likely to cause CNS side effects**, **others are lipid soluble which can cause nightmares (cross blood brain barrier).**

    B. **Intrinsic sympathomimetic activity** (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors. **(Oxprenolol, Pindolol, Acebutolol, Carteolol, Mepindolol and Celiprolol)** have intrinsic sympathomimetic activity; they tend to **cause less bradycardia** than the other beta-blockers and may also **cause less coldness of the extremities.**

    C. **Vasodilation effect: (Labetalol, Celiprolol, Carvedilol, and Nebivolol)** are beta-blockers that have an arteriolar vasodilation action, by different mechanisms, and thus lower peripheral resistance.

    D. **Membrane stabilizing activity:** or local Anesthetic activity **(Acebutolol, Betaxolol, Pindolol and Propranolol)** due their ability to block Na^+ channels.

    E. **Anti-Oxidant effect: (Carvedilol and Nebivolol)** only.

    F. **Calcium Channel Blocking effect: (Carvedilol, Betaxolol and Bevantolol)**
13. The β-blockers **decrease libido and cause impotence**, Drug-induced sexual dysfunction can severely reduce patient compliance, Beta-blockers are **also associated with fatigue, coldness of the extremities** (may be less common with those with ISA, see above), **and sleep disturbances with nightmares** (may be less common with the water-soluble beta-blockers, see notes above).
14. Obviously, **BBs are not the same**, below some more interesting facts:

A) A new classification **divides BBs into three different generations**, the 1st generation being non-selective, the 2nd generation being beta1-selective (Cardioselective), and the 3rd generation showing additional vasodilating effects.

B) Some BBs exert additional properties independent of beta-receptors:

1) **Propranolol**, its D-enantiomer **inhibits the conversion of Thyroxin (T4) to Triiodothyronine (T3)**, whereas only the L-enantiomer shows beta-blocking effects.

2) **Nebivolol**, the drug with the **highest beta1-selectivity**, it **causes NO-derived vasodilation**, this vasodilating effect has clinical relevance since it has been shown that the beta-blocking potency of 5 mg **Nebivolol** is comparable to that of 25 mg **Atenolol**, whereas the blood pressure lowering effect of 5 mg **Nebivolol** is comparable to that of 100 mg **Atenolol**. [10]
   - Nebivolol **decreases the incidence of new onset diabetes** compared to placebo. [11]
   - Nebivolol **does not decrease nocturnal melatonin release** (cause less sleeplessness).
   - Plasma concentrations of Nebivolol do not increase during exercise.

3) **Carvedilol**, has an additional **blocking effects on adrenergic alpha1-receptors**; Thus, this drug exerts an additional effect independent of beta-blockade that, on the one hand, **increases its blood pressure lowering effect** and, on the other hand, may **decrease potential side effects resulting from beta-blockade** since the decrease of blood pressure caused by alpha-blockade may cause a refractory increase of sympathetic tone, thus reducing beta-blocking (side) effects such as bradycardia, bronchial constriction, impotence, and metabolic side effects.
   - **Carvedilol** shows a favorable metabolic effect such as an **increase of the insulin sensitivity index** and a **decrease in triglyceride plasma concentrations.** (12)
   - Carvedilol **does not reduce nocturnal melatonin release** (cause less sleeplessness).
   - Carvedilol shows an **increase in heart rate in healthy subjects** with the administration of increasing doses of the drug, thus being a unique finding in the class of **beta-blockers that increasing doses may cause increasing heart rates.** (13,14)

4) **Bisoprolol,** has the **lowest drug-drug interaction profile** compared with other BBs, thus, making it a very good option when the patient has many medications.
   - **Comes in 2nd place in Beta1-selectivity, after Nebivolol.**
   - Bisoprolol **inhibits renin secretion by about 65%.**

Scientific name	D. form	Trade name	Conc.
Cardio-Selective β blockers			
Atenolol	Tab	Tenormin® , Novaten® ,Vascoten®	25 mg , 50 mg , 100 mg
	Amp	Tenormin®	0.5 mg/ml (10 ml amp)
Bisoprolol	Tab	Concor cor® , Zebeta®	1.25 mg , 2.5 , 5 , 10 mg
Metoprolol (Tartrate) *	Tab	Hypopresor® , Lopress®	50 mg , 100 mg , 200 mg
	Amp	Betaloc®	1 mg/ml (5 ml amp)
Metoprolol (Succinate) *	Tab	Betaloc® , Toprol XR®	50 mg , 100 mg , 200 mg
		MetoHexal®	23.75 mg , 50 mg , 100 mg
Nebivolol	Tab	Bystolic® , Nebilet®	2.5 mg , 5 mg , 10 mg
Landiolol	Amp	Onoact®	50 mg/amp
Tilisolol	Tab	Selecal®	10 mg , 20 mg
Non-Cardio-Selective β blockers			
Propranolol	Tab	Inderal® , Becardin®	10 mg , 40 mg
	Cap	Innopran®	80 mg , 120 mg , 160 mg
	Amp	Inderal®	1 mg/1 ml
Nadolol	Tab	Corgard®	40 mg , 80 mg
Mixed α and β blockers			
Carvedilol	Tab	Dilatrend® , Coreg®	3.125 mg , 6.25 mg , 12.5 mg , 25 mg
	Cap	Coreg CR®	10 mg , 20 mg , 40 mg , 80 mg
Bucindolol	Tab	Gencaro®	50 mg
Labetalol	Tab	Trandate®, Lobet®	50 , 100 , 200 , 400 mg
	Inj. Amp	Trandate®	5 mg /ml (20 ml amp)
β blockers with Intrinsic sympathomimetic activity (ISA)			
Acebutolol	Cap	Sectral®	100 mg , 200 mg , 400 mg
Pindolol	Tab	Visken®	5 mg , 10 mg , 15 mg
Celiprolol	Tab	Celectol®	200 mg , 400 mg
Penbutolol	Tab	Levatol®	20 mg , 40 mg
Oxprenolol	Tab	Trasicor®	20 mg , 40 , 80 , 160 mg

Cardio-selective

Other β blockers			
Betaxolol	Tab	Kerlone®	10 mg , 20 mg
Esmolol	Inj.	Brevibloc®	10 mg/ml (10 ml vial)
Sotalol	Tab	Sotacor®	20 mg , 40 mg , 80 mg
Timolol	Tab	Betim®	10 mg
β blockers: Dosage Form As Drops			
Betaxolol	Eye drop	Betoptic®	0.5% , 0.25%
Timolol	Eye drop	Timolol® , Ophtamolol® , Timoptof®	0.5% , 0.25%
Carteolol	Eye drop	Ocupress® , Carteol®	1% , 2%
Levobunolol	Eye drop	Betagan®	0.5% , 0.25%
Metipranolol	Eye drop	Optipranol®	0.3%

*** Metoprolol Succinate** is an extended-release medication, and **Metoprolol Tartrate** is an immediate-release medication.

➢ For combination with diuretics ↦ For combination with other drugs see section 8 below (2 fixed products)

Diuretics and Beta-Blockers Combos:
- Bendroflumethiazide—Nadolol (Corzide®)
- Chlorthalidone—atenolol (Tenoretic®)
- Hydrochlorothiazide—propranolol (Inderide®)
- Hydrochlorothiazide—metoprolol (Lopressor HCT®)
- Hydrochlorothiazide—bisoprolol (Ziac®)

3.7- Calcium-channel blockers (CCBs)

- They dilate blood vessels by **relaxing the muscle layer in the blood vessel walls and heart (they does this by blocking the entry of calcium into the cells of the heart and blood vessels),** thus prevents constriction (as Vasodilators); Blood is more easily pumped through the dilated vessels; this reduces the strain on the heart, they also improve blood flow and thus the oxygen supply.

1. **CCBs include:**
   A. **Dihydropyridine (DHP) CCBs (ex: Amlodipine, Nifedipine):** They have a greater **selectivity for vascular smooth muscle** than for cardiac muscles and therefore their main effect is vasodilatation; **(They don't dilate veins).**
   B. **Non-Dihydropyridine CCBs (ex: Diltiazem and Verapamil):** They have **selectivity for both Cardiac and vascular smooth muscle.**
2. **The main use of CCBs** is in the management of **Angina Pectoris and Hypertension** (**both types of CCBs**); some are also used in **cardiac arrhythmias** (**non-Dihydropyridine CCBs).**
   - ➢ All CCBs are valuable in **angina associated with coronary vasospasm**.
   - ➢ Some CCBs are used as **Tocolytics** to delay preterm delivery (**Nifedipine**), See chapter 7
   - ➢ Some CCBs are used **Topically to treat Hemorrhoids**, see chapter 2; section 15.
3. **Nifedipine** is a **short acting;** therefore, it is commonly formulated as **sustained release (SR) formulation** (long acting dosage form).
   - ➢ **Nifedipine** is also indicated for **Raynaud's syndrome**, postponement of premature labor, and **hiccup** in palliative care.
4. **Nimodipine** is related to **Nifedipine** but the smooth muscle relaxant effect preferentially acts on cerebral arteries; It's approved in the **prevention and treatment of vascular spasm following aneurysmal subarachnoid hemorrhage**.
5. When using CCBs (especially Dihydropyridine CCBs); a **Dose-dependent peripheral vasodilatation occurs,** leading to **pedal edema, ankle edema (swelling), dizziness, headache, eye pain, and facial flushing.**
   - ➢ The **peripheral edema** can be reduced by combining with an **ACEI** or an **ARB**.
   - ➢ **Edema** may **respond only partially to diuretics**.

6. **Ankle edema** is a troublesome side effects, more than 69% of patients may discontinue their CCBs therapy due ankle edema; **so, is there a CCB without that side effect?**
   - **Unfortunately, No …** But the risk of **peripheral edema with Lipophilic Dihydropyridine (DHP) CCBs was 57% lower than with traditional DHP CCBs**.
     - Lipophilic DHP CCBs include: (Manidipine, Lacidipine, Lercanidipine, Nicardipine).
   - Also, the **Incidence of peripheral edema in patients on DHPs was 12.3% compared with 3.1% with non-DHPs (Diltiazem, Verapamil).**
7. **Chronic use of CCBs can lead to gum hyperplasia.**
8. Dihydropyridine CCBs can **worsen proteinuria** in patients with nephropathy.
9. **Verapamil** and **Diltiazem** should be **avoided in heart failure** because they may further depress cardiac function and cause clinically significant deterioration.
   - **Verapamil** is used also as **prophylaxis of cluster headache and prevention of Migraine.**
   - **Verapamil** can **prevent diabetes and enhance β-cell survival and function**; (inhibits thioredoxin-interacting protein, that leads to the death of the pancreatic beta cell). [19]
   - **Diltiazem** has a **less negative inotropic** effect than **Verapamil** and significant myocardial depression occurs rarely.
   - **Diltiazem** and **Verapamil** are **useful in diastolic HF** (HF with preserved ejection fraction).
   - For **supraventricular tachycardia (PSVT)**, **Diltiazem** appears to be as effective as **Verapamil** in treating re-entrant supraventricular tachycardia.
   - **Diltiazem** is also indicated for **Atrial fibrillation** or **Atrial flutter**; The initial bolus should be 0.25 mg/kg, intravenous (IV).

Scientific name	Dosage form	Trade name	concentration
Dihydropyridine CCBs			
Amlodipine	Tab	Istin® , Amlong® , Amady®	2.5 mg , 5 mg , 10 mg
	Cap	Norvasc®	5 mg
Nifedipine	Tab	Adalat® , Epilat® , Adakate®	10 mg , 20 mg
	Tab Ex R	Procardia® , Adalat XL®	30 mg , 60 mg , 90 mg
Nimodipine*	Tab	Nimotop®	30 mg
	Vial	Nimotop®	200 mcg
Manidipine	Tab	Artedil®	10 mg , 20 mg
Nisoldipine	Tab	Sular®	8.5 mg , 17 mg , 34 mg
Clevidipine	Infusion Solu.	Cleviprex®	0.5 mg/ml
Isradipine	Tab	Prescal® , DynaCirc®	2.5 mg
Lacidipine	Tab	Motens® , Lacipil®	2 mg , 4 mg
Lercanidipine*	Tab	Zanidip®, Lercadip®	10 mg , 20 mg
Felodipine	Tab , Tab XR	Plendil® , Cabren®	2.5 mg , 5 mg , 10 mg
Nicardipine	Cap	Cardene®	20 mg , 30 mg
Nitrendipine	Tab	Baypress® , Cardif®	10 mg , 20 mg
Non-Dihydropyridine CCBs			
Diltiazem	Cap SR	Mono-Tildiem®	200 mg , 300 mg
	Tab	Tildia®, Progor®, Altiazem®,	60 mg , 90 mg , 120 mg
Verapamil	Tab	Danistole® , Calan® , Isoptin®	40 mg , 80 mg
	Cap SR	Verapress® , Univer®	120 mg , 180 mg , 240 mg
Gallopamil **	Tab , Cap	Procorum®	50 mg
Fendiline	Tab , Cap	Sensit® , Difmecor®	50 mg , 75 mg , 100 mg

*** Nimodipine** can pass the blood-brain barrier and is used to prevent cerebral vasospasm.

* **Lercanidipine** prevents renal damage induced by angiotensin II and demonstrates anti-inflammatory, antioxidant, and anti-atherogenic properties through an increasing bioavailability of endothelial nitric oxide; its displays a **renal protection** with a significant decrease of microalbuminuria and improvement of creatinine clearance.

** **Gallopamil** is an analog of **Verapamil**.

3.8 - Fixed-dose Combination Products

A) Two fixed products:

Several fixed-dose combination products are available; **their use can reduce the number of tablets or capsules taken by patients.** This has been demonstrated to **improve adherence compared with using two separate single-drug products**. Improved adherence may increase the likelihood of achieving goal BP values.

Trade name	D. form	Scientific name	concentration
Diuretics + ACEIs			
Delapride®	Tab	Indapamide + Delapril	2.5 mg/15 mg , 2.5 mg/30 mg
Coversyl Plus®	Tab	Indapamide + Perindopril	1.25 mg/5 mg , 2.5 mg/10 mg
CCBs + ACEIs			
Coveram®, Prestalia®	Tab	Amlodipine + Perindopril	5mg/5mg , 5mg/10mg, 10mg/10mg
Lotrel®, Amlobenz®	Tab	Amlodipine + Benazepril	5mg/10mg , 10mg/20mg
Hipril-A®	Tab	Amlodipine + Lisinopril	5mg/10mg
Eneas®	Tab	Nitrendipine + Enalapril	10mg/20mg
Lexxel®	Tab	Felodipine + Enalapril	5mg/5mg
Triapin®	Tab	Felodipine + Ramipril	2.5mg/2.5mg , 5mg/5mg
Vivace®	Tab	Manidipine + Delapril	10 mg/30 mg
Tarka®	Tab	Verapamil + Trandolapril	180mg/2mg , 240mg/2mg
CCBs + ARBs			
Exforge®	Tab	Amlodipine + Valsartan	5 mg/80 mg , 5mg/160mg , 10mg/160mg
Twynsta®	Tab	Amlodipine + Telmisartan	5mg/40mg , 10mg/40mg
Azor® , Sevikar®, ***Vocado®***	Tab	Amlodipine + Olmesartan	5mg/20mg , 10mg/20mg 10mg/40mg
CCBs + BBs			
Amlong-A®	Tab	Amlodipine + Atenolol	5mg/50mg
Tenif® , Beta-Adalat®	Cap	Nifedipine + Atenolol	20mg/50mg
Logimax®	Tab	Felodipine + Metoprolol	5 mg/47.5 mg , 10 mg/95 mg
ARBs + BBs			
Byvalson®	Tab	Valsartan + Nebivolol	80mg/5mg

B) Three Fixed-dose combination products (Triple products)

Trade name	D. form	Scientific name	concentration
Exforge HCT®	Tab	Amlodipine + Valsartan + Hydrochlorothiazide	(5 mg/160 mg/12.5), (10 mg/160 mg/12.5 mg), (5 mg/160 mg/25 mg), (10 mg/160 mg/25 mg)
Tribenzor®, Sevikar HCT®, ***Vocado HCT®***	Tab	Amlodipine + Olmesartan + Hydrochlorothiazide	(5 mg/20 mg/12.5 mg), (5 mg/40 mg/25 mg) (10 mg/40 mg/25 mg)
Triplixam®, Coveram Plus®	Tab	Amlodipine + Perindopril + Indapamide	(5 mg + 5 mg + 1.25 mg), (10 mg + 5 mg + 1.25 mg), (10 mg + 10 mg + 1.25 mg)
Amturnide®	Tab	Amlodipine + Aliskiren + Hydrochlorothiazide	5mg/10mg/12.5 mg , 10mg/20mg/25 mg

3.9 - Centrally acting (α) agonists Vasodilators:

1. They have been used in the past as alternatives to initial Antihypertensives, their use in mild-to-moderate hypertension has been reduced, and they are used today in Emergency Hypertension or in Hypertension Crisis.
2. **Methyldopa** is commonly used in pregnancy associated Hypertension.
   - Methyldopa has dual mechanisms, first its converted into a false transmitter in the CNS, leading to central α2 agonism, causing a decrease in norepinephrine and renin and ↓ BP; also, it acts as a competitive inhibitor of dopa-decarboxylase (that converts L-dopa to dopamine).
   - Common side effects of **Methyldopa** include orthostatic hypotension, fluid accumulation (in the absence of a diuretic), and **rebound hypertension on abrupt withdrawal;** Sedation is a common finding upon initiating therapy and when increasing doses; Fever and other flu-like symptoms occasionally occur.
3. **Minoxidil** should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilatation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention; For this reason, the addition of a beta-blocker and a diuretic (usually furosemide, in high dosage) are mandatory.
   - **Minoxidil** is being less used these days as an emergency antihypertensive.
   - **Its cause Hypertrichosis (increased hair growth) as a side effect,** thus it's used topically to reverse hair fall and boldness. (see dermatology chapter for more info).
4. **Clonidine** does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the **treatment of hypertension complicated by renal disease.**
   - Also Used for **prevention of recurrent migraine** and **prevention of vascular headache**.
   - Clonidine has the **disadvantage** that sudden withdrawal of treatment may **cause severe rebound hypertension**, (causing a life-threatening hypertensive crisis).
5. **Hydralazine** is used to treat moderately severe hypertension; it is almost always administered in combination with a β-blocker, such as Propranolol, Metoprolol, or Atenolol (to balance the reflex tachycardia) and a diuretic (to decrease sodium retention).
   - **Hydralazine infusion is used for hypertensive emergencies** (including during pregnancy).
   - **Hydralazine in combination with nitrate is also used for heart failure** (patients who cannot tolerate an ACEI or ARB, or in whom they are contra-indicated, may be given Isosorbide dinitrate (ISDN) with hydralazine; The combination may be considered in addition to standard therapy with an ACEI and a β-blocker in patients who continue to remain symptomatic.
   - **A lupus-like syndrome can occur with high dosage (usually occurs as sudden weight loss, arthritis, and un-explained pain),** it is reversible on discontinuation of the drug.
6. **Moxonidine** is licensed for mild to moderate essential hypertension; It may have a role when thiazides, calcium-channel blockers, ACEIs, and beta-blockers are not appropriate or have failed to control blood pressure.
7. **Nitroprusside** cause excessive plasma concentration of the Cyanide (because its molecule contains CN); causing tachycardia, sweating, hyperventilation, arrhythmias, metabolic acidosis.

Scientific name	Dosage form	Trade name	concentration
Hydralazine	Tab	Apresoline®	25 mg , 50 mg
	Inj.	Apresoline®	20 mg/1ml
Methyldopa	Tab	Aldomet®	250 mg , 500 mg
Nitroprusside Na+	Vial	Nipride®, Nitropress®	50 mg
Clonidine	Tab	Catapress®, Duraclon®	0.1 mg , 0.2 mg , 0.3 mg
	Inj. Solu.		100 mcg/ 1ml
Minoxidil	Tab	Loniten®	5 mg , 10 mg
Moxonidine	Tab	Physiotens®, Cynt®	200 mcg , 400 mcg
Guanfacine *	Tab	Tenex®, Intuniv®	1 mg , 2 mg , 3 mg , 4 mg

*** Guanfacine is commonly mistaken with Guaifenesin (expectorant), so be careful.**

*** Guanfacine** in Extended release tab (Intuniv®) is approved for the treatment of attention-deficit hyperactivity disorder **(ADHD)** in people ages 6–17 years, **also used as an Anxiolytic.**

Combination products of Centrally acting (α) agonists Vasodilators			
Scientific name	D. form	Trade name	concentration
Methyldopa + Hydrochlorothiazide	Tab	Aldomet Plus®	(250 mg + 15 mg), (250 mg + 25 mg)
Clonidine + Chlorthalidone	Tab	Clorpres® , Combipres®	(0.1 mg + 15 mg), (0.3 mg + 15 mg)
Hydralazine + Hydrochlorothiazide	Cap	Apresazide®	(25 mg + 25 mg), (50 mg + 50 mg)
Hydralazine + Isosorbide dinitrate	Tab	BiDil®	37.5 mg + 20 mg

3.10- selective α1 adeno receptor antagonists

1. They act by blocking nerve signals that trigger constriction of blood vessels; **Only Prazosin, terazosin**, **Doxazosin are FDA approved to treat hypertension**; this group of drugs is available for hypertensive patients who have not responded to initial antihypertensive therapy.
   - **Prazosin, terazosin and Doxazosin** have α-blocking and vasodilator properties.
   - **Prazosin** cause slight improvement in symptoms of **Raynaud's disease.**
   - **Prazosin** is used in treating patients with **posttraumatic stress disorder (PTSD) induced nightmares** due to its ability to block the effects of norepinephrine.
2. **Others are used for the treatment of Benign Prostate Hyperplasia (BPH).**
3. These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate; Thus, long-term tachycardia does not occur, but salt and water retention does.
4. Concomitant use of a β-blocker may be necessary to blunt the short-term effect of reflex tachycardia.
5. **First-dose phenomenon with α1 adeno receptor antagonists:** A syncopal episode may occur within 30 to 90 minutes of the first dose; similarly associated are postural hypotension, nausea, dizziness, headache, palpitations, and sweating. To minimize these effects, the first dose should be limited to a small dose (1 mg) and administered just before bedtime.
6. **Yohimbine**, a selective **α2 receptor blocker**, it increases norepinephrine; thus, **raises blood pressure and heart rate**; its medically used for general sexual problems in both men and women, **arouse sexual excitement, for erectile dysfunction (ED)**, sexual problems caused by selective-serotonin reuptake inhibitors (SSRIs).
   - It acts by **increasing blood flow and nerve impulses** to the penis or vagina.

Scientific name	D. form	Trade name	concentration
Doxazosin	Tab	Cardura® , Cardosyr®	1 mg , 2 mg , 4 mg
	Tab MR	Cardura XL®	8 mg
Prazosin	Tab	Minipress® , Hypovase® , Prazo®	1 mg , 2 mg , 5 mg
Prazosin + Polythiazide	Cap	Minizide®	1 mg/0.5 mg , 2 mg/0.5 mg
Terazosin	Tab	Hytrin®	1 mg , 2 mg , 5 mg , 10 mg
Alfuzosin	Tab	Xatral®	2.5 mg , 5 mg , 10 mg
Tamsulosin*	Cap	Flomax® , Omnic®	0.4 mg
Silodosin	Cap	Rapaflo® , Urorec®	4 mg , 8 mg
Indoramin	Tab	Doralese®	25 mg
α2 receptor blocker			
Yohimbine	Cap	Aphrodien®	2.5 mg , 6 mg , 10 mg

* **Tamsulosin**: α1-blocker with greater selectivity for prostate muscle, has been used in the treatment of benign prostatic hyperplasia. It is also used to dilate the ureter and helps to pass kidney stones. (it may ↓ outlet resistance and ↓ leak point pressures in patient with neurogenic bladder [2]

** **See chapter 8 for benign prostatic hyperplasia.**

3.11 – Drugs for Pheochromocytoma (non-selective α blockers)

1. **Pheochromocytoma (PCC)** is a neuroendocrine tumor of the medulla of the adrenal glands (originating in the chromaffin cells), or extra-adrenal chromaffin tissue that failed to involute after birth and secretes high amounts of catecholamine's, mostly norepinephrine, plus epinephrine to a lesser extent; **Sign and symptoms include:** Elevated heart rate, Palpitations, Anxiety (resembling that of a panic attack), Diaphoresis (excessive sweating), and Headaches.
   - Long-term management of Pheochromocytoma involves surgery; However, surgery should not take place until there is adequate blockade of both alpha and beta-adrenoceptors; the optimal choice of drug therapy remains unclear. Alpha-blockers are used in the short-term management of hypertensive episodes in Pheochromocytoma.
   - Once alpha blockade is established, tachycardia can be controlled by the cautious addition of a beta-blocker (a cardio selective beta-blocker is preferred).
2. **Phenoxybenzamine** is a very powerful **alpha-blocker (non-selective irreversible)**, its effective in the management of **Pheochromocytoma** but it has many side-effects.
   - Also indicated for **Bladder Management Micturition disorders**.
3. **Phentolamine** is a short-acting **alpha-blocker (non-selective)** used mainly during surgery of Pheochromocytoma, also used for **hypertensive emergencies**, **hypertensive crisis**.
   - Used for **Erectile Dysfunction** by **intracavernous injection** (a direct inj. To the penis!).

Scientific name	Dosage form	Trade name	concentration
Phenoxybenzamine	Cap , Inj. Solu.	Dibenzyline®	10 mg (cap) , 50 mg/ml (inj.)
Phentolamine	Inj. Solu.	Regitine® , Oraverse®	10 mg/ml
Metyrosine	Cap	Demser®	250 mg
Tolazoline	Inj. Solu.	Priscoline®, Tolazil®	100 mg/ml

4.12- Nitrates, Vasodilators and Anti-Anginal Drugs:

a. **Angina** is **chest pain produced when insufficient oxygen reaches the heart muscle**; This is usually caused by a **narrowing of the blood vessels** (coronary arteries) that carry blood and oxygen to the heart muscle, in the most common type of angina (classic angina), pain usually occurs during physical exertion or emotional stress. In variant angina, pain may also occur at rest.
   - In classic angina, the narrowing of the coronary arteries results from deposits of fat, known as atheroma, on the walls of the arteries. In the variant type, however, angina is caused by contraction (spasm) of the muscle fibers in the artery walls.

b. Frequent episodes of angina can be disabling and, if left untreated, can **lead to an increased risk of a heart attack**; Drugs can both **relieve angina attacks and reduce their frequency**, people who suffer only occasional episodes are usually prescribed a rapid acting drug to take at the first signs of an attack, or before an activity that is known to bring on an attack (**Glyceryl trinitrate**).
   - Nitrates **dilate blood vessels by relaxing the muscle layer** in the blood vessel walls

c. If attacks become more frequent or more severe, regular preventative treatment may be advised. Beta blockers, long-acting nitrates, and calcium channel blockers are used as regular medication to prevent attacks; **Drugs can often control angina for many years**, but they cannot cure the disorder. When severe angina cannot be controlled by drugs, then surgery to increase the blood flow to the heart may be recommended.

Notes:

1. **Nitrates** are **peripheral and coronary vasodilators** used in the management of **angina pectoris**, heart failure, and myocardial infarction [(1)].
2. **Sublingual** (or aerosol spray) of **glyceryl trinitrate (GTN)** are used to provide **rapid symptomatic relief of acute Anginal attack** while and **transdermal patches** of **glyceryl trinitrate** are used the **long-term prophylaxis** of angina.

3. Other Nitrate available are: **Isosorbide Dinitrate (ISDN) and Isosorbide Mononitrate (ISMN)** which are commonly given by **oral route.**
   - **Isosorbide Dinitrate** ISDN needs to be dosed **three times** a day.
   - **ISMN has longer duration than ISDN**: The advantage of ISMN is **twice** daily dosing (or **once daily with sustained release** products) which mean better compliance.
   - **Isosorbide dinitrate** (ISDN) and **Isosorbide Mononitrate** (ISMN) are most commonly prescribed for long-term prevention (**prophylaxis**) of angina episodes.
4. Nitrate can cause **headache** that is usually **transient**, typically lasting several days to few weeks. Patients can use simple analgesics (as Paracetamol) when required to control any headaches.
5. Nitrates should not be used within **24 hours of taking Sildenafil or Vardenafil** or within **48 hours of taking Tadalafil** because of the potential for life-threatening **hypotension**; This may cause death.
6. **Nitrate tolerance** is a major problem with the long-term use of nitroglycerin and long-acting nitrates; Several agents such as **ACEIs, N-Acetyl Cysteine (NAC), L-Methionine and diuretics have been shown to reverse nitrate tolerance by increasing the availability of sulfhydryl radicals;** However, practical considerations suggest that less frequent administration (8 to 12 hrs. of nitrate-free intervals) is effective without introducing additional agents, **(Free period is usually at night).**
   - **Carvedilol** and **Nebivolol** (BBs with antioxidant + vasodilator effects) may reduce nitrate tolerance.
7. **Patient education about using sublingual glyceryl trinitrate**:
   - **A.** In the event of an acute attack, patients should be instructed to sit or lie down, place the dose (spray or tablet) under the tongue, and not swallow the tablet. Relief of pain should occur within 5 minutes; If the pain persists or is unimproved 5 minutes after the first dose of GTN, the patient should call an ambulance transport as they may be experiencing an MI; If patient needs more than one tablet, he can take a maximum of three tablets in 15 minutes.
   - **B.** SL nitrates can also be used to prevent acute episodes if given 2 to 5 minutes prior to activities known to produce angina; protection can last for up to 30 minutes.
   - **C.** The tablets should be dispensed in the original, unopened manufacturer 's container and stored in the original brown bottle.
   - **D.** The bottle should be stored in a cool, dry place, but not refrigerated. The bottle should be closed tightly after each opening.
   - **E.** GTN tablets should be supplied in glass containers of not more than 100 tablets closed with a foil-lined cap, and containing no cotton wool wadding; they are discarded after 8weeks of use.
   - **F.** Expiration dating should be monitored closely, and tablets should be replaced immediately if they are exposed to excessive light, heat, moisture, or air.
8. Sometimes **glyceryl trinitrate GTN is used topically** as a cream/gel for the **treatment of Hemorrhoids,** due its vasodilator effect**,** for more details see chapter 2, section 15.

A) Nitrates:

Scientific name	Dosage form	Trade name	concentration
Glyceryl trinitrate	Sublingual Tab	Angiseed® , Nitrostat®	0.5 mg
	Patch	Nitroderm®	10 mg , 20 mg
	Infusion	Tridil® , Nitrobid®	25 mg , 50 mg /250ml
	Sublingual Spray	Glytrin®	0.4 mg/puff
Isosorbide mono nitrate	Tab	Isosorbide mono nitrate®	10 mg , 20 mg , 40 mg
	Tab	Imdur®	60 mg
Isosorbide di nitrate	Tab	Isosorbide di nitrate®	10 mg , 20 mg , 40 mg
	Sublingual Spray	Angitak®	12.5 mg/puff
	Inj. (amp)	Isoket®	1 mg/ml (10 ml)

B) Other Anti-Anginal drugs:

These include: **Ranolazine**, **Nicorandil**, **Trimetazidine** and **Ivabradine**; each one has a special feature and many advantages compared with traditional antianginals:

1. **Ranolazine** inhibits the late phase of the sodium current (late INa) **improving the oxygen supply-and-demand equation** (2), is an **anti-ischemic agent**; Has an advantage over traditional antianginal agents that it **has no negative effect on heart rate and BP**, which makes it useful in patients in need of further antianginal therapy (who remain symptomatic while on standard angina pharmacotherapy) but who have marginal BP or heart rates preventing titration of conventional antianginal agents.
2. **Nicorandil** is a vasodilator **(K Channel Activator)**; has both arterial and venous vasodilating properties and is **licensed for the prevention and long-term treatment of angina**; Nicorandil may produce additional symptomatic benefit in combination with other antianginal drugs.
3. **Trimetazidine** acts as **fatty acid oxidation inhibitor**, thus shifting to glucose oxidation → stimulates glucose utilization → ATP production with less oxygen consumption „„„ It's also used as anti-vertigo and in tinnitus. (2), **C.I. in Parkinson disease and renal failure**.
4. **Ivabradine** is a **pure heart rate lowering agent**, acting by selective and specific inhibition of the cardiac pacemaker If current that controls the spontaneous diastolic depolarization in the sinus node and regulates heart rate, **indicated in Symptomatic treatment of chronic stable angina pectoris, and in chronic heart failure**. (2) Decrease CV death for HF by 18%.
   - It is licensed for the treatment of angina in patients who are in normal sinus rhythm in combination with a β-blocker, or when β-blockers are contraindicated or not tolerated.
   - licensed for mild to severe stable chronic heart failure (in combination with a β-blocker unless contra-indicated or not tolerated), in patients who are in sinus rhythm.
   - **If there is no improvement within 3 months; Ivabradine should be discontinued.**

Scientific name	Dosage form	Trade name	concentration
Ranolazine	Tab	Ranexa®	500 mg , 750 mg , 1000 mg
	Tab PR		375 mg , 500 mg
Nicorandil	Tab	Ikorel®, Dancor®, Sigmart®	10 mg , 20 mg
Trimetazidine	Tab , Tab MR	Vastrel® , Tricardia®	30 mg , 35 mg
Menthol + Menthyl isovalerate *	Sub-Lingual Tab	Validol®	60 mg
Ivabradine	Tab	Procoralan®, Corlanor®	5 mg , 7.5 mg

*** Validol**® produces **a sedative effect**, at sublingual administration the effect is produced in 5 minutes and 70 % of the preparation is released in 3 minutes; **used in cases of heart disease, angina, motion sick-ness, nausea, vomiting when seasick or airsick, hysteria, nervousness, headaches from taking nitrates.**

C) Other Central Vasodilators:

These include: **Molsidomine**, **Isoxsuprine.**

1. **Molsidomine** is a long acting vasodilating drug, its metabolized in the liver to the active metabolite **linsidomine**, which is the compound that **releases nitric oxide (NO)** upon decay as the actual vasodilating compound; thus, relaxing the smooth muscles of blood vessels.
   - used for **the prevention and long-term treatment of stable and unstable angina pectoris**, with or without left heart failure; also used to treat angina in the context of an acute myocardial infarction; Also has a role in **pulmonary hypertension**.
2. **Isoxsuprine** is also a **beta-adrenergic agonist** that causes **direct relaxation of uterine and vascular smooth muscle**, used also for treatment of **premature labor (Tocolytic)**.

Scientific name	Dosage form	Trade name	concentration
Molsidomine	Cap	Corvasal®	2 mg , 4 mg
Isoxsuprine	Tab	Duvilane®	10 mg

D) Peripheral Vasodilators and Vasoprotective agents:

Peripheral vascular disease can be either **occlusive** (intermittent claudication) in which occlusion of the peripheral arteries is caused by atherosclerosis, or **vasospastic** (Raynaud's syndrome), treatment option includes: **Cilostazol**, **Pentoxifylline** and **Vincamine.**

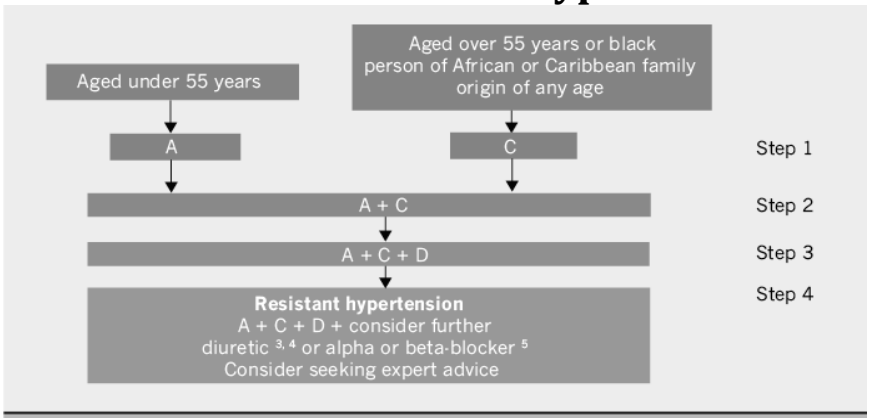
1. **Cilostazol** is a **vasodilator and an anti-platelet**; licensed for **use in intermittent claudication** to improve walking, also used for **secondary stroke prevention**.
   - **Cilostazol** and its metabolites are **inhibitors of phosphodiesterase III**; As a result, cyclic AMP is increased leading to reversible inhibition of platelet aggregation, vasodilation, and inhibition of vascular smooth muscle cell proliferation.
   - Based on the American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy, **Cilostazol is an effective and recommended alternative antithrombotic to either aspirin or Clopidogrel in a dual antiplatelet regimen** when allergy or drug intolerance to either agent occurs in patients who have undergone elective PCI with bare metal or drug-eluting stent placement.
   - Based on the American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy, **Cilostazol is an effective and recommended alternative antithrombotic in patients with a history of non-cardio embolic ischemic stroke or TIA.**
   - Also used in the **Prevention of stent thrombosis and restenosis after coronary stent placement** (adjunct with aspirin and Clopidogrel).
2. **Pentoxifylline** (also called **Oxpentifylline**); a xanthine derivative; **improves blood flow by decreasing blood viscosity and increasing RBC Flexibility**; thus, increasing oxygen supply.
   - Has been shown to **increase leukocyte deformability and to inhibit neutrophil adhesion and activation;**
   - **Tissue oxygen levels have been shown to be significantly increased** by therapeutic doses of Pentoxifylline in patients with peripheral arterial disease.
   - Uses include improving psychopathological symptoms in patients with cerebrovascular insufficiency, in diabetic angiopathies, transient ischemic attacks, leg ulcers, sickle cell anemia's, strokes, Raynaud phenomenon and in male infertility (enhance sperms quality).
3. **Vincamine;** an **Alkaloid** found in the leaves of (Vinca minor); it's a **Peripheral Vasodilator** that acts by **increasing cerebral blood circulation**, also it's considered as a **Nootropic agent**; is used for the treatment, control, prevention, and improvement of **Cerebrovascular disorders** and **Hypertension;** in Europe its indicated for the **treatment of primary degenerative and vascular dementia.**
   - **Vinpocetine** (Caventona® **AMS**) is a synthetic derivative **of Vincamine.**

Scientific name	Dosage form	Trade name	concentration
Cilostazol	Tab	Pletal®	50 mg , 100 mg
Inositol Nicotinate	Tab	Hexopal®	500 mg , 750 mg
Moxisylyte	Tab	Opilon®	40 mg
Naftidrofuryl	Cap	Praxilene®	100 mg , 200 mg
Pentoxifylline	Tab	Trental®	400 mg
Calcium Dobesilate	Cap	Doxium®	500 mg
Vincamine	Cap SR	Oxybral®	30 mg
	Amp		15 mg/2 ml
Oxerutins	Cap	Paroven®	250 mg
Trimetazidine	Tab MR	Vastrel® , Tricardia®	30 mg , 35 mg

Notes

1. **Moxisylyte = Thymoxamine,** they are the same drug.
2. **Doxium®** is an exclusive **Vasoprotective** used is **Chronic Venous Insufficiency, In Hemorrhoids and in Diabetic Retinopathy.**

Guide-Line of Hypertension Treatment lines (4)



Reproduced from NICE clinical guideline 127 with kind permission

Key: A = angiotensin-converting enzyme (ACE) inhibitor or low-cost angiotensin receptor blocker (ARB)[a]; C = calcium channel blocker (CCB)[a]; D = thiazide-like diuretic; BHS = British Hypertension Society

(1) Choose a low-cost ARB. (2) A CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure. (3) Consider a low dose of spironolactone[a] or higher doses of a thiazide-like diuretic. (4) At the time of publication (August 2011), spironolactone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented. (5) Consider an alpha- or beta-blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective.

**** Mild Pregnancy hypertension is usually treated acutely with (labetalol) to prevent maternal cerebrovascular complications.**
**** Avoid ACEIs, ARBs and Aliskiren** because these drugs may cause fetal injury or death.
**** Nitroprusside is C.I. in the later stages of pregnancy** due to possible fetal cyanide poisoning if used for more than 4 hours.

3.13 – Emergency Antihypertensive drugs:

Scientific name	Dosage form	Trade name	concentration
Nicardipine	Infusion	Cardene®	20 mg/200 ml , 40 mg/200 ml
	Inj. Solu.		2.5 mg/ml
Nitroprusside Na+	Vial	Nipride®, Nitropress®	50 mg
	Inj. Solu.		25 mg/ml
Fenoldopam	Inj. Solu.	Corlopam®	10 mg/ml
Nitroglycerin	Inj. Solu.	NTG® , Tridil®	400 mcg/ml
Hydralazine	Inj. Solu.	Apresoline®	20 mg/1ml
Labetalol	Inj. Solu.	Trandate®	5 mg /ml
Enalaprilat	Inj. Solu.	Epaned® , Vasotec®	1.25 mg/ml , 2.5 mg/ml
Trimetaphan	Inj. Solu.	Arfonad®	25 mg , 50 mg
Esmolol	Inj. Solu.	Brevibloc®	10 mg/ml , 20 mg/ml
Phentolamine	Vial	Regitine® , Oraverse®	5 mg , 0.4 mg/1.7 ml

3.14 - Anti-Arrhythmic Drugs:

1. The heart contains two upper and two lower chambers, which are known as the atria and ventricles. The pumping actions of these two sets of chambers are normally coordinated by electrical impulses that originate in the heart's pacemaker and then travel along conducting pathways so that the heart beats with a regular rhythm.
   - If this coordination breaks down, the heart will beat abnormally, either irregularly or faster or slower than usual; The general term for abnormal heart rhythm is **arrhythmia**.
   - Arrhythmias may occur as a result of a birth defect, coronary heart disease, or other less common heart disorders, a variety of more general conditions, including over-activity of the thyroid gland, and certain drugs, such as caffeine and anticholinergic drugs, can also disturb heart rhythm.
2. Arrhythmias can be divided into two groups: **Tachycardias** (as atrial fibrillation), in which the heart rate is faster than normal; and **Bradycardias** (as heart block), in which the rate is slower.
3. Minor disturbances of heart rhythm are common and do not usually require drug treatment. However, if the heart's pumping action is seriously affected, the circulation of blood throughout the body may become inefficient, and drug treatment may be necessary.

4. Drugs may be taken to treat individual attacks of arrhythmia, or they may be **taken on a regular basis to prevent or control abnormal heart rhythms**; The particular drug prescribed depends on the type of arrhythmia to be treated, but because **people differ in their response, it may be necessary to try several in order to find the most effective one**; When the arrhythmia is sudden and severe, it is necessary to inject a drug immediately to restore normal heart function.
   - The heart pumping action is governed by electrical impulses under the control of the sympathetic nervous system; These signals pass through the heart muscle, causing the two pairs of chambers – the atria and ventricles – to contract in turn.
   - **All anti-arrhythmic drugs alter the conduction of electrical signals in the heart**; However, each drug or drug group has a different effect on the sequence of events controlling the pumping action:
     - Some **block the transmission of signals to the heart** (beta blockers).
     - Some **affect the way in which signals are conducted within the heart** (digitalis).
     - Others **affect the response of the heart muscle to the signals received** (calcium channel blockers, Disopyramide, and Procainamide).
   - **They don't cure arrhythmia**; they usually **reduce the frequency** and the severity.
   - They may further **disrupt heart rhythm**, and therefore they are used only when the likely benefit outweighs the risks.
   - **Anti-Arrhythmics may cause arrhythmias itself if used improperly**, most of them is called pro-arrhythmic.
   - **Should be initiated in the hospital** (minimum of 3-day stay) so that QTc interval, serum electrolytes, and renal function can be monitored.

Common types of Arrhythmias:

A) Atrial fibrillation: in this type of arrhythmia, the atria contract irregularly at such a high rate that the ventricles cannot keep pace. The condition is treated with **digoxin**, **verapamil**, **amiodarone**, or a **beta blocker**.

B) Ventricular tachycardia: This condition arises from abnormal electrical activity in the ventricles that causes the ventricles to contract rapidly. Treatment with **Disopyramide**, **procainamide**, or **amiodarone** may be effective, although implanted defibrillators are replacing drug treatment for this condition.

C) Supraventricular tachycardia: This condition occurs when extra electrical impulses arise in the pacemaker or atria, stimulating the ventricles into contracting rapidly. Attacks may disappear on their own without treatment, drugs used: **adenosine**, **digoxin**, **verapamil**, or **propranolol**.

D) Heart block: When impulses are not conducted from the atria to the ventricles, the ventricles start to beat at a slower rate. Some cases of heart block do not require treatment. For more severe heart block accompanied by dizziness/fainting, the fitting of an artificial pacemaker is necessary.

Notes about Anti-Arrhythmics:

1. **Atropine** is used for **bradycardia** and **AV nodal blockade**; In patients with hemodynamically unstable or unresponsive to atropine, epinephrine or dopamine may be administered.
2. **Adenosine** is the drug of choice for pharmacologic termination of **paroxysmal supraventricular tachycardia (PSVT).**
3. Hemodynamically stable **torsade de pointes** is often treated with **I.V magnesium**.
4. Hemodynamically unstable PSVT, ventricular tachycardia, atrial fibrillation, torsade de pointes, or ventricular fibrillation (already hemodynamically unstable) should be terminated immediately using **direct current cardioversion (DCC).**
5. **Flecainide** and **Propafenone** can be considered **first-line therapies for patients without structural heart disease**; **Propafenone** displays independent **nonselective β-blocking properties** (which may cause bronchospasm, thus its best be avoided in patients with asthma); **both drugs are Contraindicated in patients with structural heart disease** (including CHD, HF, left ventricular hypertrophy, and valvular heart disease).

6. **Sotalol** is also a Beta Blocker (non-selective), **used for ventricular and supra- ventricular arrhythmias** (2), Contraindicated in patients with uncontrolled HF; CrCl less than 40 mL/minute; QTc interval greater than 450 milliseconds; and second- or third-degree AV block.
7. **Amiodarone** is the most commonly used antiarrhythmic agent; It is used for **rate and rhythm control of atrial fibrillation** and to treat and prevent **ventricular arrhythmias**.
   - Reserved for patients with life-threatening arrhythmias due to its substantial toxicity.
   - **Contains an Iodine moiety that contributes to its thyroid toxicity.**
   - Patients should be monitored routinely for the possible development of **hepatic dysfunction**, **thyroid disorders (hyperthyroidism, hypothyroidism**), and **photosensitivity**.
   - Because of the possibility of **phototoxic reactions**, patients taking amiodarone should be advised to shield the skin from light during treatment and for several months after discontinuing amiodarone.
   - **Oral loading dose required** (400 mg 2 or 3 times per day for 2 weeks and then 400 mg/day for 4 weeks, followed by a 200-mg/day maintenance dose); and Achieving a loading dose of 10 gm is desirable.
   - Has a very **Long half-life of about 60 days.**
8. **Dronedarone**: An **Amiodarone analog;** lacking the iodine moiety that contributes to the thyroid toxicity of amiodarone, but may result in acute kidney injury, that reversible on discontinuation.
9. **Digoxin** is a cardiac **glycoside** that **increases the force of myocardial contraction** (so used for Heart Failure HF) **and reduces conductivity within the atrioventricular (AV) node** (so used for atrial fibrillation or flutter) (2), its Half-life is about 36 hours.
   - **Digoxin does not improve survival in patients with HF;** but does provide symptomatic benefits only; (digoxin is added for patients who remain symptomatic despite an optimal HF regimen consisting of an ACEI or ARB, β-blocker, and diuretic.
   - **Digoxin** is also prescribed routinely in patients with HF and concurrent atrial fibrillation (AF) to slow ventricular rate regardless of HF symptoms.
   - Loading dose of **digoxin** (**Rapid digitalization**) is usually given for atrial fibrillation or flutter; (half of the total loading dose administered as the first dose, with the remaining portion divided and administered every 6–8 hours initially).

A) Class I (Na^+ Channel Blockers)

Scientific name	Dosage form	Trade name	concentration
Disopyramide (Ia)	Cap , Cap ER	Norpace® , Rythmodan®	100 mg , 150 mg
Procainamide (Ia)	Tab	Pronestyl® , Procan®	250 mg , 500 mg
Quinidine (Ia) *	Tab	Quinidex®, Quinacard®	200 mg , 300 mg
Lidocaine (Ib) **	Inj. Solu.	Xylocaine® , Lidopen®	10 mg/ml
Mexiletine (Ib)	Cap	Mexitil®	150 mg , 200 mg
Flecainide (Ic)	Tab	Tambocor®	50 mg , 100 mg
Propafenone (Ic)	Tab , Cap	Rythmol®, Rythmonorm®	150 mg (tab) , 225 mg (cap)

* **Quinidine** is also anti-malarial.

** **Lidocaine** is also a Local anesthetic used as Ointment and Cream for topical use.

B) Class II (Beta Blockers)

Only (**Esmolol, Metoprolol, propranolol, Acebutolol**) is FDA approved as Anti-Arrhythmic.

Scientific name	D. form	Trade name	Cone.
Propranolol	Tab	Inderal® , Becardin®	10 mg , 40 mg
	Inj.	Inderal®	1 mg/1 ml
Metoprolol	Tab	Betaloc® , Hypopresor®	50 mg , 100 mg
	Inj.	Betaloc®	1 mg/1 ml
Esmolol	Inj. Solu.	Brevibloc®	10 mg/1 ml , 20 mg/1 ml
Acebutolol	cap	Sectral®	200 mg , 400 mg

C) Class III (K^+ Channel Blockers)

Scientific name	Dosage form	Trade name	concentration
Amiodarone	Tab	Codaron®	100 mg , 200 mg
	Inj. Solu.	Codaron® , Nexterone®	50 mg/ml
Sotalol	Tab	Betapace®	80 mg , 120 mg , 160 mg
	Inj. Solu.	Sorine®	15 mg/ml
Dronedarone	Tab	Multaq®	400 mg
Ibutilide	Inj. Solu.	Corvert®	0.1 mg/ml
Dofetilide	Cap	Tikosyn®	125 mcg , 250 mcg , 500 mcg
Vernakalant *	Inj. Solu.	Brinavess®	500 mg/25 ml

* **Vernakalant** blocks atrial potassium channels, thereby prolonging repolarization; It differs from typical class III agents by blocking a certain type of potassium channel, the cardiac transient outward potassium current, with increased potency as the heart rate increases; This means that it is more effective at high heart rates, while other class III agents tend to lose effectiveness under these circumstances; It also slightly blocks the hERG potassium channel, leading to a prolonged QT interval.

D) Class IV (Ca^+ Channel Blockers)

Only (**Diltiazem, Verapamil**) is FDA approved as Anti-Arrhythmic. (See Above)

E) Other Anti-Arrhythmics

Scientific name	Dosage form	Trade name	concentration
Adenosine	Inj. Solu.	Adenocard®	3 mg/ml
Digoxin	Tab	Lanoxin®	0.125 mg , 0.25 mg
	Elixir		0.05 mg/ml
	Inj. Solu.		0.1 mg/ml , 0.25 mg/ml
Digitoxin *	Tab	Digitoxin®	100 mcg

*** Digitoxin** has a long half-life**, about 7 days.**

Note: too much antiarrhythmics?? Don't worry;

The following table summarize the effects of antiarrhythmic drugs:

Class	Agent	Physiological effect	Result on ECG parameters
Class I (Na channel Blockers)			
IA (intermediate)	Quinidine Disopyramide Procainamide	↓ Conduction velocity, ↑ refractory period	↑ QRS complex, ↑ QT interval
IB (fast)	Lidocaine Mexiletine	↓ Conduction velocity, ↓ refractory period	↓ QT interval
IC (Slow)	Flecainide Propafenone	↓ Conduction velocity (highly decrease), Ø refractory period	↑ QRS complex
Class II (BBs)	Metoprolol Esmolol Atenolol	↓ Conduction velocity, ↑ refractory period	↓ HR ↑ PR interval
Class III (K channel Blockers)	Amiodarone Dronedarone Dofetilide Ibutilide	Ø Conduction velocity, ↑ refractory period (highly increase)	↑ QT interval
Class IV (Ca channel Blockers)	Diltiazem Verapamil	↓ Conduction velocity, ↑ refractory period	↓ HR ↑ PR interval
Class V	Digoxin Digitoxin Adenosine	↓ Conduction velocity, ↑ refractory period	↑ PR interval

** Ø = no effect, ↓ = decrease, ↑ = increase.

3.15 - Lipid-regulating drugs (Anti-Lipemic agents)

1. **Cholesterol** and **triglycerides are two of the major fats in the blood;** One or both may be raised, influencing the choice of lipid-lowering drug.
   - **Cholesterol** is essential for making a number of critical hormones, including the stress hormone cortisol; Cholesterol is also used to make the sex hormones testosterone, progesterone, and estrogen; The liver also uses cholesterol to make bile, a fluid that plays a vital role in the processing and digestion of fats; the body also needs cholesterol to make vitamin D, as in the presence of sunlight, cholesterol is converted into vitamin D.
     - High Cholesterol may contribute to hardening of the arteries or thickening of the artery walls (arteriosclerosis); which increases the risk of stroke, heart attack and heart disease.
   - **Triglycerides (TG)**: when we eat, the body converts any calories it doesn't need to use right away into triglycerides; The triglycerides are stored in your fat cells. Later, hormones release triglycerides for energy between meals.
     - High levels of TGs can increase the risk of heart disease; heart attack or stroke (due to atherosclerosis).
     - Extremely high TGs can also cause acute inflammation of the pancreas (pancreatitis).
2. **The normal level of cholesterol in the blood is less than 200 mg/dl.**
3. **The normal level of TG is less than 150 mg/dl.**
4. There is a common notion that the restricted diet for cholesterol-rich foods and the sport is the foundation and starting point in the treatment of high blood cholesterol; the truth of this information is correct, but inaccurate due to the amount of cholesterol reaching into the body daily is distributed as follows:
   - **80% is made endogenously in the liver without being related to food intake and 20% is of the incoming food;** Therefore, effective treatment and principal of the high blood cholesterol in the case of increase for the limit of 240 is essentially pharmacological and especially with group Statins, and accompanied by a diet
   - **The diet itself needs 6-12 month to take effect and lower cholesterol,** and that's a lot especially for patients who have other risk factors, **diet is useful in patients who are still in the borderline cholesterol control.**
5. **Cholesterol** and **Triglycerides (TG)** are transported from the liver to blood stream and vice versa through a carrier called **Lipoproteins,** which are **divided into 4 types** according to their actions:
   a. **Chylomicrons** carry triglycerides from the intestines to the liver, to skeletal muscle, and to the adipose tissue (for storage).
   b. **Very-low-density lipoproteins (VLDL)** carry (newly synthesized) triglycerides from the liver to the adipose tissue (for storage).
   c. **Low-density lipoproteins (LDL)** carry 3,000 to 6,000 fat molecules (phospholipids, cholesterol, triglycerides) around the body; LDL particles are referred to as **"bad" lipoprotein** because their increase correlate with atherosclerosis progression.
   d. **High-density lipoproteins (HDL)** collect fat molecules (phospholipids, cholesterol, triglycerides) from the body's cells/tissues, and take it back to the liver to get metabolized and broken down; HDLs are referred to as "**good" lipoprotein** because higher concentrations correlate with low rates of atherosclerosis progression and/or regression.
6. When treating high levels of lipids, it's important to focus on two parameters: LDL-C and HDL-C as:
   - **Each 1% reduction in LDL-C equals a 1% reduction in CHD risk.**
   - **Each 1% increase in HDL-C reduces CHD risk by 1-3%.**
7. Lipid regulating drugs are used to modify blood lipid concentrations in the management of **hyperlipidemias and for the reduction of cardiovascular risk**, The principal groups of lipid regulating drugs are:
   a. **Statins** like (Atorvastatin, Rosuvastatin, and Simvastatin)
   b. **Fibrates** like Gemfibrozil and Fenofibrate.
   c. **Bile acid Sequestrants** like Colesevelam and Colestipol.
   d. **Others** like Ezetimibe, Omega 3 Fatty Acids.

A) Regarding Statins:

1. They act by **inhibiting HMG CoA reductase,** the rate-limiting step in cholesterol synthesis.
2. Statins are **more effective than other lipid-regulating drugs at lowering LDL-cholesterol** concentration but they are **less effective than the fibrates in reducing triglyceride concentration**.
3. They **reduce LDL-C by (24–60%); reduce TG by (7–30%); raise HDL-C by (5–15%).**
4. Cholesterol synthesis in the liver peaks during the early morning (midnight to 3 am), **thus most of statins should be taken in at night.**
   - **An exception for that are Rosuvastatin, Atorvastatin;** which both have long half-lives that allows them to be administered any time a day and still overs the HMG peak time; (Rosuvastatin 19 – 24 hrs., Atorvastatin 11 – 14 hrs.).
   - **Simvastatin** is used topically for **accelerating wound healing** in diabetes by enhancing angiogenesis and lymph-angiogenesis (off-label use), it's also has a **neuroprotective function** and thus it's preferred by neurologists.
   - **Atorvastatin** is a **Lipid-soluble** statin, and it's preferred in patients with renal failure.
   - **Rosuvastatin** is a **Water-soluble** statin, preferably avoided in End stage renal disease.
5. The most common adverse effects reported include **muscle pain and weakness** (**myalgia**), headache, GI symptoms, including dyspepsia, flatus, constipation, and abdominal pain, and skin rashes; These symptoms are usually mild and often dissipate with continued therapy.
   - **Co-Q10 supplementations** are sometimes used to **treat statin-associated myopathy**.
6. **Some studies claim that Statins (Atorvastatin, Rosuvastatin) can be given every other day, or 3 or 2 times weekly, and once weekly for Rosuvastatin.**
   - This is supported by the fact that it takes several weeks for cholesterol levels to return to baseline after treatment with statins is stopped, Rosuvastatin with a 19-hr. half-life and Atorvastatin with an 11–14 hr. half-life, are particularly useful for this approach.
   - Review of studies comparing alternate-day dosing with daily dosing of statins indicates that the magnitude of LDL cholesterol reduction with alternate-day dosing is nearly the same, with obvious cost savings and less side effects specially muscle aches and myalgia.
   - **Relative LDL-C-Lowering Efficacy of Statins**

Atorva (mg)	Fluva (mg)	Pitava (mg)	Lova (mg)	Prava (mg)	Rosuva (mg)	Ezetimibe/ Simva (mg)	Simva (mg)	%↓ LDL
—	20–40	1	20	10–20	—	—	10	30
10	80	2	40	40	—	—	20	38
20	—	4	80	80	5	10/10	40	41
40	—		—	—	10	10/20	—	47
80	—		—	—	20	10/40	—	55
	—		—	—	40	—	—	63

high-intensity statin; lowers LDL by ≥ 50%. | moderate-intensity statin; lowers LDL-C by 30% to < 50%. | low-intensity statin; lowers LDL by <30%.

Note that Rosuvastatin has the highest LDL lowering effect.

Scientific name	Dosage form	Trade name	concentration
Atorvastatin	Tab	Lipitor® , Avas® , Astatin®	10 , 20 , 40 , 80 mg
Simvastatin	Tab	Zocor® , Simvas® , Simvor®	10 , 20 , 40 , 80 mg
Fluvastatin	Cap	Lescol®	20 mg , 40 mg
	Tab (MR)	Lescol XL®	80 mg
Lovastatin	Tab	Mevacor® , Atloprev®	10 , 20 , 40 mg
Pravastatin	Tab	Pravachol®, Lipostat®	10 , 20 , 40 , 80 mg
Pitavastatin	Tab	Livalo®	1 mg , 2 mg , 4 mg
Rosuvastatin	Tab	Crestor® , Stage®, Rosogard®	10 mg , 20 mg , 40 mg

B) Regarding Fibrates:

1. Fibrate **reduces the rate of lipogenesis** in the liver, thus lowering TG and cholesterol levels.
   - mainly used for the treatment of **hypertriglyceridemia** (hyper TG).
   - Recommendations for fibrate use were not included in the 2016 ACC guideline.
   - When initiation therapy with Fibrates; evaluate renal status at baseline, within 3 months after initiation, and every 6 months thereafter.
   - Due to a rare paradoxical decrease in HDL-C seen in some patients on Fenofibrate, the FDA recommended that the HDL-C levels be checked within the first few months after initiation of fibrate therapy; If a severely depressed HDL-C level is detected, fibrate therapy should be withdrawn, and the HDL-C level monitored until it has returned to baseline.
   - Fibrates Use has been associated with PE (pulmonary Embolism) and DVT (deep vein thrombosis); Use with caution in patients with risk factors for VTE.
2. They **lower LDL-C by 5–20%** (with normal TG); but may raise LDL-C with very high TG levels.
3. They **Lower TG by 20–50%;** and **raise HDL-C by 10–20%.**
4. Fibrates may cause Dyspepsia, and because these drugs increase biliary cholesterol excretion, they **lead to the formation of gallstones (Lithiasis).**
   - Thus C.I. in pre-existing gallbladder disease.
   - Also C.I. in Severe renal or hepatic disease.
5. **Increased risk of myopathy and rhabdomyolysis when co-administered with statins**; Risk is greater with gemfibrozil than with Fenofibrate.
6. **Bezafibrate** and **Fenofibrate** are given with or just after food; while **Gemfibrozil** is given 30 to 60 minutes before food.

Scientific name	Dosage form	Trade name	concentration
Gemfibrozil	Tab	Lopid®	600 mg
Fenofibrate	Tab , Cap	Tricor®, Lipofen®, Lipanthyl®	145mg (tab) , 200mg (cap)
	Tab	Supralip®	160 mg
Bezafibrate	Tab	Bezalip®	200 mg , 400 mg
Ciprofibrate	Tab	Ciprofib®	100 mg

C) Bile acid Sequestrants (binders)

1. Bile salts contain a large amount of cholesterol and are normally released into the bowel to aid digestion before being reabsorbed into the blood; so, drugs that bind to bile salts reduce cholesterol levels by blocking their reabsorption, allowing them to be lost from the body.
2. **Bile acid Sequestrants** are anion exchange resins that bind negatively charged bile acids and bile salts in the small intestine; the resin/bile acid complex is excreted in feces, thus preventing the bile acids from returning to the liver by the entero-hepatic circulation.
   - Lowering the bile acid concentration causes hepatocytes to ↑ conversion of cholesterol to bile acids, resulting in a replenished supply of these compounds → the intracellular cholesterol concentration decreases.
   - Bile acid Sequestrants interfere with the absorption of fat-soluble vitamins; supplements of vitamins A, D, K, and folic acid may be required when treatment is prolonged.
   - Adverse effects include: GI distress, constipation.
3. They **reduce LDL-C by 15–27%**, and **raise HDL-C by 3–5%**, but may increase TG concentrations; (thus **C.I. with raised TG concentrations** especially greater than 400 mg/dl).
   - **Colesevelam** is FDA approved for use in type 2 diabetes to improve glycemic control.
   - **Cholestyramine** is used for **pruritus associated with partial biliary obstruction** and **primary biliary cirrhosis**, it also used for diarrhea associated with Crohn's disease, ileal resection vagotomy, diabetic vagal neuropathy, and radiation.

Scientific name	Dosage form	Trade name	concentration
Colesevelam	Tab , Cap	WelChol®, Cholestagel®	625 mg
Colestipol	Tab , Granules	Colestid®	1 gm (tab) , 5 gm (granules)
Cholestyramine	Powder for Susp.	Questran®, Prevalite®	4 gm/sachet

D) Injectable Anti-Lipemic drugs:

These include Evolocumab, Alirocumab and Mipomersen.

1. **Evolocumab** and **Alirocumab** are both **PCSK9 Inhibitors**; Monoclonal antibodies that inhibit a protein called PCSK9, thus increasing cholesterol clearance from the liver.
   - **Lower LDL-C by an additional 45–68%** when combined with statin therapy; Evolocumab reduces CV events when added to statin therapy.
   - Both administered by SC inj. Every 2 weeks, or at a double dose each month.
   - Adverse effects: Injection-site reactions, respiratory infections.
2. **Mipomersen** is an **Oligonucleotide inhibitor**, which targets the messenger RNA for Apo-lipoprotein B-100 → inhibit VLDL & LDL synthesis, it **lowers LDL-C by about 25%.**
   - administered by SC inj. Once weekly; should only be prescribed in the context of a risk management plan by specialist.
   - The drug has a black box warning **about the risk of liver damage**; specifically, it can cause elevations in the levels of transaminases and causes fatty liver disease.

Scientific name	Dosage form	Trade name	concentration
Mipomersen	S.C. Inj.	Kynamro®	200 mg/ml
Alirocumab	S.C. Inj.	Praluent®	75 mg/ml , 150 mg/ml
Evolocumab	S.C. Inj.	Repatha®	140 mg/ml

E) Other Anti-Lipemic drugs: (2)

These include: Ezetimibe, Omega 3 Fatty acids, Lomitapide and Niacin (vitamin B_3).

1. **Ezetimibe** selectively **inhibits absorption of dietary and biliary cholesterol** from the small intestine; may be used alone or in combination with a statin or Fenofibrate along with diet for the management of dyslipidemia, specifically to lower LDL-C.
   - It **lowers LDL-C by 18–20%**; Can **raise HDL-C by 1–5%**; **lowers TG by 5–10%**.
   - In combination with a statin, it demonstrates an additive effect, enhancing LDL-C lowering by an additional 10% to 20%.
2. **Omega 3 Fatty acids**, Contains **Eicosapentaenoic acid (EPA)** and **Docosahexaenoic acid (DHA),** which differs from the traditional fish oil.
   - **Mainly used for reduction of TG;** it acts by reduction of hepatic production of VLDLs; with a possible reduction in hepatic synthesis of TG; and increased hepatic β-oxidation.
   - **A safer option compared with Fibrates.**
   - **Lowers TG by 26–45%,** and **raises HDL-C by 5–14%.**
   - But **may raise LDL-C up to 45%** when TG concentrations are very High.
   - **Effective Dose: 2–4 gm/day** as a single dose or in two divided doses.
3. **Omega-3 carboxylic acids** are derived from fish oil and are a purified mixture of the polyunsaturated free fatty acids **Docosahexaenoic acid (DHA)** and **Eicosapentaenoic acid (EPA);** used in addition to changes in diet to reduce triglyceride levels in adults.
   - **Lowers TG 20-35%,** and **raises HDL-C by 5%**
   - But **may raise LDL-C up to 25%** when TG concentrations are very High.
   - **Effective Dose: 2–4 gm/day** as a single dose or in two divided doses.
   - Following the recommendation from an independent Data Monitoring Committee, AstraZeneca has decided to close the Phase III STRENGTH trial for Epanova (omega-3 carboxylic acids) due to its **low likelihood of demonstrating a benefit** to patients with mixed dyslipidemia (MDL) who are at increased risk of cardiovascular (CV) disease.

4. **Lomitapide**, a **Selective microsomal TG protein inhibitor;** directly bind and inhibit Microsomal Triglyceride Transfer protein (MTP), thus preventing Apo-B Lipoprotein Assembly → **inhibit synthesis of Chylomicrons and VLDL**.
   - **Lowers LDL-C by about 45%,** but has a high profile in GIT side effects (hepatotoxic).
   - Should be given only under the supervision of a specialist.
   - C.I in pregnancy and moderate liver impairment.
5. **Niacin (vitamin B3)**, inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver and reduces synthesis of TG, VLDL, and LDL-C
   - It **lowers LDL-C by 5–25%**; **lowers TG by 20–50%**; and **raises HDL-C by 15–35%**.
   - its value as anti-Lipemic is limited by its side-effects, especially vasodilatation.
   - Can **cause an intense cutaneous flush and pruritus**; Administration of aspirin prior to taking niacin decreases the flush.
6. **Bempedoic acid** is a non-statin, targeted therapy that is designed to primarily work in the liver to inhibit cholesterol biosynthesis.
   - Inhibits adenosine triphosphate citrate lyase (ACL); an enzyme two steps upstream from HMG-CoA reductase, along the cholesterol biosynthesis pathway.
   - By inhibiting ACL, Bempedoic acid reduces cholesterol synthesis, resulting in LDL receptor upregulation and increased clearance of LDL from the bloodstream
   - In a study, it reduced LDL cholesterol by about 20 mg/dl compared to placebo and had no more side effects than placebo.
   - Regardless of other lipid lowering therapy, fixed dose Bempedoic acid + Ezetimibe combo lowered LDL-C levels by a 36-38% when compared with placebo, versus 23% for ezetimibe alone and 17% for Bempedoic acid alone. (EAS 2019).

Scientific name	D. form	Trade name	concentration
Niacin (Vit. B_3)	Tab	Niaspan®, Niacor®	*Various conc.*
Acipimox	Cap	Olbetam®	250 mg
Ezetimibe	Tab	Ezetrol® , Zetia® , Zetex®	10 mg
Omega 3 Fatty Acids	Cap	Lovaza® , Omacor®	1 gm
Omega 3 Carboxylic acids	Cap	Epanova®	1 gm
Icosapent **	Cap	Vascepa®	1 gm
Lomitapide	Cap	Juxtapid®	5 mg , 10 , 20 , 40 , 60 mg
Bempedoic acid	Tab	Bempo®	180 mg

**** Icosapent** is an Eicosapentaenoic acid (ethyl ester) an Omega Fatty acid, which ↓ VLDL-TG synthesis, ↓ lipogenesis in liver, ↑ plasma lipoprotein lipase activity.

F) Anti-Lipemic Combos:

Trade name	D. form	Scientific name	concentration
Inegy®, Vytorin®, AlkorPlus®	Tab	Ezetimibe + Simvastatin	10mg/20mg , 10mg/40 mg
Liptruzet®	Tab	Ezetimibe + Atorvastatin	10mg/20mg , 10mg/40 mg
Rosuzet®	Tab	Ezetimibe + Rosuvastatin	10mg/10mg , 10mg/20 mg
Bempoplus®	Tab	Ezetimibe + Bempedoic acid	10mg/180mg
Advicor®	Tab	Lovastatin + Niacin	20mg/500mg
Simcor®	Tab	Simvastatin + Niacin	20mg/500mg
Lipikind F®, Statring plus®	Tab	Fenofibrate + Atorvastatin	160mg/10mg , 160mg/20mg
Rosulip F®	Tab	Fenofibrate + Rosuvastatin	145mg/10mg , 145mg/20mg
Lipid Free®	Tab	Fenofibrate + Rosuvastatin	160 mg/40 mg
Pravafen®	Cap	Fenofibrate + Pravastatin	160mg/40mg

3.16 - Drugs used to prevent Abnormal Blood Clotting

a. Blood clots normally form only as a response to injury, in some people, however, there is a tendency for clots to form in the blood vessels without apparent cause; Disturbed blood flow occurring as a result of the presence of fatty deposits (atheroma) inside the blood vessels increases the risk of the formation of this type of abnormal clot (or thrombus); In addition, a portion of a blood clot (known as an embolus) formed in response to injury or surgery may sometimes break off and be removed in the bloodstream.

- The likelihood of this happening is increased by long periods of little or no activity.
- When an abnormal clot forms, there is a risk that it may become lodged in a blood vessel, thereby blocking the blood supply to a vital organ such as the brain or heart.

b. There are Three main types of drugs are used to prevent and disperse clots: Antiplatelet drugs, Anticoagulants, and Thrombolytics.

1. Antiplatelet Drugs

- Taken regularly by people with a tendency to form clots in the fast-flowing blood of the heart and arteries, **these drugs are also given to prevent clots from forming** after heart surgery (such as PCI); They reduce the tendency of platelets to stick together when blood flow is disrupted.
- The most widely used antiplatelet drug is **Aspirin**, which has an antiplatelet action even when given in much lower doses than would be necessary to reduce pain; Other antiplatelet drugs are **Clopidogrel** and **dipyridamole**.

2. Anticoagulants

- They help to maintain normal blood flow in people at risk from clot formation; **They can either prevent the formation of blood clots in the veins or stabilize an existing clot** so that it does not break away and become a circulation-stopping embolism.
- All anticoagulants reduce the activity of certain blood clotting factors, but each drug's mode of action differs. These medicines do not dissolve clots that have already formed, however: these are treated with thrombolytic drugs.
- Anticoagulants fall into two groups: those that are given by intravenous injection and act immediately, and those that are given by mouth and take effect after a few days.
  - **A. Injectable Anticoagulants:** such as **Heparin,** the most widely used drug of this type and it is used mainly in hospital during or after surgery. It is also given during kidney dialysis to prevent clots from forming in the dialysis equipment. Because heparin cannot be taken by mouth, it is less suitable for long term treatment in the home, other Injectable Anticoagulants include **Enoxaparin**, **Dalteparin**.
  - **B. Oral Anticoagulants:** such as **Warfarin**, the most widely used of the oral anticoagulants. These drugs are mainly prescribed to prevent the formation of clots in veins and in the chambers of the heart (they are less likely to prevent clot formation in arteries). Oral anticoagulants may be given following injury or surgery (in particular, heart valve replacement) when there is a high risk of embolism.
- Oral Anticoagulants are also given long-term as preventative treatment to people at risk of strokes. A common problem with these drugs is that over dosage may lead to bleeding from the nose or gums, or in the urinary tract. For this reason, the dosage needs to be carefully calculated; regular blood tests are performed to ensure that the clotting mechanism is correctly adjusted, although this is not necessary with new oral anticoagulants such as **Dabigatran** and **Rivaroxaban**; The action of oral anticoagulants may be affected by many other drugs, and it may therefore be necessary to alter the dosage of anticoagulant when other drugs also need to be given. In particular, no anticoagulant should be taken together with aspirin except on the direction of a doctor.

3. Thrombolytics

- Also known as **Fibrinolytics**, these drugs are **used to dissolve clots that have already formed**. They are usually given in hospital intravenously to clear a blocked blood vessel (in coronary thrombosis, for example); **The sooner they are given after the start of symptoms, the more likely they are to reduce the size and severity of a heart attack**.
- Thrombolytic drugs may be given either intravenously or directly into the blocked blood vessel; The main Thrombolytics are **Streptokinase** and **Alteplase**, which act by increasing the blood level of plasmin, the enzyme that breaks down fibrin, when given promptly, **Alteplase appears to be tolerated better than streptokinase.**
- The most common problems with these drugs are increased susceptibility to bleeding and bruising, and allergic reactions to streptokinase, such as rashes or breathing difficulty. Once streptokinase has been given, patients are given a card indicating this, because further treatment with the same drug may be less effective and an alternative (such as Alteplase) used instead.

First: Antiplatelet drugs

- **It is important to distinguish between thrombi and emboli**; a clot that adheres to a vessel wall is called a "thrombus," whereas an intravascular clot that floats in the blood is termed an "embolus." Thus, a detached thrombus becomes an embolus.
  - Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients.
  - **Arterial thrombosis usually consists of a platelet- rich clot, venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than arterial clots.**

1. Antiplatelet drugs **reduce platelet aggregation** and are **used to prevent further thromboembolic events** in patients at risk (ex: patients who have suffered myocardial infarction, ischemic stroke or transient ischemic attacks, or unstable angina), and for primary prevention of a thromboembolic event in patients at risk.
2. They Also **inhibit thrombus formation in the arterial circulation**, because in faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin.
3. The most commonly used Antiplatelet drugs are **aspirin** (at low dose) and **Clopidogrel** and less commonly is **Dipyridamole**.
   a. **Clopidogrel** may be given as **an alternative to aspirin** (in patients who cannot take aspirin), **Clopidogrel** may be given **in combination with aspirin** in some conditions like **myocardial infarction** for **synergistic effect**.
   b. Aspirin tablet commonly formulated as **enteric coated tablet** to decrease GIT irritation.
   c. **Pregnant women** who are at **high risk of developing preeclampsia**, or if they have had hypertension during a previous pregnancy; these women **are advised to take aspirin once daily** (unlicensed indication) from week 12 of pregnancy until the baby is born.
   d. Owing to an association with **Reye's syndrome**, aspirin-containing preparations should not be given to children under 16 years, unless specifically indicated, as for Kawasaki disease.

4. Types of Antiplatelet (According to mechanism of Action)

a) **Aspirin** (inhibition of COX-1 → decreased thromboxane A2 synthesis)
b) **Clopidogrel, Ticlopidine, Ticagrelor** and **Prasugrel** (inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen & to each other)
c) **Eptifibatide** and **Tirofiban** (blocking the GP IIb/IIIa receptor)
d) **Abciximab** (monoclonal antibody which blocks GP IIb/IIIa receptor)
e) **Dipyridamole** (coronary vasodilator, increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in ↓ thromboxane A2 synthesis)
f) **Cilostazol** (vasodilator, inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP)
g) **Anagrelide** (inhibit phosphodiesterase type III)

Scientific name	Dosage	Trade name	concentration
Aspirin	Tab , EC Tab	(Various)	75 , 81 , 100 , 300 mg
P2Y12 antagonists (Thienopyridines)			
Clopidogrel	Tab	Plavix®	75 mg , 300 mg
Ticlopidine	Tab	Ticlid®	250 mg
Ticagrelor	Tab	Brilinta® , Brillique®	90 mg
Cangrelor	Inj. Solu.	Kengreal®	50 mg/vial
Prasugrel	Tab	Effient®	5 mg , 10 mg
Glycoprotein IIb/IIIa inhibitors			
Eptifibatide	Inj. Solu.	Integrilin®	2 mg/ml (10 ml vial)
	Infusion		750 mcg (100 ml vial)
Tirofiban	Inj. Solu.	Aggrastat®	50 mcg/ml
Abciximab	Inj. Solu.	ReoPro®	2 mg/ml (5 ml vial)
Other antiplatelets			
Dipyridamole	Tab	Procardin® , Persantin®	25 mg , 50 mg , 75 mg
	Cap MR	Persantin®	200 mg
	Inj. Solu.	Persantine®	5 mg/ml
Cilostazol	Tab	Pletal®	50 mg , 100 mg
Vorapaxar	Tab	Zontivity®	2.08 mg
Atopaxar	Pending FDA approval		
Anagrelide	Cap	Agrylin®	0.5 mg , 1 mg

Notes:

1. All antiplatelet drugs can cause prolonged bleeding for **which there is no antidote.**
2. **About P2Y12 antagonists:**
   a. **Ticagrelor** is more potent (more effective) than **Clopidogrel**, same potent as **Prasugrel** but with less side effects **(Ticagrelor have less bleeding tendency than Prasugrel).**
   b. **Prasugrel** is more potent than **Clopidogrel**, but **Prasugrel** is only indicated for PCI.
   c. **Ticlopidine** is associated with neutropenia that requires frequent monitoring of the CBC during the first 3 months of use.
   d. **Clopidogrel** is given once daily (300 mg LD, 75 mg MD), **Prasugrel** is given once daily (60 mg LD, 10 mg MD) and **Ticagrelor is given twice daily** (180 mg LD, 90 mg MD).
   e. In a study published by **JAMA, Ticagrelor** was found to have a **bactericidal activity** against all gram-positive strains tested, including drug-resistant strains MRSE, MRSA. [15]
3. **Glycoprotein IIb/IIIa inhibitors** are indicated for the prevention of cardiac ischemic complications in patients undergoing PCI only.
   a. **Abciximab** has a high potential for bleeding, especially if used with anticoagulants, Abciximab is expensive, limiting its use in some settings.
   b. **Eptifibatide, Tirofiban** are only available as IV formulations because oral preparations of these GP IIb/IIIa blockers are too toxic. The major adverse effect of both drugs is bleeding.
4. **Dipyridamole causes vasodilation** when given at high doses for a short time.
   a. has been shown to lower pulmonary hypertension without significant drop of systemic blood pressure, also has been shown to increase myocardial perfusion and left ventricular function in patients with ischemic cardiomyopathy.
   b. It can be used for myocardial stress testing as an alternative to exercise-induced stress methods such as treadmills.
   c. A combination of dipyridamole and aspirin is FDA-approved for the secondary prevention of stroke; However, it is not licensed as monotherapy for stroke prophylaxis.
5. **Anagrelide** is also used to **treat essential Thrombocytosis** and **Thrombocythemia.**
   a. It also has been **used in the treatment of chronic myeloid leukemia.**

6. **Cilostazol** is an **oral antiplatelet** agent that also has **vasodilating activity; It is FDA approved to reduce the symptoms of intermittent claudication.**
   a. **It is also used in the treatment of Buerger disease** (the recurring progressive inflammation and thrombosis (clotting) of small and medium arteries and veins of the hands and feet), **vascular sclerosis** complicating diabetes mellitus, and used for the improvement of symptoms in patients with chronic cerebral ischemia.
   b. **Cilostazol is contraindicated in patients with congestive heart failure of any severity**, and it should be used cautiously in patients with a history of any cardiac disease.
   c. Based on the American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy, **Cilostazol is an effective and recommended alternative antithrombotic to either aspirin or Clopidogrel in a dual antiplatelet regimen** when allergy or drug intolerance to either agent occurs in patients who have undergone elective PCI with bare metal or drug-eluting stent placement.
   d. Based on the American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy, **Cilostazol is an effective and recommended alternative antithrombotic in patients with a history of non-cardio embolic ischemic stroke or TIA.**
   e. Also used in the **Prevention of stent thrombosis and restenosis after coronary stent placement (adjunct with aspirin and Clopidogrel).**

Anti-platelet combinations:

Trade name	D. form	Scientific name	concentration
Aggrenox®	Cap ER	Aspirin + Dipyridamole	25 mg + 200 mg
Dospin®, Cugrel-A®	Tab	Aspirin + Clopidogrel	75 mg + 75 mg
Dospin-A®, ***Atormac Gold®***	Tab, Cap	Aspirin + Clopidogrel + Atorvastatin	(75mg+75mg+10mg) Dospin-A (75mg+75mg+20mg) Atromac G
Cargrel®	Cap	Aspirin + Clopidogrel	150 mg + 75 mg

Notes:

1. In trials in which a regimen of Dipyridamole plus aspirin was compared with aspirin alone, Dipyridamole provided **no additional beneficial effect** (Antithrombotic Trialists' Collaboration, 2002)
2. A recent study comparing this combination with Clopidogrel for secondary prevention in patients with stroke or transient ischemic attacks **showed no advantage** of Dipyridamole plus aspirin.

Second: Anticoagulants

1. Anticoagulants are used in the **treatment and prophylaxis** of **thromboembolic disorders**, or **extension of an existing thrombus** in the slower-moving venous side of the circulation in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells.
2. **Anticoagulants are of less use in preventing thrombus formation in arteries**, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin.
3. **Anticoagulants available:**
   a) **Injectable Anticoagulants:**
      - Unfractionated heparin
      - Low-molecular-weight heparins **(LMWHs)** (Enoxaparin, Dalteparin, Tinzaparin)
      - Fondaparinux
      - Direct thrombin inhibitors (Lepirudin, Bivalirudin, Argatroban, Desirudin)
   b) **Oral anticoagulants** (as Warfarin), and direct acting as: (Dabigatran, Rivaroxaban).

4. Anticoagulants can **cause bleeding**; therefore, their anticoagulant effects must be **monitored by laboratory test to avoid excessive bleeding:**
    A. **Warfarin** is monitored by a test called **international normalized ratio INR.**
    B. **Unfractionated heparin** is monitored by a test called **activated partial thromboplastin time (APTT).**

5. **Heparin** and **LMWHs** are the **anti-coagulants of choice for treating pregnant women** with prosthetic heart valves or venous thromboembolism, because these agents do not cross the placenta (due to their large size and negative charge).

6. Regarding **Warfarin**:
    - it inhibits the **production of vitamin K–dependent clotting factors**
    - **it has no effect on circulating coagulation factors that have been previously formed**, and its therapeutic antithrombotic activity is delayed for 5 to 7 days
    - In patients with acute VTE, a rapid-acting anticoagulant (UFH, LMWH, or Fondaparinux) **should be overlapped with warfarin** for a minimum of 5 days and until the INR is greater than 2 and stable.
    - **Hemorrhagic complications** ranging from mild to severe and life-threatening can occur at anybody site; The GI tract and nose are the most frequent sites of bleeding.
    - **Intracranial hemorrhage** is the most serious complication and often results in permanent disability and death.
    - Because of the large number of foods–drug and drug–drug interactions with warfarin, close monitoring and additional INR determinations may be indicated whenever other medications are initiated, or discontinued, or an alteration in consumption of vitamin K–containing foods is noted
    - **Vitamin K is the antidote of Warfarin**.

7. Regarding **Heparin (unfractionated Heparin UFH)**:
    - **UFH** can be administered via the intravenous (IV) or subcutaneous (SC) route.
    - Drug of choice for using in pregnant women **(don't cross the placenta).**
    - dose in **MI** (60 mg/kg LD, 12 mg/kg MD) and in **DVT** (80 mg/kg LD, 18 mg/kg MD).
    - adverse effects include: Hypersensitivity reactions (chills, fever), Thrombocytopenia, Long-term UFH has been reported to cause alopecia, priapism, hyperkalemia, and osteoporosis
    - **Heparin-induced thrombocytopenia (HIT)** is a serious immune-mediated problem that requires immediate intervention (discontinue heparin and initiate alternative anticoagulation with a parenteral direct thrombin inhibitor)
    - **UFH** can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion (because it's short acting).
        - If major bleeding occurs, discontinue UFH and give **I.V. protamine sulfate.**

8. Regarding **LMWHs**:
    - **Advantages of LMWHs over UFH include**: predictable anticoagulation dose response, improved SC bioavailability, dose-independent clearance, longer biologic half-life, lower incidence of thrombocytopenia, and less need for routine laboratory monitoring [4]
    - **LMWHs can be easily administered in the outpatient setting**, thus enabling the treatment of VTE at home
    - Because LMWH anticoagulant response is predictable when given by SC injection, routine laboratory monitoring is unnecessary.
    - As with other anticoagulants, bleeding is the most common adverse effect of LMWH therapy, but **major bleeding may be less common than with UFH**; If major bleeding occurs, administer protamine sulfate IV, although it cannot neutralize the anticoagulant effect completely
    - Thrombocytopenia can occur with LMWHs, **but the incidence of HIT is three times lower than with UFH**

- **Enoxaparin** LD is 30 mg I.V bolus, normal dose is 1 mg/kg every 12 hours.
  - **Enoxaparin 1 mg = 100 IU**.
  - **Enoxaparin** maybe administered via inhalation route for the prevention of exercise-induced Bronchoconstriction.
- **Tinzaparin** was withdrawn from the USA markets due to the presence of particulate matter found in the injection solution, also due to poor sales. It also increases the risk of death in patients over 70 years old with renal disease.

9. Regarding **Direct Oral Anticoagulants:**

- These currently include two categories: **direct thrombin (factor IIa) inhibitor (DTI)** (Dabigatran) and **direct Xa inhibitors** (Rivaroxaban, Apixaban, and Edoxaban).
- As compared to warfarin, these oral anticoagulants **have a more rapid onset, shorter half-life, wider therapeutic window, and more predictable pharmacokinetics**.
  - These features allow for sole oral therapy without the need for an overlapping parenteral agent (with the exception of Edoxaban for VTE), **no need for titration or dose adjustments** in patients with normal renal function, and **no need for routine monitoring.**
- Compared to warfarin, **they have a lower risk of intracranial hemorrhage**.
- Issues of concern include the lack of antidotes, and risk of thrombosis due to missed doses.
- **Dabigatran** dose is dependent on CrCl:
  - CrCl greater than 30 mL/minute: **150 mg twice daily**
  - CrCl 15–30 mL/minute: **75 mg twice daily**.
  - **Dabigatran** has the highest half-life (17 hour), and the **only direct oral anticoagulant that is dialyzable.**
  - **Idarucizumab** is a monoclonal antibody fragment used to reverse **Dabigatran** anticoagulation.
- **Rivaroxaban** dose is also dependent on CrCl: **once daily dosing**
  - CrCl greater than 50 mL/minute: **20 mg/day with evening meal.**
  - CrCl 15–50 mL/minute: **15 mg/day with evening meal.**
  - Also, the **dose is regarded to the indication** as follows:
    - **DVT prophylaxis for** Knee replacement 10 mg/day for 12 days.
    - **DVT prophylaxis** for Hip replacement 10 mg/day for 35 days.
    - **Non valvular AF** 20 mg/day
    - **DVT or PE treatment** 15mg twice for 21 days, then 20 mg/day.
    - **Reduction risk of recurrence of DVT, PE** 10 mg/day.
    - **Reduction risk of major cardiovascular events** 2.5 mg twice + Aspirin.
- **Apixaban** is dosed **5 mg twice daily** unless: In patients with at least two of the following characteristics: (age 80 years or older, body weight of 60 kg or less, or SCr of 1.5 mg/dl or greater) the recommended dose is 2.5 mg twice daily.

10. Regarding **Parenteral direct thrombin inhibitors:**

- injectable DTIs include: Lepirudin, Bivalirudin, Argatroban, and Desirudin.
- Parenteral DTIs are considered the drugs of choice for the treatment of VTE in patients with a diagnosis or history of HIT.
- Used with caution in patients with renal insufficiency as no antidote exists.

11. Regarding **Parenteral Xa inhibitor (Fondaparinux):**

- Selectively inhibits only Factor Xa, **do not increase PT and PTT.**
- synthetically derived **with no variable biologic activity.**
- safe and effective alternative to LMWH for treatment of VTE. It is also being approved for prevention of VTE following orthopedic or abdominal surgery
- Patients receiving Fondaparinux do not require routine coagulation testing.
- **FDA warning:** Fondaparinux should not be used in the setting of lumbar puncture or spinal cord surgery, due to risk of epidural or spinal hematomas.

Oral Anticoagulants			
Warfarin	Tab	Coumadin®, Marevan®	1 mg , 2 mg , 3 mg , 4 mg , 5 mg
	Vial (powder)	Jantoven®	5 mg/vial
Acenocoumarol	Tab	Sinthrome®	1 mg
Phenindione	Tab	Phedone®, Dindevan®	10 mg , 25 mg , 50 mg
Dabigatran	Cap	Pradaxa®	75 mg , 110 mg , 150 mg
Apixaban	Tab	Eliquis®	2.5 mg , 5 mg
Rivaroxaban	Tab	Xarelto®	10 mg , 15 mg , 20 mg
Edoxaban	Tab	Savaysa® , Lixiana®	15 mg , 30 mg , 60 mg
Betrixaban	Cap	Bevyxxa®	40 mg , 80 mg
Vorapaxar	Tab	Zontivity®	2 mg
Injectable Anticoagulants			
Unfractionated Heparin	Inj. Solu.	Heparin®, Poliparin®	1000 IU/ml , 2500 IU/ml , 5000 IU/ml
LMW Heparins			
Enoxaparin	Prefilled Syringe	Lovenox®, Clexan®	2000 IU , 4000 IU , 6000 IU
	Multidose Vial		100 mg/ml (3 ml vial)
Dalteparin	Prefilled Syringe	Fragmin®	2500 IU , 5000 IU , 7500 IU
	Inj. Solu.		10,000 IU/ml , 25,000 IU/ml
Tinzaparin *	Multidose Vial	Innohep®	20,000 IU/2ml , 40,000 IU/2ml
	Prefilled Syringe		3500 IU , 7000 IU , 10,000 IU
Bemiparin	Inj. Solu.	Ivor®, Hibor®	1000 IU/ml , 5000 IU/ml
Nadroparin	Inj. Solu.	Fraxiparine®	9500 IU/ml , 19,000 IU/ml
Ardeparin	Prefilled Syringe	Normiflo®	5000 IU , 10,000 IU
Reviparin	Prefilled Syringe	Clivarine®	1432 IU , 3436 IU
	Multidose Vial		34,356 IU
Injectable Direct Thrombin Inhibitors			
Lepirudin	Vial (powder)	Refludan®	50 mg/vial
Desirudin	Inj. Solu.	Iprivask®	15 mg/vial
Bivalirudin	Vial (powder)	Angiomax® , Angiox®	250 mg/vial
Argatroban	Inj. Solu.	Acova®, Exembol®	100 mg/ml (2.5 ml vial)
Selective Factor Xa inhibitors			
Fondaparinux	Prefilled Syringe	Arixtra®	2.5 mg , 5 mg , 7.5 mg , 10 mg
Idraparinux	Prefilled Syringe	Idra®	2.5 mg
Idrabiotaparinux	Prefilled Syringe	----------	----------
Other Anticoagulants			
Danaparoid	Inj. Solu.	Orgaran®	1250 IU/ml (0.6 ml amp)
Epoprostenol	Infusion	Flolan®	500 mcg/vial
Sulodexide	Cap , Amp	Vessel Due F®	250 LSU (cap) , 600 LSU (amp)

Notes:

1. **Danaparoid** is a Heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing general or orthopedic surgery**, it also has a role in patients who develop heparin-induced thrombocytopenia.**
2. **Epoprostenol** (prostacyclin) can be given to inhibit platelet aggregation during renal dialysis when heparins are unsuitable or contra-indicated. It is also licensed for the treatment of primary pulmonary hypertension resistant to other treatments (see section 20)
3. **Sulodexide** is an Anticoagulant, Antiplatelet and a Fibrinolytic.

Notes:

1. **Protamine sulfate** is used to treat over-dosage of unfractionated or LMWH (only partially reverses the effects of LMWHs); **The long half-life of LMWH should be taken into consideration** when determining the dose of protamine sulfate; the effects of LMWH can persist for up to 24 hours.
   - Dosed as 1-1.5 mg per each 100 units of Heparin.
   - Dosed as 0.5-1 mg per each 100 units of LMWHs.
   - Excessive doses of protamine can have an anticoagulant effect.
2. **Idarucizumab** is a monoclonal antibody fragment used to reverse **Dabigatran** anticoagulation.
   - Dosed as 5 gm infused I.V. either as a bolus or separated 2.5 gm vials
3. **Andexanet Alfa** is specifically indicated for patients treated with **Rivaroxaban** and **Apixaban**, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
   - Administer as an intravenous (IV) bolus, with a target rate of 30 mg/min, followed by continuous infusion for up to 120 minutes.

Scientific name	Dosage form	Trade name	concentration
Protamine Sulfate	Inj. Solu.	Protamine®	10 mg/ml (10 ml amp)
Idarucizumab	Inj. Solu.	Praxbind®	2.5 gm/50 ml vial
Andexanet Alfa	Vial	AndexXa®	100 mg/vial

Third: Thrombolytic drugs (Fibrinolytics)

1. Acute thromboembolic disease in selected patients (usually in emergency State) may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots.
2. The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug; Thus, hemorrhage is a major side effect .
3. **Thrombolytic drugs** are indicated for any patient with **acute myocardial infarction**, Trials have shown that the benefit is greatest in those with ECG changes that include **ST segment elevation** (especially in anterior infarction) and in patients with bundle branch block.
   a. **Alteplase, streptokinase, and Urokinase** can be used for other thromboembolic disorders such as deep-vein thrombosis and pulmonary embolism (massive emboli).
   b. **Alteplase** is also used for acute ischemic stroke.
   c. **Urokinase** is also licensed to restore the patency of occluded intravenous catheters and cannulas blocked with fibrin clots.
4. **Alteplase** should be given within 6–12 hours of MI symptom onset, **Reteplase** and **Streptokinase** within 12 hours of symptom onset, **but ideally all should be given within 1 hour**; use after 12 hours requires specialist advice; **Tenecteplase** should be given as early as possible and usually within 6 hours of symptom onset
   - **Alteplase** may cause **Angioedema**.
5. Practice guidelines **indicate that a more fibrin-specific agent (Alteplase, Reteplase, or Tenecteplase) is preferred over the non–fibrin-specific agent streptokinase**, because Fibrin-specific agents open a greater percentage of infarct arteries, which results in smaller infarcts and lower mortality, doses are given as below:
   - **Streptokinase:** 1.5 MU IV over 60 min.
   - **Alteplase:** 15 mg IV bolus followed by 0.75 mg/kg IV over 30 min (max 50 mg) followed by 0.5 mg/kg (max 35 mg) over 60 min (maximum total dose = 100 mg).
   - **Reteplase:** 10 units IV x 2, 30 min apart.
   - **Tenecteplase**: according to weight, less than 60 kg (<132 lbs.) = 30 mg IV bolus
     60 - 69.9 kg (132–153 lbs.) = 35 mg IV bolus
     70 - 79.9 kg (154–176 lbs.) = 40 mg IV bolus

6. **Intra-Cranial Hemorrhage (ICH)** and major bleeding are the most serious side effects. The risk of ICH is higher with fibrin-specific agents than with streptokinase; However, the risk of systemic bleeding other than ICH is higher with streptokinase than fibrin-specific agents.
7. **Defibrotide** is indicated for the treatment of severe hepatic veno-occlusive disease (only).
8. **Relative and Absolute contraindications of Thrombolytics:**

Relative Contraindications	Absolute Contraindications
BP > 180/110 mm Hg on presentation or history of chronic poorly controlled HTN	ANY prior hemorrhagic stroke
History of ischemic stroke > 3 months prior	Ischemic stroke within 3 months (except in past 4½ hours)
Recent major surgery (< 3 weeks prior)	Intracranial neoplasm or arteriovenous malformation
Traumatic or prolonged CPR (> 10 minutes)	Active internal bleeding
Recent internal bleeding (within 2–4 weeks)	Aortic dissection
Active peptic ulcer	Considerable facial trauma or closed-head trauma in past 3 months
Noncompressible vascular punctures	Intracranial or intraspinal surgery within 2 months
Pregnancy	Severe uncontrolled HTN (unresponsive to emergency therapy)
Known intracranial pathology (dementia)	For streptokinase,[a] treatment within previous 6 months (if considering streptokinase again)
Oral anticoagulant therapy	

Scientific name	Dosage form	Trade name	concentration
Alteplase	Powder for Inj.	Activase® , Actilyse® , TPA®	2 mg , 50 mg , 100 mg
Reteplase	Powder for Inj.	Retavase®, Rapilysin®	10.4 units
Tenecteplase	Powder for Inj.	Metalyse® , TNKase®	40 mg , 50 mg
Streptokinase*	Powder for Inj.	Streptase®, Kabikinase®	25 mg
Anistreplase	Powder for Inj.	Eminase®	30 units
Defibrotide	Solu. For infusion	Defitelio®, Noravid®	80 mg/ml
Urokinase **	Powder for Inj.	Abbokinase® , Kinlytic® Syner-KINASE®	10,000 units 25,000 units

* **Streptokinase** is a foreign protein and it is an antigenic. Rashes, fever, and anaphylaxis occur.
** **Urokinase** is produced naturally in the body by the kidneys. Therapeutic Urokinase is isolated from human kidney cells and has low antigenicity.

3.17 - Drugs used to Prevent Bleeding (anti-Fibrinolytics)

a. When bleeding occurs as a result of injury or surgery, the body normally acts swiftly to stem the flow by sealing the breaks in the blood vessels; This occurs in two stages; first when cells called platelets accumulate as a plug at the opening in the blood vessel wall, and then when these platelets produce chemicals that activate clotting factors in the blood to form a protein (fibrin).

b. Vitamin K plays an important role in this process; An enzyme in the blood called plasmin ensures that clots are broken down when the injury has been repaired.
- If the blood does not clot, there is a danger of excessive blood loss.

c. It is sometimes useful to promote blood clotting in non-hemophiliacs when bleeding is difficult to stop (for example, following surgery); In such cases, blood clots are sometimes stabilized by reducing the action of plasmin with an **anti-fibrinolytic** (or **hemostatic**) drug like **Tranexamic acid**; this is also occasionally given to hemophiliacs before minor surgery as tooth extraction.

1. **Tranexamic acid** and **Aminocaproic acid**: They are used to **prevent bleeding** or to **treat bleeding** as (bleeding associated with menorrhagia); **excessive menstrual bleeding**, given 3 times daily.
   - **a) Tranexamic acid is 10x times more potent than Aminocaproic acid).**
   - **b)** Tranexamic acid is used in hereditary angioedema, epistaxis, and in thrombolytic overdose.
   - **c)** In 2010, the CRASH-2 trial showed that **Tranexamic acid** safely **reduces mortality in bleeding trauma patients.**
   - **d)** It also **reduces rates of mortality and urgent surgery in** patients with upper GI hemorrhage.
   - **e)** Also used successfully to **control bleeding in pregnancy (category B).**

2. **Aprotinin** may **cause fatal anaphylactic or anaphylactic reactions (including kidney dysfunction)**; The drug was temporarily withdrawn worldwide in 2007 after studies suggested that its use increased the risk of complications or death, In February 2012 the European Medicines Agency (EMA) scientific committee reverted its previous standpoint regarding **Aprotinin**, and has recommended that the suspension be lifted.
   a) In cardiac surgery with a high risk of significant blood loss, **Aprotinin significantly reduced bleeding, mortality and hospital stay**; Beneficial effects were also reported in high-risk orthopedic surgery; In liver transplantation, initial reports of benefit were overshadowed by concerns about toxicity.

3. **Etamsylate** is a hemostatic drug, it acts by **increasing capillary endothelial resistance** and **promoting platelet adhesion**; indicated for Prophylaxis and control of hemorrhages from small blood vessels, neonatal intra-ventricular hemorrhage capillary bleeding of different etiology, including: menorrhagia, hematuria, epistaxis, prevention of periventricular hemorrhages in prematurely born children.
   - It is also possible that Etamsylate would **reduce reperfusion hemorrhage** in ischemic areas of the brain, preventing secondary damage.

Note: A tendency to **bleed may also occur with deficiency of vitamin K**, which is required for the production of several blood clotting factors. Vitamin K is absorbed from the intestine in fats, but some diseases of the small intestine or pancreas cause fat to be poorly absorbed; As a result, the level of vitamin K in the circulation is low, causing impaired blood clotting.

- A similar problem sometimes occurs in newborn babies due to absence of vitamin K (because Vit. K cannot reach the baby while its still in the uterus, and in his first days of life the baby cannot produce Vit. K because there are no bacteria present in his intestine yet); causing **hemorrhagic disease of the newborn**; thus, all newborn infants are routinely given Vit. K.
- Injections of **Phytomenadione**, a vitamin K preparation, are used to restore levels to normal.
- **I.V. administration of Vit. K should be very slowly**, not exceeding 1 mg/minute, severe hypersensitivity reaction (including anaphylactic shock and deaths) have been reported following rapid I.V. administration.

Scientific name	Dosage form	Trade name	concentration
Anti-Fibrinolytics			
Tranexamic acid	Amp	Exacyl® , Lysteda®	100 mg , 50 mg
	Tab	Cyklokapron®	500 mg , 650 mg
Aminocaproic acid	Tab	Amicar® , Cyclo-C®	500 mg
Aprotinin	Inj. Solu.	Trasylol®	10 million IU/ml
Etamsylate	Tab , Amp	Dicynone®	250 mg
Vitamin K products			
Phytomenadione (Vit K_1) *	Amp	Konakion MM®	10 mg/1 ml
	Amp	Konakion MM Pediatric®	2 mg/0.2 ml

* Can be taken orally, by I.M. injection or I.V. route.

3.18- Drugs that raise low blood pressure (Anti-Hypotensive)

1. The causes of low blood pressure can range from dehydration to serious medical or surgical disorders (ex: heart failure, diabetes or hypothyroidism), Low blood pressure is treatable, but it's important to find out what's causing it so that it can be properly treated.
   - Low blood pressure that either doesn't cause signs or symptoms or causes only mild symptoms, such as brief episodes of dizziness when standing, rarely requires treatment.
   - When low blood pressure is caused by medications, treatment usually involves changing the dose of the medication or stopping it entirely.

2. **Here are several ways to increase low blood pressure:**
   a. **Use more salt:** Sodium can raise blood pressure, sometimes dramatically. For people with low blood pressure, that can be a good thing.
   b. **Drink more water:** Fluids increase blood volume and help prevent dehydration, both of which are important in treating hypotension.
   c. **Morning dose of Caffeine,** as in coffee, Tea or tablet form.
   d. **Medications:** Several medications, either used alone or together, can be used to treat low blood pressure that occurs when you stand up (orthostatic hypotension).

3. **Commonly we have four medications:**
   a. **Fludrocortisone**: is a **Corticosteroid** intended for use as a mineralocorticoid only, it causes Na^+/water retention; thus, increasing blood pressure.
      - It is also used to replace the missing hormone aldosterone in various forms of adrenal insufficiency such as **Addison's disease** and the classic salt wasting form of **congenital adrenal hyperplasia;** Usual dose is 1 tab daily (0.1 mg once).
      - Used with caution in Diabetes, Congestive Heart Failure and Glaucoma

   b. **Etilefrine** (cardiac stimulant); it is a direct-acting a **sympathomimetic agent stimulating both α and β receptors**; but it has a high affinity for α receptors.
      - Tablet and drops dosed 3 times daily, while the MR dosage form is given once daily.

   c. **Midodrine**: works by restricting the ability of blood vessels to expand (α1 agonist), which raises blood pressure, it also acts on β receptors and has a positive inotropic action.
      - The usual dose is 1 tablet (10 mg) every 8 hours (3 times daily).
      - Also indicated for the treatment of **stress incontinence** (off-label).

   d. **Droxidopa** is approved at Jan. 2014 for **Neurogenic Orthostatic Hypotension;** it acts as a prodrug to the neurotransmitter norepinephrine (noradrenaline).
      - Unlike norepinephrine, Droxidopa is capable of crossing the protective blood–brain barrier (BBB).
      - Also used for **Intradialytic hypotension** (IDH) or **hemodialysis-induced hypotension.**

4. Other drugs act by raising blood pressure in different mechanisms, they are used in chronic hypotension, and in emergency cases when blood pressure drops to a critical point.
   - These include (Epinephrine, Norepinephrine, Dopamine and Dobutamine).

Scientific name	D. form	Trade name	concentration
Etilefrine	Tab	Effortil® , Vascon®	5 mg
	Tab MR	Vascon MR®	25 mg
	Drop		7.5 mg/ml
Midodrine	Tab	Orvaten® , Gutron® , ProAmatine®	2.5 mg , 5 mg , 10 mg
Fludrocortisone	Tab	Florinef®	0.1 mg
Heptaminol *	Tab	Corasore®	150 mg
Droxidopa	Cap	Northera®	100 mg , 200 mg , 300 mg

*** Heptaminol** has a +ve inotropic effect, also has a mild peripheral vasoconstrictor effect.

3.19-Volume Expanders (I.V. Fluids)

1. When blood is lost; the greatest immediate need is to stop further blood loss. The second greatest need is replacing the lost volume. By This way the remaining red blood cells can still oxygenate body tissue.
2. Normal human blood has a significant excess oxygen transport capability, only used in cases of great physical exertion. Provided blood volume is maintained by volume expanders.
3. There are two main types of volume expanders: **crystalloids and colloids.**

A. **Crystalloids:** The most commonly used crystalloid fluid is **Normal Saline (N/S)**, a solution of **sodium chloride at 0.9%** concentration, which is close to the concentration in the blood (isotonic). **Ringer's lactate** or **Ringer's acetate** is another isotonic solution often used for large-volume fluid replacement. A solution of **5% dextrose in water**, sometimes called **D5W**, is often used instead if the patient is at risk for having low blood sugar or high sodium. The choice of fluids may also depend on the chemical properties of the medications being given. (4)

Solution	Contains	$[Na^+]$(mmol/L)	[Cl](mmol/L)	[Glucose](mmol/L)
D_5W	5% Dextrose	0	0	278
2/3 D & 1/3 S	3.3% Dextrose + 0.3% saline	51	51	185
Half-normal saline	0.45% NaCl	77	77	0
Normal saline	0.9% NaCl	154	154	0
Ringer's lactate	Lactated Ringer	130	109	0
D_5NS	5% Dextrose + Normal Saline	154	154	278

Notes about Crystalloids:

1. **Lactated Ringer** solution may be preferred because it is unlikely to cause the hyperchloremic metabolic acidosis seen with infusion of large amounts of normal saline.
    - One liter of lactated Ringer's solution contains: 130 mEq of sodium ion = 130 mmol/L, 109 mEq of chloride ion = 109 mmol/L, 28 mEq of lactate = 28 mmol/L, 4 mEq of potassium ion = 4 mmol/L, 3 mEq of calcium ion = 1.5 mmol/L
2. **Ringer Solution** is a standard isotonic solution 6.5 g NaCl, 0.42 g KCL, 0.25 g $CaCl_2$ and 1 mole of sodium bicarbonate is dissolved in one liter of distilled water.
3. Crystalloids are administered at a rate of 500 to 2,000 mL/hour, depending on the severity of the deficit, degree of ongoing fluid loss, and tolerance to infusion volume.
4. **Advantages of crystalloids** include rapidity and ease of administration, compatibility with most drugs, absence of serum sickness, and low cost.
5. **The primary disadvantage** is the large volume necessary to replace or augment intravascular volume. Approximately 4 L of normal saline must be infused to replace 1 L of blood loss. In addition, dilution of colloid oncotic pressure leading to pulmonary edema is more likely to follow crystalloid than colloid resuscitation.
6. **Best Selection of Crystalloids:**
    - **If the patient has high BP** → choose Glucose water D_5W.
    - **If the patient has High blood Glucose level** → choose Normal Saline 0.9% NaCl.
    - **If the patient has Hepatic Coma** (this will lead to 2ndry hyperaldosteronism with salt and water retention) thus → Avoid Normal Saline 0.9% NaCl.
    - **If the patient has Gastroenteritis** → choose Ringer Solution or Lactated Ringer, to replenish Electrolyte Loss.

B. Colloids: Colloids preserve a high colloid osmotic pressure in the blood, they are larger molecular weight solutions (>30,000 Daltons) that have been recommended for use in conjunction with or as replacements for crystalloid solutions. They Include (**Albumin, starch, dextran, Hetastarch, Succinylated gelatin).**

Scientific name	Dosage form	Trade name	concentration
Albumin (I.V.)	Inj. Solu.	Bumibate® , Flexbumine®	5% , 25%
Dextran	Inj. Solu.	Rheomacrodex® , Gentran®	6% , 10%
Hetastarch	Inj. Solu.	Hespan® , Hextend®	6%
Succinylated gelatin	Infusion Solu.	Gelofusine®	4%

Notes about Colloids:

1. **The theoretical advantage of colloids** is their prolonged intravascular retention time compared with crystalloid solutions. Isotonic crystalloid solutions have substantial interstitial distribution within minutes of IV administration, but colloids remain in the intravascular space for hours or days, depending on factors such as capillary permeability.
2. **The 5% albumin** solution is relatively iso-oncotic, whereas **25% albumin** is hyperoncotic and tends to pull fluid into the compartment containing the albumin molecules.
    - The current evidence-based indications for plasma expansion with human albumin in **patients with cirrhosis** are the treatment of hepatorenal syndrome, the prevention of circulatory dysfunction which follows therapeutic paracentesis, and the prevention of circulatory dysfunction and hepatorenal syndrome in patients with spontaneous bacterial peritonitis.
3. **Hetastarch** may cause elevations in serum amylase concentrations but does not cause pancreatitis.
4. **Adverse effects of colloids are generally extensions of their pharmacologic activity** (e.g., fluid overload and dilutional coagulopathy). Albumin and dextran may be associated with anaphylactic reactions or anaphylaxis. Bleeding may occur in certain patients receiving Hetastarch and dextran.

3.20 - Positive Inotropics

- These **increase myocardial contractility**, and are used to support cardiac function in conditions such as decompensated congestive heart failure, Shock (hypovolemic shock, cardiogenic shock, and septic shock), myocardial infarction, cardiomyopathy, etc.

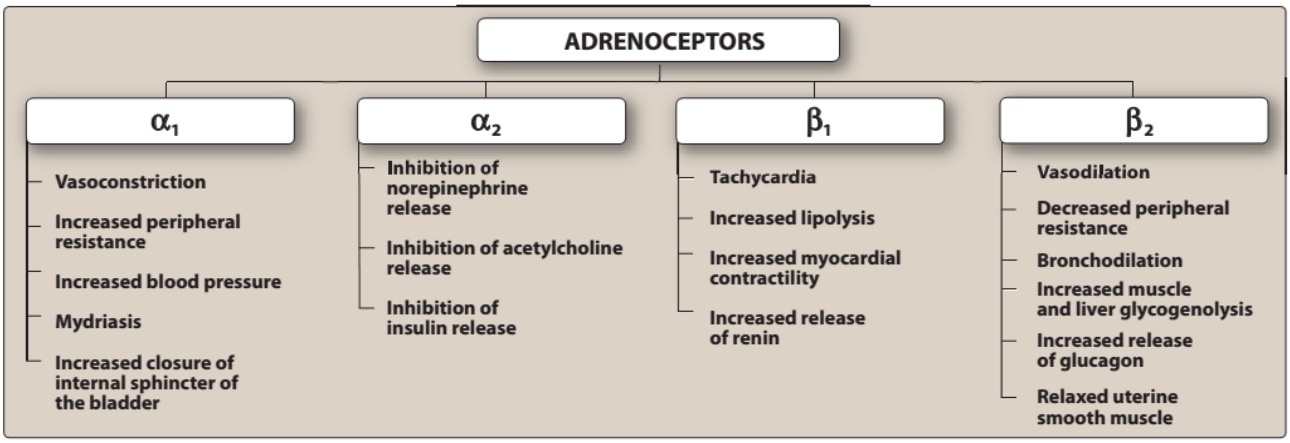
Scientific name	Dosage form	Trade name	concentration
Dopamine	Inj. Solu.	Intropin®	40 mg/ml & 80 mg/ml
Dobutamine	Inj. Solu.	Dobutrex®	12.5 mg/ml
Dopexamine	Solu. for infusion	Dopacard®	50 mg/5ml
Epinephrine	Inj. Solu.	EpiPen® , Adrenalin®	0.1 mg/ml & 1 mg/ml
Isoproterenol	Inj. Solu.	Isuprel®	0.2 mg/ml
	Aerosol		0.131 mg/inhale
Norepinephrine	Inj. Solu. , amp	Levophed® , Noradrenalin®	1 mg/ml , (4 mg/4 ml amp)
Phenylephrine	Inj. Solu.	Neo-Synephrine®	10 mg/ml
Milrinone	Inj. Solu.	Primacor®	1 mg/ml
Inamrinone **	Inj. Solu.	Inocor®	5 mg/ml
Enoximone	Inj. Solu.	Perfan®	5mg/ml (20 ml)

** was named **(Amrinone),** but changed in 2000 to prevent confusion with **Amiodarone.**

Notes About positive Inotropics:

A) For easy memorization remember:

- **Epinephrine:** acts on **(α1, α2, β1, β2).**
- **Norepinephrine:** acts on **(α1, α2, β1).**
- **Isoproterenol:** acts on **(β1, β2).**
- **Dopamine:** acts on **(α1, β1) and dopaminergic receptors.**
- **Dobutamine:** acts **specifically** on **(β1), with very mild activity on (β2, α1)**
- **Phenylephrine:** acts **only on (α1)**



B) Specific notes:

1. **Dopamine** is the **drug of choice for cardiogenic and septic shock** and is given by continuous infusion. It raises the blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance. In addition, **it enhances perfusion to the kidney and splanchnic areas; increased blood flow to the kidney enhances the glomerular filtration rate and causes sodium diuresis.**
    - **Low dose increases renal blood flow, intermediate dose has a beta effect, higher doses has an alpha effect.**
2. **Dobutamine** is primarily a selective β1-agonist with mild β2 and vascular α1 activity, resulting in strong positive inotropic activity without concomitant vasoconstriction. **Increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs.**
    - **It Has a short plasma half-life.**
3. **Epinephrine** is the primary drug used in the emergency treatment of any condition of the respiratory tract when bronchoconstriction has resulted in diminished respiratory exchange. Thus, **in treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice.**
    - **Epinephrine** is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens
    - Local anesthetic solutions usually contain 1:100,000 parts **epinephrine to increase the duration of the local anesthesia.**
4. **Norepinephrine** is a combined α- and β-agonist, but it primarily produces vasoconstriction.
5. **Phenylephrine** is a **pure α1 -agonist** and is thought to increase BP through vasoconstriction. It may also increase contractility and CO.
    - Phenylephrine may be beneficial in septic shock because of its selective α-Agonism, vascular effects, rapid onset, and short duration.
    - **Phenylephrine may be a useful alternative in patients who cannot tolerate the tachycardia or tachy-dysrhythmias with use of dopamine or norepinephrine.**

3.21 – Drugs for Pulmonary Hypertension

1. **Pulmonary hypertension (PH)** is an increase of blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, leading to shortness of breath, dizziness, fainting, leg swelling and other symptoms.
2. Capillaries become narrowed, blocked or destroyed, this makes it harder for blood to flow through the lungs, and raises pressure within lung arteries, as the pressure builds, the heart right ventricle must work harder to pump blood through the lungs, eventually causing the heart muscle to weaken and eventually fail), Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure.
3. **Pulmonary hypertension isn't curable,** treatments available can help lessen symptoms and improve quality of life; **Treatment options include: high dose Ca^{+} channel blockers** (ex: **amlodipine up to 20 mg** daily) with **loop diuretics, PDE-5 Inhibitors, Endothelin Antagonists** and **Prostacyclin Analogs.**
   - PDE-5 Inhibitors is not recommended in patients with either of two rare diseases often associated with PH: pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis.

Scientific name	Dosage form	Trade name	concentration
Endothelin Antagonists			
Ambrisentan	Tab	Letairis®	5 mg , 10 mg
Bosentan	Tab	Tracleer®, Bosentas®	62.5 mg , 125 mg
Macitentan	Tab	Opsumit®	10 mg
Sitaxentan	Tab	Thelin®	100 mg
Prostacyclin Analogs			
Epoprostenol	Inj. powder	Flolan® , Veletri®	0.5 mg , 1.5 mg (per vial)
ILoprost	Amp	Ventavis®	10 mcg/ml , 20 mcg/ml
Beraprost	Tab	Dorner® , Berasil®	20 mcg
Treprostinil	Tab	Orenitram®	0.125 mg , 0.25 mg , 1 mg
	Inj. Solu	Remodulin®	1 mg , 2.5 mg , 5 mg (per 1ml)
	Inhale Solu.	Tyvaso®	600 mcg/ml
Selexipaq	Tab	Uptravi®	200 , 400 , 800 , 1200 mcg
PDE-5 Inhibitors			
Sildenafil	Tab	Viagra®, Kamagra®	25 mg , 50 mg , 100 mg
	Inj. Solu.	Revatio®	10 mg/12.5 ml
Tadalafil	Tab	Cialis®	5 mg , 10 mg , 20 mg
Guanylate Cyclase Stimulator			
Riociguat	Tab	Adempas®	0.5 mg , 1 mg , 2 mg

Notes:

1. **Endothelin receptor antagonists** reverse the effect of Endothelin, a substance in the walls of blood vessels that causes them to narrow.
   a. Patients using **Bosentan, Ambrisentan** needs monthly liver monitoring, because these drugs can cause severe damage the liver.
   b. **Pfizer withdrew Sitaxentan** (Thelin®) worldwide because of fatal liver complications.
2. **Prostacyclins are Blood vessel dilators (vasodilators),** they are unstable, and therefore have to be kept on ice during administration. Since they have a half-life of 3 to 5 minutes, the infusion has to be continuous (24/7), and interruption can be fatal.
   a. **Treprostinil** (Remodulin®) can be given intravenously (IV) or subcutaneously (SC), but the subcutaneous form can be very painful.
   b. **The inhaled form of Treprostinil** has the advantage of selective deposition in the lungs with less systemic side effects; however, coughing and throat irritation commonly occur.
3. **Sildenafil and Tadalafil** works by opening the blood vessels in the lungs to allow blood to flow through more easily, also used for Erectile Dysfunction. (see chapter 8, section 5)
   a. **Tadalafil** is also indicated for the treatment of signs and symptoms of BPH.

3.22 - Miscellaneous cardiovascular drugs

Scientific name	Category	D. form	Trade name	concentration
Nesiritide	Natriuretic Analogue	Inj. Solu.	Natrecor®	1.5 mg/vial
Urapidil	Antihypertensive	Cap	Uradil®	30 mg , 60 mg , 90 mg
Guanethidine	Antihypertensive	Amp	Ismelin®	10 mg/ml
Levosimendan	Calcium Sensitizer	Inj. Solu.	Simdax®	2.5 mg/ml (5 ml vial)
Amyl Nitrite (nitrate)	Vasodilator	Amp (Solu.)	----------	0.3 ml
Papaverine	Vessels Relaxant	Cap	Para Time®	150 mg
		Inj.	Pavabid®	30 mg/mL
		Gel	TriMix®	2%
Reserpine	Antipsychotic + Antihypertensive	Tab	Serpasil®	0.1 mg , 0.25 mg
Deserpidine	Antihypertensive	Tab	Canescine®	0.25 mg , 0.5 mg
Mecamylamine	Antihypertensive	Tab	Vecamyl®	2.5 mg
Strange Combinations				
Reserpine + Polythiazide		Tab	Renese-R®	0.25 mg + 2 mg
Reserpine + Hydrochlorothiazide + Hydralazine		Tab	Ser-Ap-Es® Relazide®	0.25 mg + 25 mg + 25 mg
Deserpidine + Methyclothiazide		Tab	Enduronyl®	0.5 mg + 5 mg

Notes:

1. **Nesiritide** works to facilitate cardiovascular fluid homeostasis through counter-regulation of the renin-angiotensin-aldosterone system, stimulating cyclic guanosine monophosphate, leading to smooth muscle cell relaxation. **Nesiritide is beneficial for acute decompensated congestive heart failure.**
   - That's due the fact that **Nesiritide** is a balanced vasodilator that acts on arteries to decrease systemic vascular resistance and thereby lowers left ventricular afterload, and acts on veins to increase venous capacitance and thereby lowers left and right heart failing pressures.
2. **Urapidil** is a **sympatholytic antihypertensive** drug, it acts as an **α-1 receptor antagonist**, it is currently not approved by the U.S. FDA, but it is available in Europe.
   - Reduces blood pressure without altering heart rate.
   - the antihypertensive efficacy of **Urapidil** was lower than that of **hydrochlorothiazide** in some trials.
   - **Urapidil** does not elicit reflex tachycardia, and this may be related to its weak β1-adrenoceptor antagonist activity
3. **Guanethidine** is an antihypertensive drug that **reduces the release of catecholamines**, such as norepinephrine, **thus gradually decreasing BP and HR**; also, Intravenous nerve block (Bier block) using Guanethidine has been used to treat chronic pain caused by complex regional pain syndrome.
4. **Levosimendan** is indicated for the short-term treatment of **acutely decompensated severe chronic heart failure (ADHF)** in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate.
   - It **enhances myocardial contractility without increasing oxygen requirements**, and causes coronary and systemic vasodilation.
   - **Levosimendan** has shown **preliminary positive effects** in a range of conditions requiring inotropic support, including right ventricular failure, cardiogenic shock, septic shock.
5. **Papaverine,** an **alkaloid;** it's used to **improve blood flow** in patients with circulation problems.
   - It works by **relaxing the blood vessels** so that blood can flow more easily to the heart and through the body, its FDA approved for **the treatment of Arterial spasms.**
   - **Papaverine is also an antiarrhythmic medication** that treats certain abnormal heartbeats (ventricular arrhythmias); It works by blocking the abnormal electrical activity in the heart so a normal heart beat can return; It may help the heart beat better by increasing blood flow to the heart.
   - **Some also uses it for Erectile Dysfunctions** as an intracavernous inj. (direct inj. To the penis!).
     - It should not be injected into the penis; This practice has resulted in painful or prolonged erection that may require surgery to correct; A topical gel is also available for Erectile Dysfunction treatment, which is safer and more efficient than the injectable dosage form.

6. **Amyl Nitrate,** by inhalation of crushed amp its used for the relief of Acute Angina; (the amp is crushed and its contents is poured into a gauze and placed in front of patient's mouth).
   - Used also in **Cyanide poisoning;** (see chapter 17 for more details).
   - It is **abused** to **enhance sexual experience** or to experience a general sense of sexual pleasure and **Euphoria** (feeling instant multiple orgasms); known locally as Poppers; (The effects are felt within 30 seconds of taking the drug, and last for around 2-3 minutes), they also cause a warming sensation, feelings of excitement and relaxation of involuntary muscles, especially the anal and vaginal sphincter.
     - Taking the drug in this way is **not safe**; it can cause irregular and rapid heart rhythms and result in a syndrome called "sudden sniffing death, they also cause temporary or permanent vision loss.
7. **Reserpine** is used to **treat high blood pressure**, also used to **treat severe agitation in patients with severe mental disorders.**
   - It works by slowing the activity of the nervous system (via depletion of tissue store of catecholamines as norepinephrine, dopamine), causing heart beat to slow and the blood vessels to relax.
   - Has a high side effect profile; thus, used only in emergency HT these days.
8. **Deserpidine**, an **alkaloid**; a competitive inhibitor of the angiotensin converting enzyme (ACE); it is related to **Reserpine.**
9. **Mecamylamine** is a potent, oral antihypertensive agent and ganglion blocker, and is a secondary amine. it is indicated for the management of moderately severe to severe essential hypertension and in uncomplicated cases of malignant hypertension.

References

1- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th Ed.
4- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Ed.
5- Comprehensive Pharmacy Review for NAPLEX 8th Ed.
6- Journal of the American Society of Nephrology. 18 (9): 2509–16.
7- Lawrence A. Trissel. Handbook on injectable drugs - 15th ed. 2009.
8- Levy BL, Taddei S. Vascular legacy beyond blood pressure control. Curr. Med. Res. Opin. 2018
9- European Heart Journal Supplements (2007) 9 (Supplement E), E10–E19
10- Cockroft JR et al. Nebivolol vasodilates human forearm vasculature: Evidence for an L-arginine/NO-dependent mechanism. J Pharmacol Exp Ther 1995; 274: 1067-1071
11- Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a beta-adrenoceptor antagonist with unique characteristics. Drugs 2007; 67: 1091-1107
12- iugliano D, Acampora R, Marfella R, de Rosa N, Ziccardi P, Ragone R, de Angelis L, d'Onofrio F. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension – a randomized, controlled trial. Ann Intern Med 1997; 126: 955-959
13- Koshucharova G, Zweiker R, Maier R, Lercher P, Stepan V, Klein W, Stoschitzky K. Different beta-blocking effects of carvedilol and bisoprolol in humans. J Clin Basic Cardiol 2001; 4: 53-56
14- Stoschitzky K, Koshucharova G, Zweiker R, Maier R, Watzinger N, Fruhwald FM, Klein W. Differing beta-blocking effects of carvedilol and metoprolol. Eur J Heart Failure 2001; 3: 343-349 (Impact 2,122)
15- https://jamanetwork.com/journals/jamacardiology/fullarticle/2732487
16- https://www.nejm.org/doi/full/10.1056/NEJMoa1908655
17- https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehz754/5602478
18- https://www.webmd.com/diabetes/news/20150923
19- https://www.ncbi.nlm.nih.gov/pubmed/22442301

CENTRAL NERVOUS SYSTEM

Chapter Four: Central Nervous System

Part One: Introduction

Part Two:

4.1 - Hypnotics and Anxiolytics

- **a.** Benzodiazepines
- **b.** Barbiturates
- **c.** Other Sedative/Hypnotics and Anxiolytics

4.2 - Antipsychotic drugs

- **a.** The older agents (typical or conventional antipsychotics)
- **b.** Atypical antipsychotics (the Newer Generation)
- **c.** Antipsychotic Depot Inj.

4.3 - Anti-Depressant drugs

- **a.** selective serotonin re-uptake inhibitors (SSRIs)
- **b.** TCAs and related drugs
- **c.** Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- **d.** Atypical Antidepressants
- **e.** Monoamine Oxidase Inhibitors (MAOIs)
- **f.** Other Antidepressant drugs
- **g.** Psychotherapeutic combos

4.4 – Anti-epileptic drugs (AEDs)

4.5 - Drugs used in Parkinsonism

4.6 - Drugs used in Nausea and Vertigo

- **a.** 5HT3-receptor antagonists
- **b.** Butyrophenones
- **c.** Cannabinoids
- **d.** Miscellaneous agents

4.7 - Drugs for Dementia (Anti-Alzheimer)

4.8- CNS Stimulants

4.9 - Nootropics

4.10 - Herbals and Supplements for Cognitive function

Chapter Four: Central nervous system

Part one:

1. Introduction:

1. The human brain contains more than 100 billion nerve cells (neurons); These nerve cells receive electrochemical impulses from everywhere in the body, they interpret these impulses and send responsive signals back to various glands and muscles, the brain functions continuously as a switchboard for the human communications system; at the same time, it serves as the seat of emotions and mood, of memory, personality, and thoughts.
2. Extending from the brain is an additional, large rod-shaped cluster of nerve cells that forms the spinal cord; Together, these two elements comprise the **central nervous system.**
3. Radiating from the central nervous system is the **peripheral nervous system**, which has three parts. One branches off the spinal cord and extends to skin and muscles throughout the body, another, in the head, links the brain to the eyes, ears, nose, and taste buds, the third is a semi-independent network called the **autonomic, or involuntary, nervous system.**
   - This is the part of the nervous system that controls unconscious body functions such as breathing, digestion, and glandular activity.
   - Signals traverse the nervous system by electrical and chemical means; Electrical impulses carry signals from one end of a neuron to the other, and to cross the gap between neurons, chemical neurotransmitters are released from one cell to bind on to the receptor sites of nearby cells; Excitatory transmitters stimulate action; inhibitory transmitters reduce it.
4. **The autonomic, or involuntary, nervous system** governs the actions of the muscles of the organs and glands; such vital functions as heart beat and digestion continue without conscious direction, whether we are awake or asleep, **the autonomic nervous system is divided into two parts**, the effects of one generally balancing those of the other:
   a) **The sympathetic nervous system:** has an excitatory effect, it widens the airways to the lungs, increases the heart rate, and increases the flow of blood to the arms and legs.
   b) **The parasympathetic system:** by contrast, has an opposing effect, it slows the heart rate, narrows the large airways, and redirects blood from the limbs to the gut.
5. Although the functional pace of most organs results from the interplay between the two systems, **the muscles in the blood vessel walls respond only to the signals of the sympathetic nervous system**; whether a vessel is dilated or constricted is determined by the relative stimulation of two sets of receptor sites: **alpha sites** and **beta sites**.
   - **Blood vessels in the skin:** These are constricted by stimulation of alpha receptors by the sympathetic; the parasympathetic has no effect on them.
   - **The Heart**: The rate and strength of the heart are increased by the sympathetic and reduced by the parasympathetic.
   - **The pupils:** These are dilated by the sympathetic and constricted by the parasympathetic.
   - **The airways**: The bronchial muscles are relaxed and widened by the sympathetic and contracted and narrowed by the parasympathetic.
   - **Intestines**: The activity of the intestinal wall muscles is reduced by the sympathetic and increased by the parasympathetic.
6. **The parasympathetic nervous system** depends on the neurotransmitter **Acetylcholine** to transmit signals from one cell to another; **The sympathetic nervous system** relies on **epinephrine** (adrenaline) and **norepinephrine** (noradrenaline) for the transmission.
7. The drugs described in this chapter don't eliminate or cure nervous system disorders; Their function is to **correct or modify the communication of the signals that traverse the nervous system**, by doing so they can relieve symptoms or restore normal functioning and behavior; in some cases, as anxiety and insomnia, drugs are used to lower the level of activity in the brain, in other disorders (as depression) drugs are given to encourage the opposite effect, increasing the level of activity.

8. Drugs that act on the nervous system are also used for conditions that outwardly have nothing to do with nervous system disorders; such as Vomiting, for example, may be treated with drugs that directly affect the vomiting center in the brain or block stimulatory nerve signals to the vomiting center.

- The drugs that stimulate the sympathetic nervous system are called **Adrenergics** (or **Sympathomimetics**); They either promote the release of **epinephrine** (adrenaline) and **norepinephrine** (noradrenaline) or mimic their effects.
- Drugs that interfere with the action of the sympathetic nervous system are called **Sympatholytics**, as **Alpha blockers** act on alpha receptors; **beta blockers** act on beta receptors.
- Drugs that stimulate the parasympathetic nervous system are called **Cholinergics** (or **Parasympathomimetics**).
- Drugs that oppose the action of parasympathetic are called **Anticholinergics** (or **Parasympatholytics**).

2. What Can go wrong in the Central Nervous system

1. Disorders of the brain and nervous system may manifest as illnesses that show themselves as physical impairments, such as **epilepsy** or **strokes**, or mental and emotional impairments (for example, **schizophrenia** and **depression**).

- Illnesses causing physical impairments can result from different types of disorder of the brain and nervous system.
- Death of nerve cells resulting from poor circulation can result in **paralysis**, while electrical disturbances of certain nerve cells cause the **seizures** or **epilepsy**.
- Temporary changes in blood circulation within and around the brain are associated with **migraine headache**.
- **Parkinson's disease** is caused by a lack of dopamine, a neurotransmitter that is produced by specialized brain cells.
- The causes of disorders that trigger mental and emotional impairment are not known, but these illnesses are thought to result from the defective functioning of nerve cells and neurotransmitters.

2. **Note:** Most of the CNS drugs (like **antipsychotics**, **antidepressant**, **antiepileptics**, **anxiolytics**, **hypnotics**, **and opioid analgesics)** can **cause drowsiness**, thereby affecting the ability to drive and operate hazardous machinery and patients should be warned about this.
(Remember: the drugs in this chapter has high potentials for abuse → give ONLY by Rx).

4.1-Hypnotics and Anxiolytics

1. Difficulty in getting to sleep or staying asleep (**insomnia**) has many causes, most people have sleepless nights from time to time, usually due to a temporary worry or discomfort from a minor illness, **Persistent sleeplessness** can be caused by psychological problems including **anxiety** or depression, or the pain and discomfort of a physical disorder.
   - A certain amount of stress can be beneficial, providing a stimulus to action; But too much will often result in anxiety, which might be described as fear or apprehension not caused by any real danger or harm.
   - Clinically, **anxiety arises when the balance of certain chemicals in the brain is disturbed**, the fearful feelings increase brain activity, stimulating the sympathetic nervous system and often triggering physical symptoms, for example, breathlessness, shaking, palpitations, digestive distress, and headaches.
2. For occasional sleeplessness, simple, common remedies to promote relaxation, such as taking a warm bath or a hot milk drink before bedtime, are usually the best treatment.
3. **Sleeping drugs** (also known as **hypnotics**) are normally prescribed only when these self-help remedies have failed, and when lack of sleep is beginning to affect general health.
   - They are used to re-establish the habit of sleeping, and **should be used in the smallest dose and for the shortest possible time** (not more than three weeks).
   - It is best **not to use Hypnotics every night.**
   - **Do not use alcohol to get to sleep**; as it can cause disturbed sleep and insomnia; alcoholics when taken properly might act as **mild tranquilizers**.
4. Most sleeping drugs promote sleep by **depressing brain function**; They interfere with chemical activity in the brain and nervous system by reducing communication between nerve cells, this leads to reduced brain activity, allowing you to fall asleep more easily.
   - Because the sleep induced by drugs is not the same as normal sleep, many people find that they **do not feel as well rested by it as by a night of natural sleep**; This is the result of suppressed brain activity.
   - **Hypnotics become less effective after the first few nights** and there may be a temptation to increase the dose.
   - When **Hypnotics are suddenly withdrawn**, anxiety, seizures, and hallucinations sometimes occur; Sleeplessness will recur and may lead to a temptation to use sleeping drugs again.
5. **Anti-anxiety drugs** (also known as **anxiolytics** or **minor tranquillizers**) are prescribed for short-term relief of severe anxiety and nervousness caused by psychological problems; they also used in hospitals to calm and relax people undergoing uncomfortable medical procedures.

Notes:

1. Hypnotics are used for patients with **insomnia**, while anxiolytics are used for **anxiety**.
2. Prescribing of these drugs is widespread but **dependence** and **tolerance** occur; This may lead to **difficulty in withdrawing the drug**.
3. Hypnotics and anxiolytics should be **reserved for short courses** to alleviate acute conditions after causal factors have been established.
4. **Benzodiazepines** are the most commonly used **anxiolytics** and **hypnotics**; The most commonly Benzodiazepines available are: **(Alprazolam, Chlordiazepoxide, Diazepam,** and **Lorazepam).**
   - **Mechanism of Action:** depress activity in the part of the brain that controls emotion by promoting the action of the neurotransmitter gamma-aminobutyric acid (GABA), which binds to neurons, blocking transmission of electrical impulses and thereby reducing communication between brain cells; Benzodiazepines **increase the inhibitory effect of GABA on brain cells**, preventing the excessive brain activity that causes anxiety.

- **Short-acting or intermediate acting hypnotics** (Alprazolam) are preferable in patients with sleep onset insomnia, when sedation the following day is undesirable, or when prescribing for elderly patients.
- **Long-acting hypnotics** (Diazepam) are indicated in patients with poor sleep maintenance (ex: early morning waking) that causes daytime effects, when an anxiolytic effect is needed during the day, or when sedation the following day is acceptable.

Important: benzodiazepine indications

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or causing the patient unacceptable distress, occurring alone or in association with insomnia or short-term psycho-somatic, organic, or psychotic illness.
2. The use of benzodiazepines to treat short-term 'mild' anxiety is inappropriate.
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the patient extreme distress.

5. **Benzodiazepines** are used as **anxiolytics, hypnotics**, management of **alcohol withdrawal**, **anticonvulsants, skeletal muscle relaxants**, conscious sedation, surgical adjuncts such as Perioperative anxiolysis/sedation, and **induction and maintenance of anesthesia.**
   - Anxiolytic benzodiazepine treatment **should be limited to the lowest possible dose for the shortest possible time.**
6. **Side effects of Benzodiazepines include** drowsiness, dizziness, ataxia, CNS depression, psychomotor impairment, confusion, cognitive impairment, aggression.
   - **Withdrawal of a benzodiazepine should be gradual** because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens
   - There is a risk of neonatal withdrawal symptoms when benzodiazepines are used during pregnancy; **Avoid regular use** and use only if there is a clear indication such as seizure control, **High doses administered during late pregnancy or labor may cause neonatal hypothermia, hypotonia, and respiratory depression.**
7. **Barbiturates** have been **less used these days** due they are associated with **very severe withdrawal symptoms;** Foremost is their ability to **cause coma.**
   - The long-acting barbiturate **(Phenobarbital)** is still sometimes of value in epilepsy (see section 4) but its use as a sedative is unjustified; **Phenobarbital has been regarded as the drug of choice for treatment of young children with seizures**; However, phenobarbital can depress cognitive performance in children, and the drug should be used cautiously.
   - **Thiopental** is still used these days to induce anesthesia.
8. **Beta-blockers** do not affect psychological symptoms of anxiety, such as worry, tension, and fear, but **they do reduce autonomic symptoms, such as palpitation and Shaking (tremor).**
   - They block the action of a chemical transmitter called norepinephrine (noradrenaline) in the body, thus reducing the physical symptoms of anxiety.
   - commonly prescribed for people who feel excessively anxious in certain situations, such as interviews or public appearances.
   - The most common beta blocker given as anxiolytic is **propranolol**.

A) Benzodiazepines (BZD)

Scientific name	D. form	Trade name	concentration
Short acting BZDs			
Triazolam	Tab	Halcion®	0.125 mg , 0.25 mg
Midazolam	Tab	Versed®, Dormicum® Nayzilam®	7.5 mg
	Nasal spray		5 mg
	Inj. (Amp)		1 mg/ml , 5 mg/ml
Oxazepam	Cap	Serax® , Comedormir®	10 mg , 15 mg , 30 mg
Brotizolam	Tab	Lendormin®	0.25 mg
Loprazolam	Tab	Havlane®, Dormonoct®	1 mg
Lormetazepam	Tab	Dormagen®	0.5 mg , 1 mg

Intermediate acting BZDs			
Alprazolam	Tab	Xanax® , Niravam®	0.25 mg , 0.5 mg , 1 mg , 2 mg
	Oral Susp.		0.75 mg/ml
Lorazepam	Tab	Ativan®	0.5 mg , 1 mg , 2 mg
	Inj.		2 mg/ml , 4 mg/ml
Clonazepam	Tab	Rivotril® , Klonopin®	0.5 mg , 1 mg , 2 mg
	Oral Drops	Rivotril®	2.5 mg/5 ml (10 ml drop)
Estazolam	Tab	ProSom®	1 mg , 2 mg
Temazepam	Cap	Restoril®	7.5 mg , 10 mg , 15 mg
Nitrazepam	Tab , Susp.	Mogadon®	5 mg (tab) , 2.5 mg/5 ml (Susp)
Long acting BZDs			
Chlordiazepoxide	Tab , Cap	Librium®	5 mg , 10 mg
Diazepam	Tab	Valium® , Diastat®, Dialar®	2 mg , 5 mg , 10 mg
	Oral Solu.		1 mg/1ml , 5 mg/1ml
	Inj.		5 mg/1ml
	Nasal Spray	Valtoco®	5 mg , 10 mg , 15 mg , 20 mg
Bromazepam	Tab	Lexotanil® , Calmepam®	1.5 mg , 3 mg , 6 mg
Flurazepam	Cap	Dalmane® , Somnol®	15 mg , 30 mg
Quazepam	Tab	Doral®	7.5 mg , 15 mg
Clorazepate	Tab	Tranxene®	7.5 mg , 15 mg
Clobazam	Tab	Ofni® , Frisium®	10 mg , 20 mg

1. **Diazepam** is useful in the **treatment of skeletal muscle spasms**, as in muscle strain, and in treating spasticity from degenerative disorders, such as **multiple sclerosis** and cerebral palsy
   - **Also, some gynecologists give it as a Uterine relaxant to ease delivery in labor,** this is not (FDA) approved, but some studies support this off-label use
   - Also, some uses it **as antihypertensive,** this is also NOT (FDA) approved.
2. Only **5 BZD** are **FDA approved** as **sedative-Hypnotics;** Quazepam, Flurazepam, Temazepam, Estazolam and Triazolam; because they are rapidly absorbed and produce CNS sedation more quickly
3. **Clonazepam, Lorazepam** are usually used as anticonvulsant.
4. **Diazepam, Clorazepate, Chlordiazepoxide, and Flurazepam** have active metabolites with very long half-lives, and cumulative effects occur with chronic administration.
5. **Flumazenil** is a benzodiazepine antagonist that can be **used to treat benzodiazepine overdose**; it has a short half-life and continuous monitoring is required.

Scientific name	Dosage form	Trade name	concentration
Flumazenil	Inj.	Romazicon®	0.1 mg/ml

B) Barbiturates

Scientific name	Dosage form	Trade name	concentration
Phenobarbital	Tab	Luminal®	15 mg , 30 mg
	Elixir , Amp		20 mg/5 ml , 30 mg/ml (Amp)
Primidone*	Tab	Mysoline® , Liskantin®	50 mg , 250 mg
	Oral Susp.	Liskantin Saft®	125 mg/5 ml (250 ml)
Amobarbital	Inj. Powder	Amytal®	500 mg
Pentobarbital	Inj. Solu.	Nembutal®	50 mg/ml
Secobarbital	Cap	Seconal®	100 mg
Butabarbital	Tab	Butisol®	30 mg & 50 mg
Thiopental **	Inj. Powder	Pentothal® , Trapanal®	----------

*** Primidone** is a pro-drug, which is metabolized into **Phenobarbital, phenylethylmalonamide,** which both have an antiepileptic action**.**

**** Thiopental** Along with **Pancuronium bromide** and **potassium chloride,** is used in 34 states of the USA **to execute prisoners by lethal injection**, (Cause death without pain; like you're going to sleep).

C) Other Sedative/Hypnotics and Anxiolytics

Scientific name	Dosage form	Trade name	concentration
Chloral hydrate	Cap , Oral Solu.	Somnote® , Noctec®	500 mg , 500 mg/5 ml
Etifoxine	Cap	Stresam®	50 mg
Eszopiclone	Tab	Lunesta®	1 mg , 2 mg
Tofisopam	Tab	Grandaxin®, Sériel®	50 mg
Ramelteon	Tab	Rozerem®	8 mg
Zaleplon	Cap	Sonata® , Siesta®	5 mg , 10 mg
Zopiclone	Tab	Zimovane® , Imovane®	3.75 mg , 7.5 mg
Zolpidem	Tab	Stilnox® , Ambien®	5 mg , 10 mg
	Sub-lingual Tab	Intermezzo® , Edluar®	1.75 , 3.5 , 5 , 10 mg
Meprobamate	Tab	Miltown® , Equanil®	200 mg , 400 mg
Buspirone	Tab	Buspar®	10 mg , 30 mg
Sodium Oxybate	Oral Solu.	Xyrem®	500 mg/ml
Suvorexant	Tab	Belsomra®	5 mg , 10 mg , 20 mg
Melatonin	Tab	Meloset® , Circadin®	2 mg , 3 mg
	Tab SR , Cap		5 mg , 10 mg
	Oral Drops		3 mg/1 ml

Notes: [2-9]

1. **Chloral hydrate** is used in pediatrics for sedation before procedures, (Usually in 10% syrup).
   - Onset of **action 30-60 min,** while **duration 7-11 hours.**
   - **There is no convincing evidence that it is particularly useful in the elderly.**
2. **Etifoxine** has an anxiolytic activity and has a **mild sedative** effect.
3. **Tofisopam is only an Anxiolytic,** does not have anticonvulsant, sedative, skeletal muscle relaxant effects.
4. **Ramelteon** is a selective agonist at the MT1 and MT2 subtypes of **melatonin receptors**. Stimulation of MT1 and MT2 receptors by melatonin in the SCN is able to induce and promote sleep and is thought to maintain the circadian rhythm underlying the normal sleep–wake cycle.
   - **Thus, Ramelteon is indicated for the treatment of insomnia in which falling asleep is the primary complaint.** (Note that Ramelteon increase prolactin levels).
5. **Zaleplon, Zolpidem** and **Zopiclone** are sometimes referred to as Z-drugs, they act at the benzodiazepine receptor; they are not licensed for long-term use, although; dependence has been reported in some patients.
   - **Zolpidem and Zopiclone** have a short duration of action; **Zaleplon** is very short acting.
   - **They have no anticonvulsant or muscle-relaxing properties**; It shows few withdrawal effects and exhibits minimal rebound insomnia and little tolerance occurs in prolonged use.
6. **Eszopiclone** (isomer of **Zopiclone**), has the advantage that its **FDA approved for long-term treatment of insomnia**, (unlike other hypnotics which are only used for short terms).
7. **Buspirone** is different from other anti-anxiety drugs; it **binds mainly to serotonin receptors** and does not cause drowsiness; Its effect is not felt for at least 2 weeks after treatment has begun.
8. **European Medicines Agency (EMA)** has recommended (Jan. 2012) the suspension of all marketing for **Meprobamate** because the risks, particularly of serious CNS side-effects, outweigh the benefits.
9. **Sodium Oxybate** is a central nervous system depressant that is licensed for the treatment of narcolepsy with cataplexy.
10. **Suvorexant** exerts its therapeutic effect in insomnia through **antagonism of orexin receptors**; The orexin neuropeptide signaling system is a central promoter of wakefulness.
11. **Melatonin** is the hormone produced by the pineal gland; it regulates sleep cycles.
    - Licensed for the short-term treatment of insomnia in adults.
    - Also licensed for the **prevention of Cluster headaches, Migraine headache.**

4.2-Antipsychotic drugs (for treatment of schizophrenia)

1. **Psychosis** is a term used to describe mental disorders that prevent the sufferer from thinking clearly, recognizing reality, and acting rationally, these disorders include **schizophrenia** and **bipolar disorder (manic depression)**.
2. The precise causes of these disorders are unknown, although a number of factors, including stress, heredity, and brain injury, may be involved, Temporary psychosis can also arise as a result of alcohol withdrawal or the abuse of mind-altering drugs.
3. It is thought that some forms of mental illness are caused by an increase in communication between brain cells due to over-activity of an excitatory chemical called dopamine, this may disturb normal thought processes and produce abnormal behavior; Dopamine combines with receptors on the brain cells.
   - **Antipsychotic drugs** reduce the transmission of nerve signals by binding to these receptors, thereby making the brain cells less sensitive to **dopamine**.
   - Some **newer antipsychotic** drugs, such as clozapine, risperidone, and sertindole, also bind to receptors for the chemical **serotonin** (block serotonin-2 receptors.)
   - **Because antipsychotics depress the action of dopamine**, **they can disturb its balance with another chemical in the brain, Acetylcholine**; (increase its concentrations), if an imbalance occurs, extrapyramidal side effects (EPSE) may appear. These include restlessness, disorders of movement, and parkinsonism.
   - **Antipsychotics may block the action of noradrenaline**, another neurotransmitter in the brain; This lowers the blood pressure, especially when standing up, causing dizziness, it may also prevent ejaculation causing an Erectile Dysfunction.
   - **Antipsychotic drugs** (also called **major tranquillizers** or **neuroleptics**) do not cure the disorder, but they do help to control symptoms.
   - Some antipsychotic drugs also have a powerful action against nausea and vomiting, and are therefore sometimes used as premedication before a person has surgery.
4. Because antipsychotic drugs can have permanent as well as temporary side effects, **the minimum necessary dosage is used**; This minimum dose is found by starting with a low dose and increasing it until the symptoms are controlled.
   - Sudden withdrawal after more than a few weeks can cause nausea, sweating, headache, and restlessness; Therefore, the dose is reduced gradually when treatment needs to be stopped.
   - The most serious long-term risk of anti-psychotic treatment is a disorder known as **tardive dyskinesia**, which may develop after one to five years; it consists of repeated jerking movements of the mouth, tongue, and face, and sometimes of the hands and feet
     - The condition is **less common with the newer antipsychotics** (atypical antipsychotics) than the older drugs (typical antipsychotics).

Notes:

1. There is a little difference in efficacy between each of the antipsychotic drugs (other than clozapine), and response and tolerability to each antipsychotic drug varies. **There is no first-line antipsychotic drug which is suitable for all patients.**
2. **Choice of antipsychotic medication** is influenced by the patient's medication history, the degree of sedation required (although tolerance to this usually develops), and consideration of individual patient factors such as risk of extrapyramidal side-effects, weight gain, impaired glucose tolerance, QT-interval prolongation, or the presence of negative symptoms.
3. **Long-acting depot injections antipsychotic** are used for maintenance therapy especially when compliance with oral treatment is unreliable. Depot antipsychotics are administered by deep intramuscular injection at intervals of 1 to 4 weeks
4. **All antipsychotics carry a black box warning against use in older adults with dementia**; First Generation Antipsychotics may have a **higher mortality rate** than Second Generation Antipsychotics when used in older adults with dementia.

First: The older agents (typical or conventional antipsychotics).

1. They can also be classed by chemical structure (**phenothiazine** and **non-phenothiazine**).
2. Examples include: **haloperidol, Fluphenazine, chlorpromazine, and Thioridazine**.
3. The typical antipsychotic drugs act predominantly by **blocking dopamine D_2 receptors** in the brain; **They are not selective** for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly **extrapyramidal symptoms (EPS) and elevated prolactin levels.**
   - **Typical antipsychotics have a large side effect profile;** they may cause Neurological side effects (Tardive dyskinesia, Dystonia, Parkinsonism), Drowsiness and sedation, Anticholinergic side effects, **and sexual dysfunction**.
4. **Extrapyramidal symptoms (EPS**) consist of:
   a. **Parkinsonian symptoms** (including tremor), which may occur more commonly in adults.
   b. **Dystonia** (abnormal face and body movements) and dyskinesia, which occur more commonly in children or young adults.
   c. **Akathisia** (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated.
   d. **Tardive dyskinesia** (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, also may occur after withdrawal of the drug.
5. The likelihood of certain adverse effects occurring is directly related to the potency of the antipsychotic; It is a relationship where the higher potency agents (lower mg dose), bind more tightly to the dopamine D2 receptors; **The higher the potency the more likely the agent is to cause neurological side effects. The lower the potency the more likely the agent is to cause the non-neurological side effects.**
6. **Must be avoided in** patients with **history of Parkinson's disease**, convulsive disorders, severe Cardiac disease, narrow angle glaucoma, or previous neuroleptic malignant disorder.
7. **Electrocardiographic (ECG) changes occur with 1st Gen. antipsychotics**; QTc prolongation can predispose the patient to ventricular arrhythmias, including torsade's de pointes syndrome.
   - The risk appears highest with chlorpromazine, haloperidol, and Thioridazine.
8. **Venous thromboembolism (VTE):** Three case-control studies and a retrospective study suggest an increased risk of VTE in patients taking antipsychotics. The risk may be higher in older adults and women. The risk appears greatest within the first 3 months of therapy.

Scientific name	Dosage	Trade name	concentration
Chlorpromazine	Tab	Largactil®, Thorazine®	50 mg , 100 mg , 200 mg
	Amp		25 mg/5 ml , 25 mg/ml
Prochlorperazine	Tab	Stemetil® , Compazine®	5 mg , 10 mg
	Amp	Promotil®	12.5 mg/1 ml
Fluphenazine	Tab	Modicate® , Prolixin®	2.5 mg , 5 mg , 10 mg
	Elixir		2.5 mg/5 ml
	Amp	Modicate HCL®	2.5 mg/ml
	Depot Inj.	Modicate Deconate®	25 mg/ml
Perphenazine	Tab	Fentazin®	2 mg , 4 mg
Promazine	Tab	ProMaz®	25 mg , 50 mg
Sulpride	Tab	Dogmatil®	200 mg , 400 mg , 500 mg
Haloperidol	Tab	Haldol® , Peridol®	0.5 mg , 1 mg , 2 mg , 5 mg
	Amp	Haldol Lactate®	5 mg/ml
	Oral Solu.	Dozic®	5mg/5 ml
	Depot Inj.	Haldol Deconate®	50 mg/ml , 100 mg/ml
Pimozide	Tab	Orap®	1 mg , 2 mg , 4 mg
Mesoridazine	Tab	Serentil®	25 mg , 100 mg

Levomepromazine	Tab	Nozinan®	25 mg
	Amp		25 mg/ml (1 ml amp)
Pericyazine	Tab	Perzyst®	2.5 mg , 10 mg
	Cap	Neuleptil®	5 mg , 10 mg , 20 mg
	Oral Drops	Neuleptil®	4% , 10%
Thiothixene	Cap	Navane®	1 mg , 2 mg , 5 mg
Loxapine	Cap	Loxitane®	5 mg , 10 mg , 25 mg
	Inhaler	Adasuve®	10 mg (single use Inhaler)
Thioridazine	Tab	Mellaril®, Sonapax®, Ridazin®	10 mg , 25 mg
Trifluoperazine	Tab	Stelazine®	1 mg , 2 mg , 5 mg
Flupenthixol	Tab	Depixol®	3 mg
	Amp	Fluanxol® , Depixol®	50 mg/0.5 ml
	Amp depot	Fluanxol Depot®	100 mg/2 ml
Zuclopenthixol	Tab	Clopixol®	2 mg , 10 mg , 25 mg
	Amp	Clopixol Acuphase®	50 mg/ml (1 ml amp)
	Amp depot	Clopixol Depot®	200 mg/ml
Benperidol	Tab	Anguil®	2.5 mg

Notes:

1. concerning **Chlorpromazine (Largactil®)**:
   a. It is used in the alleviation of **intractable hiccup,** (usually 12.5 mg once).
   b. **It is widely abused in our market by some addicts.**
2. **Prochlorperazine** is usually used as **antiemetic.**
3. **Haloperidol** is used for Treatment of severe nausea and emesis in postoperative and palliative care, **also for Treatment of intractable hiccups, hyperactivity, and aggression**.
4. **Fluphenazine causes Euphoria,** thus abused by some addicts.
5. **Loxapine** is indicated for acute treatment of agitation associated with schizophrenia or bipolar disorder in adults.
6. **Thioridazine was withdrawn worldwide in 2005** Due to concerns about cardio-toxicity and retinopathy at high doses this drug.
7. **Trifluoperazine** comes with **Isopropamide** (anticholinergic) in a combination Known as **Stelabid®** for the treatment of irritable bowel syndrome (IBS).
8. **Both Flupenthixol** and **Zuclopenthixol** are long-acting injection given once in every two or three weeks, **(although they are not approved to use in USA).**
9. **Flupenthixol** comes with **Melitracen** (a tricyclic antidepressant) in combination Known as **Deanxit®** It is designed as antidepressant combo **for short term usage only, it's banned in USA, the UK, Ireland, Canada, Japan, and Australia** due association with potentially serious neurological side effects; And it's still used in our market for IBS!
10. **Valbenazine,** was (FDA) approved on April 11, 2017, **as the first drug to carry an indication for tardive dyskinesia**; reversibly and selectively inhibits the vesicular monoamine transporter 2 (VMAT2); **Valbenazine** thus regulates the packaging of dopamine and other monoamines in the neuronal cytoplasm into vesicles for storage and release into synapses, decreasing the amount of **dopamine released, which in turn results in fewer postsynaptic dopamine receptors and less dyskinetic movement.**

Scientific name	Dosage	Trade name	concentration
Valbenazine	Cap	Ingrezza®	40 mg , 80 mg

Second: Atypical antipsychotics (the Newer Generation)

1. Newer antipsychotics such as **clozapine, Risperidone, Olanzapine and Quetiapine** are often referred to as atypical antipsychotics **because of their reduced tendency to cause the extrapyramidal side-effects (EPS),** (1) (better tolerated than other antipsychotic drugs).
   - Has the ability to block serotonin-2 receptors is present; This property may improve activity for the negative symptoms of schizophrenia and reduce the risk of EPS; This may also be related to their efficacy in mood disorders.
2. But still have the **Drowsiness** and **sedation**, **Anticholinergic side effects**, **Cause Prolactin elevation and sexual dysfunction**.
   - **Aripiprazole;** unlike other antipsychotic drugs, **lowers prolactin.**
   - **All antipsychotics lowers the seizure threshold.**
3. **Major additional side effect**: association with weight gain, **development of type 2 diabetes** and dyslipidemia, precipitation of DKA have also been reported.
4. Also; **Electrocardiographic (ECG) changes occur with 2nd Gen. antipsychotics**; QTc prolongation can predispose the patient to ventricular arrhythmias, including torsade's de pointes syndrome; (Clozapine, Ziprasidone, and iloperidone appear to have the highest risk).

Scientific name	Dosage form	Trade name	concentration
Clozapine	Tab	Clozaril® , Leponex® , Zaponex®	50 mg , 100 mg , 200 mg
	Oral Susp.	Versacloz®	50 mg/ml
Risperidone	Tab	Risperdal® , Rison®	0.5 mg , 1 mg , 2 mg , 4 mg
	Oro Desp. tab		1 mg , 2 mg , 3 mg , 4 mg
	Oral Solu.		1 mg/ml
Olanzapine	Tab	Zyprexa® , Olan® , Olapex®	2.5 mg , 5 mg , 10 mg
	Oro Desp. tab		2.5 mg , 5 mg , 10 mg
	Inj. (I.M.)		10 mg
Quetiapine	Tab	Seroquel® , Xeroquel®, Serex®	25 mg , 100 mg , 200 mg
	Tab XR	Seroquel XR®	50 mg , 200 mg , 300 mg
Aripiprazole	Tab	Abilify®, Lemidal®	2 mg , 5 mg , 10 mg
	Oral Solu.		1 mg/ml
	Inj. (I.M.)	Aristada®	7.5 mg/ml (1.3 ml amp)
Brexpiprazole	Tab	Rexutii®	0.25 , 0.5 , 1 , 2 , 4 mg
Amisulpride	Tab	Solian®	50 mg , 100 mg , 200 mg
Paliperidone	Tab	Invega®	3 mg , 6 mg , 9 mg
Asenapine	Subling. Tab	Saphris®	2.5 mg , 5 mg , 10 mg
Lurasidone	Tab	Latuda®	20 mg , 40 mg , 80 mg
Cariprazine	Cap	Vraylar®	1.5 mg , 3 mg , 6 mg
Pimavanserin	Tab	Nuplazid®	17 mg
Iloperidone	Tab	Fanapt®	1 mg , 2 mg , 4 mg , 6 mg
Sertindole	Tab	Serdolect®, Serlect®	4 mg , 16 mg , 20 mg
Ziprasidone	Cap	Geodon® , Zeldox®	20 mg , 40 mg , 60 mg , 80 mg
	Inj. powder		20 mg

Notes:

1. **Clozapine** can cause **agranulocytosis**; **Periodic monitoring of blood counts is a MUST.**
   - **FDA Black box warning**: May cause seizures, Myocarditis, and respiratory arrest.
2. **Olanzapine:** This drug is structurally similar to clozapine and has a similar pharmacologic profile, but unlike clozapine, it has not been associated with agranulocytosis.
   - Olanzapine carries **the highest risk of diabetes**.
   - It Comes with **Fluoxetine** (SSRI) in combo (Symbyax®) for treatment-resistant depression.

3. **Risperidone:** This drug is a **potent dopamine D_2 antagonist** and a **serotonin-2 antagonist**; It has limited anticholinergic activity, at doses of up to 6 mg/day, the incidence of EPS has been no higher than with placebo in clinical studies.
   - **Risperidone**, the first drug **approved for children with autism** and the most widely used, improves some children's behavior, effectively treats the explosive and aggressive behavior that can accompany autism.
   - Off-label uses include treatment of other symptoms of autistic disorder, including aggression, self-injurious behavior, hyperactivity, and inattention.
   - Risperidone has shown promise in **treating therapy-resistant obsessive–compulsive disorder**, when serotonin reuptake inhibitors are not sufficient.
4. **Paliperidone**: is the **active metabolite of Risperidone;** Its pharmacologic profile is similar to that of the parent drug.
   - Invega® is an extended release formulation of Paliperidone that uses the OROS extended release system to allow for **once-daily dosing.**
5. **Aripiprazole** is also used as an add-on treatment in major depressive disorder, tic disorders and irritability associated with autism.
   - Aripiprazole; unlike other antipsychotic drugs, **lowers prolactin**.
   - Aripiprazole **has the lowest risk in most forms of EPS**, including tardive dyskinesia.
   - Also available in a once monthly dosage form (Abilify Maintena®).
6. **Quetiapine**: it has in addition to **antagonism at the D_2 and serotonin-2 receptors**, it has a **high affinity for histamine-1 receptors**
   - **Quetiapine** offers a low incidence of EPS; For this reason, it is often **used for psychosis associated with Parkinson disease.**
   - **Quetiapine** does not decrease agitation among people with Alzheimer's; **Quetiapine worsens intellectual functioning** in the elderly with dementia and therefore is not recommended.
   - Used as tranquilizer for **major Depressive disorder.**
   - **Used (off-label) as 25 mg at bed time for insomnia.**
7. **Pimavanserin** is indicated only for **Parkinson Disease Psychosis.**
8. **Ziprasidone** is also used off-label for depression, bipolar maintenance, mood disorders, anxiety, aggression, dementia, attention deficit hyperactivity disorder, obsessive compulsive disorder, autism, and post-traumatic stress disorder.

Third: Antipsychotic Depot Injections

1- There is no clear-cut division in the use of the conventional antipsychotics, but **Zuclopenthixol** may be suitable for the treatment of agitated or aggressive patients whereas **Flupenthixol** can cause over-excitement in such patients.

2- **Zuclopenthixol Decanoate** may be more effective in preventing relapses than other conventional antipsychotic depot preparations.

3- The incidence of extrapyramidal reactions is similar for the conventional antipsychotics.

Scientific name	Dosage form	Trade name	concentration
Flupenthixol Decanoate	Inj. oily	Depixol®	20 mg/ml , 100 mg/ml , 200 mg/ml
Zuclopenthixol Decanoate	Inj. oily	Clopixol®	200 mg/ml , 500 mg/ml
Fluphenazine Decanoate	Inj. oily	Modecate®	25 mg/ml , 100 mg/ml
Haloperidol Decanoate	Inj. oily	Haldol®	25 mg/ml , 50 mg/ml
Olanzapine Embonate	Vial (powder)	ZypAdhera®	210 mg , 300 mg , 405 mg (per vial)
Paliperidone Palmitate	Prefilled inj.	Xeplion®	50 mg , 75 mg , 100 mg , 150 mg
Pipotiazine Palmitate	Inj. oily	Piportil®	50 mg/ml
Risperidone	Vial (powder)	Risperdal Consta®	25 mg , 50 mg (per vial)

4.3 - Anti-Depressant drugs

1. Normally, the brain cells release sufficient quantities of certain chemicals (known as neurotransmitters such as serotonin and dopamine) in the brain to stimulate neighboring cells, the neurotransmitters are constantly reabsorbed into the brain cells, where they are broken down by an enzyme called **monoamine oxidase**.
2. Depression is thought to be caused by a reduction in the level of neurotransmitters in the brain.
   - **Antidepressants raise the levels of these neurotransmitters.**
   - Available Antidepressant classes include:

Class of Antidepressant		Example(s)
1.	Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
2.	Tricyclic antidepressants (TCAs) and tetracyclic antidepressants	Amitriptyline, Desipramine, Dosulepin, Doxepin, Lofepramine, Imipramine, Nortriptyline, Mianserin (tetracyclic), Trimipramine
3.	Norepinephrine and dopamine reuptake inhibitor (NDRI)	Bupropion
4.	Mixed serotonergic effects (Mixed 5-HT)	Nefazodone, Trazodone, Vilazodone, Vortioxetine
5.	Serotonin and α2-adrenergic antagonist	Mirtazapine
6.	Monoamine oxidase inhibitors (MAOIs)	Phenelzine, Selegiline, Tranylcypromine
7.	Melatonin receptor agonist	Agomelatine
8.	Noradrenaline reuptake inhibitors	Reboxetine
9.	Serotonin and noradrenaline re-uptake inhibitors.	Duloxetine, Venlafaxine

Notes:

1. Antidepressant drugs are effective for treating moderate to severe depression associated with psychomotor and physiological changes such as **loss of appetite** and **sleep disturbance**; **improvement in sleep is usually the first benefit of therapy.**
2. The major classes of antidepressant drugs available include: the tricyclic and related antidepressants (TCAs), the selective serotonin re-uptake inhibitors (SSRIs), the serotonin norepinephrine re-uptake inhibitors (SNRIs), and the monoamine oxidase inhibitors (MAOIs).
3. There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual patient's requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy.
   a. There may be an interval of 2 weeks before the antidepressant action takes place.
   b. Electroconvulsive treatment may be required in severe depression when delay is hazardous or intolerable.
   c. During the first few weeks of treatment, **there is an increased potential for agitation, anxiety, and suicidal ideation.**
4. Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment, And the treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to switch antidepressant due to lack of efficacy.
   a. In cases of partial response, continue for a further 2–4 weeks (elderly patients may take longer to respond).
   b. Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly).

A) The selective serotonin re-uptake inhibitors (SSRIs)

1. **SSRIs** include: **Citalopram, Escitalopram, Fluoxetine, Paroxetine,** and **Sertraline.**
   - These selectively inhibit the reuptake of serotonin into the presynaptic neuron and desensitize the presynaptic serotonin auto-receptor, resulting in increased serotonin concentrations.
2. **SSRIs are generally chosen as first-line antidepressants** because of their safety in overdose and improved tolerability compared with earlier agents; The **SSRIs produce fewer sedative, anticholinergic, and cardiovascular adverse effects** than the TCAs and are less likely to cause weight gain than the TCAs.
   a. In patients with unstable angina or who have had a recent myocardial infarction, **sertraline has been shown to be safe.**
   b. **All these medications are given at night, Except Fluoxetine;** which is given at morning, due it has a **Cognitive stimulant effect**.
3. **Important**: In the treatment of **depression** the usual initial dose of Fluoxetine is 20 mg once daily; US product information recommends **giving this dose in the morning**.
4. Some SSRIs are also used as part of the management of generalized anxiety disorder, obsessive-compulsive disorder, panic disorders, some are useful in neuropathic pain management, **Fluoxetine** is also used in the treatment of **premenstrual syndrome**.
5. The most **common adverse effects** associated with this class of agents include **GI complaints, insomnia, restlessness, headache,** and **sexual dysfunction**.
   - **Sertraline** is used off-label in the treatment of **premature ejaculation** (due its side effect).
6. **Co-administration** of monoamine oxidase inhibitors (MAOI) **is CONTRAINDICATED,** Due Potential for producing a **potentially lethal serotonin syndrome** (characterized by nausea, vomiting, flushing, agitation, hyperthermia, diaphoresis, tachycardia, autonomic instability, tremor, hyperreflexia, myoclonus, and rigidity) and that is **due to dangerously high levels of brain serotonin.**
7. **The antidepressant effects of SSRIs may not appear until 3 to 6 weeks after initiation of treatment, (Never stop them abruptly).**
8. **To minimize occurrence of discontinuation syndromes**, all antidepressants should be slowly tapered (25% dose reduction per week), rather than abruptly discontinued.
9. Within days of abrupt cessation, patients may suffer from dizziness, nausea, fatigue, muscle aches, chills, anxiety, and irritability, while not dangerous, discontinuation side effects can be distressing and uncomfortable, often lasting 1-2 weeks.
10. **SSRIs appear to increase the risk of bleeding**; Several mechanisms have been proposed, including the inhibition of serotonin activation of platelets, case-control and cohort studies also suggest an **increased incidence of both vertebral and non-vertebral bone fractures**. Hyponatremia is a potential adverse effect, particularly in older adults.

Scientific name	Dosage form	Trade name	concentration
Fluoxetine	Cap	Prozac®	20 mg , 40 mg
	Cap DR	Sarafem®	90 mg
Paroxetine	Tab	Seroxat® , Paxil® , Pexeva®	10 mg , 20 mg , 40 mg
	Cap	Seroxat CR®	30 mg
Sertraline	Tab	Zoloft® , Lustra®	50 mg , 100 mg
Citalopram	Tab	Celexa® , Cipramil®	10 mg , 20 mg , 40 mg
Escitalopram	Tab	Lexapro®, Cipralex®	5 mg , 10 mg , 20 mg
Fluvoxamine	Tab	Luvox® , Faverin®	25 mg , 50 mg , 100 mg
	Cap ER		100 mg , 150 mg
Dapoxetine	Tab	Priligy®, Longus®, Joypox®	30 mg , 60 mg

Notes:

1. **Fluoxetine** differs from the other members of the class in two respects; First, it has a much longer half-life (50 hours) and is **available as a sustained-release preparation allowing once-weekly dosing;** Second, it **has Cognitive stimulant effect**, useful in patients with somnolence.
2. **Paroxetine** and **Fluvoxamine** are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping; Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating antidepressants, such as **fluoxetine or sertraline.**
   - **Fluvoxamine** is indicated only for **obsessive-compulsive disorder (OCD).**
   - **Paroxetine** have also a delayed release formulation capsules that is given **once weekly.**
3. **Escitalopram** is the pure S-enantiomer of **citalopram.**
   - Used for **Insomnia** due to depression or due to panic disorder.
   - Used for **vasomotor symptoms** associated with **Menopause.**
4. About **Sertraline:**
   a. Food increases its absorption.
   b. Safe to use in patients with unstable angina or myocardial infarction**.**
5. **Dapoxetine** is the first compound developed specially for the **treatment of premature ejaculation (PE) in men** 18–64 years old, although it was rejected by the FDA in 2011

B) TCAs and related antidepressants

1. Examples are **Amitriptyline, Clomipramine,** and **Imipramine.**
   - They act by blocking serotonin and norepinephrine re-uptake.
2. TCAs are strong antidepressants, **but their use has diminished because of the availability of equally effective therapies that are safer on overdose and better tolerated**.
   a. Some tricyclic antidepressants (TCAs) are used in the **management of panic** and other **anxiety disorders**, as (Doxepin), other are useful in **migraine prophylaxis**.
   b. Some TCAs have a role in some forms of **neuralgia** (**neuropathic pain**), as (Amitriptyline).
   c. Also, some used in **nocturnal enuresis** in children, as (Imipramine).
3. TCAs have α-adrenergic blockade, antihistaminic effects, and anticholinergic effects, **which lead to orthostasis, sedation, and anticholinergic side effects, respectively.**
   - **They also lead to cardio toxic effects (Life-threatening arrhythmias)**.
   - These drugs are **not recommended in patients with cardiac disease or seizure disorders**.
4. Tricyclic antidepressant drugs **have Antimuscarinic activity**, and therefore caution is needed in patients with prostatic hypertrophy, chronic constipation, increased intra-ocular pressure, urinary retention, or those with a susceptibility to angle-closure glaucoma.
5. TCAs cause **Sexual dysfunction**, as evidenced by **Erectile dysfunction** in men and **Anorgasmia** in women; although some of them are used for **premature Ejaculation** in men.
6. TCAs and related antidepressants **should be withdrawn slowly**, because of dangerous withdrawal symptoms such as influenza-like symptoms (chills, myalgia, sweating, headache, and nausea), insomnia and vivid dreams.

Scientific name	D. form	Trade name	concentration
Amitriptyline	Tab	Deprezole®, Elavil® , Levate®	10 mg , 25 mg , 50 mg
	Tab	Tryptizole®	75 mg
Nortriptyline	Tab	Allegron®	10 mg , 25 mg
Amoxapine	Tab	Asendin®	10 mg , 25 mg
Imipramine	Tab , Cap	Tofranil®	10 mg , 25 mg & 75 mg (Cap)
Clomipramine	Tab , Cap	Anafranil® , Anafranil SR®	25 mg , 50 mg & 75 mg (SR)
Desipramine	Tab	Norpramin®	10 mg , 25 mg , 50 mg

Scientific name	D. form	Trade name	concentration
Lofepramine	Tab	Feprapax®	70 mg
Protriptyline	Tab	Vivactil®	5 mg , 10 mg
Trimipramine	Cap	Surmontil® , Trimip®	25 mg , 50 mg
Dosulepin *	Tab , Cap	Prothiaden®	25 mg , 75 mg
Doxepin	Tab , Cap	Sinequan® , Sinepin®	10 mg , 25 mg , 50 mg
Related antidepressants			
Maprotiline	Tab	Ludiomil®	25 mg , 50 mg , 75 mg
Mianserin	Tab	Miarin®	10 mg , 30 mg
Trazodone	Tab , Cap	Molipaxin®, Desyrel®, Oleptro®	50 mg , 100 mg , 150 mg

1. **Imipramine** has been used to control bed-wetting in children (older than age 6 years) by causing contraction of the internal sphincter of the bladder. At present, it is used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems.
2. **Amitriptyline**, have been used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of the pain is unclear.
3. **Dosulepin = Dothiepin**, they are the same drug.
4. **Doxepin** can be used to treat insomnia.
5. **Maprotiline** have antidepressant, sedative, anxiolytic, and sympathomimetic activities.
6. **Trazodone** also has antianxiety (anxiolytic/hypnotic) effects, also used for Erectile Dysfunction.
    - Has a strange side effect (**causing priapism**; a painful erection that lasts more than 4 hrs.).

C) Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

1. They act by blocking the reuptake of norepinephrine and serotonin; Unlike TCAs, they have low or negligible effects at other receptors that cause anticholinergic or antihistaminic adverse effects; Examples include: **Duloxetine, Venlafaxine, Desvenlafaxine.**
2. They are **effective in treating depression in patients in whom SSRIs are ineffective,** also depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective. **This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS,** Both SNRIs and TCAs, with their dual actions of inhibiting serotonin and norepinephrine reuptake, are sometimes effective in relieving physical symptoms of neuropathic pain such as diabetic peripheral neuropathy.
3. **Duloxetine** is also used in the treatment of **generalized anxiety disorder**, treatment of **diabetic peripheral neuropathic**, and the treatment of moderate to severe **stress urinary incontinence** in women, also indicated for the treatment of **Fibromyalgia**.
    - Recommended as a first line agent for the **treatment of chemotherapy-induced neuropathy** by the American Society of Clinical Oncology.
    - On November 4, 2010, the FDA approved Duloxetine to **treat chronic musculoskeletal pain, including discomfort from osteoarthritis and chronic lower back pain.**
    - **Deceased appetite/weight loss** is considered a common side effect of Duloxetine, with about 10% of users reporting one or both of these side effects.
4. **Venlafaxine** is a pure SNRI; it **lacks the sedative and Antimuscarinic effects** of the tricyclic antidepressants, but treatment with venlafaxine is associated with a higher risk of withdrawal effects compared with other antidepressants.

Scientific name	Dosage form	Trade name	concentration
Duloxetine	Cap , Cap CR	Cymbalta®	30 mg , 60 mg
Reboxetine	Tab	Edronax®	4 mg
Venlafaxine	Tab	Effexor®	25 mg , 50 mg
	Cap	Effexor XR®	75 mg , 150 mg
Desvenlafaxine	Tab	Pristiq® , Khedezla®	50 mg , 100 mg
Milnacipran *	Tab	Savella®	12.5 mg , 25 mg , 50 mg
levoMilnacipran	Cap	Fetzima®	20 mg , 40 mg , 80 mg

* **Milnacipran** is used in the clinical treatment of fibromyalgia.

D) Atypical Antidepressants

1. The atypical antidepressants are a mixed group of agents that have action at several different sites, this group includes **bupropion, mirtazapine, Nefazodone** and **trazodone.**
2. They are not any more efficacious than the TCAs or SSRIs, but their side effect profiles are different.

Scientific name	D. form	Trade name	concentration
Bupropion	Tab	Wellbutrin® , Zyban®	75 mg , 100 mg , 150 mg
Mirtazapine	Tab	Remeron®	7.5 mg , 15 mg , 30 mg
Nefazodone	Tab	Serzone®	50 mg , 100 mg , 150 mg
Trazodone	Tab	Molipaxin®, Desyrel® , Oleptro®	50 mg , 100 mg , 150 mg

Notes:

1. **Bupropion** (weak norepinephrine-dopamine reuptake inhibitor); it is also used in **smoking cessation**, it assists in decreasing the craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking; Its use should be **avoided** in patients at **risk for seizures (lowers seizure threshold);** or who have **eating disorders (such as bulimia).**
2. **Mirtazapine** (antagonist of presynaptic α2-autoreceptors and heteroreceptorsis); **markedly sedating, due its potent antihistaminic activity**, but it does not cause the Antimuscarinic side effects of the TCAs, or interfere with sexual functioning, as do the SSRIs.
   - It also blocks 5-HT_2 and 5-HT_3 receptors; also, it's a Potent H1 antagonist
   - It can cause an increased appetite, and weight gain.
3. **Nefazodone** sale **was discontinued in 2003** in some countries due to the rare incidence of hepatotoxicity (liver damage), **could lead to the need for a liver transplant, or even death.**
4. **Trazodone** (both 5-HT_2 serotonin antagonist and serotonin reuptake inhibitor); it has antianxiety (anxiolytic/hypnotic) effects, also used for erectile dysfunction.
   - May cause marked sedation, Priapism (painful erection), and orthostatic hypotension.
5. Both **Nefazodone** and **Trazodone** have mild to moderate α1-receptor antagonism contributing to orthostasis and dizziness side effects.

E) Monoamine Oxidase Inhibitors (MAOIs)

1. **Monoamine Oxidase** (MAO) in the neurons acts as a safety valve to oxidatively deaminate and inactivate any excess neurotransmitters (as Norepinephrine, Dopamine and Serotonin).
2. **MAOIs** acts by **blocking the enzyme** responsible for the breakdown of these neurotransmitters; There are two forms of this enzyme (MAO-A and MAO-B), and drugs can block one or both of them; **either reversibly or irreversibly** causing accumulation of neurotransmitters within the presynaptic neuron, leading to leakage into the synaptic space.
3. **Their use these days are limited due to:**
   a. **The Severe and often unpredictable side effects**
   b. The drug-food interaction (usually **Tyramine**) and drug-drug interactions **(complicated dietary restrictions required of patients taking them.).**
4. **Tyramine** (found in aged cheese, preserved meats, Soya bean); causes the release of large amounts of stored catecholamines from nerve terminals, **resulting in what is termed a "hypertensive crisis,"** with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and stroke.
   - **Patients must be educated to avoid Tyramine containing foods.**
5. **MAOIs and SSRIs should not be co-administered** due to the risk of the **life-threatening serotonin syndrome.** Both types of drugs require washout periods of at least 2 weeks before the other type is administered.
6. **Combination of MAOIs and bupropion can produce seizures.**
7. They are **contraindicated in pregnancy.**

Scientific name	Dosage form	Trade name	concentration
Isocarboxazid	Tab	Marplan®	10 mg
Phenelzine	Tab	Nardil®	15 mg
Selegiline*	Tab , Cap	Eldepryl®	1.25 mg (Tab) , 5 mg (Cap)
	Patch	Emsam®	6 mg , 9 mg , 12 mg / 24 hr.
Tranylcypromine	Tab	Parnate®	10 mg
Moclobemide **	Tab	Manerix®	150 mg , 300 mg
Safinamide	Tab	Xadago®	50 mg , 100 mg

* **Selegiline** is also used for the treatment of early-stage Parkinson's disease, and senile dementia.

** **Moclobemide** is indicated for major depression and social anxiety disorder; it is reported to act by **reversible inhibition of monoamine oxidase** type A (it is therefore termed a RIMA). It should be reserved as a second-line treatment.

F) Other Antidepressants/Psychoanaleptics drugs:

Scientific name	Dosage form	Trade name	concentration
Melatonin	Tab , Oral drops	Meloset® , Circadin®	2 mg , 3 mg , 5 mg , 10 mg
Agomelatine	Tab	Valdoxan®, Thymanax®	25 mg
Tianeptine	Tab	Stablon®	12.5 mg
Reboxetine	Tab	Edronax® , Norebox®	4 mg
Esketamine	Nasal Spray	Pravato®	28 mg/device
Vilazodone	Tab	Viibryd®	10 mg , 20 mg , 40 mg
Vortioxetine	Tab	Brintellix®, Trintellix®	5 mg , 10 mg , 15 mg

1. **Melatonin** is the hormone produced by the pineal gland; it regulates sleep cycles.
   - Licensed for the short-term treatment of insomnia in adults.
   - Also licensed for the prevention of Cluster headaches, Migraine headache.
2. **Agomelatine** is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist, it has no effect on monoamine uptake and has no affinity for adrenergic, histaminergic, cholinergic, dopaminergic and BZD receptors, indicated in Treatment of major depressive episodes.
3. **Tianeptine** is used mainly in the treatment of major depressive disorder, although it may also be used to **treat anxiety, asthma, and irritable bowel syndrome**.
   - It has **antidepressant and anxiolytic effects** with a relative lack of sedative, anticholinergic, and cardiovascular side effects, but it can induce euphoria.
     Used in **Parkinson's disease**, **post-traumatic stress disorder**; also **effective for asthma**
   - Effective in men with **depression and erectile dysfunction**, also has **anticonvulsant** and **analgesic effects** (useful in **treating pain due to fibromyalgia**), for **attention-deficit hyperactivity disorder.**
4. **Reboxetine** is a norepinephrine reuptake inhibitor (NRI); used in the treatment of major depression, although it has also been used off-label for panic disorder and attention deficit hyperactivity disorder.
5. **Esketamine** is indicated for treatment-resistant depression.
6. **Vortioxetine, Vilazodone** (both 5-HT1A agonist and serotonin reuptake inhibitor); are indicated to treat adults with major depressive disorder.

G) Psychotherapeutic combos:

These combos are usually given in some cases that require additive therapy, or in severe cases that doesn't response to single agent therapy; All given for a short time ONLY.

Scientific name(s)	D. form	Trade name	concentration
Amitriptyline + Perphenazine	Tab	Etrafon®, Triptafen®	10mg/2mg , 25mg/2mg
Amitriptyline + Chlordiazepoxide	Tab	Limbitrol®	12.5mg/5mg , 25mg/10mg
Nortriptyline + Fluphenazine	Tab	Movital®	10 mg + 0.5 mg
Fluoxetine + Olanzapine	Cap	Symbyax®	25mg/3mg , 25mg/6mg
Alprazolam + Melatonin	Tab	Destres®	0.25 mg + 3 mg
Flupenthixol + Melitracen*	Tab	Deanxit®	0.5 mg/10 mg

*** (Flupenthixol + Melitracen)** Deanxit®, It's designed for short term usage only, it's banned in USA, the UK, Ireland, Canada, Japan, and Australia due association with potentially serious neurological side effects, and it's still used in our market for IBS!

4.4 – Anti-epileptic drugs (AEDs)

1. Electrical signals from nerve cells in the brain are normally finely coordinated to produce smooth movements of the arms and legs, but these signals can become irregular and chaotic, and trigger the disorderly muscular activity and mental changes that are characteristic of a seizure (also called a fit or convulsion).
- In an epileptic seizure, uncontrolled electrical activity starts in one part of the brain and spreads to other parts, causing uncontrolled stimulation of brain cells.
- Most of the anticonvulsants have an inhibitory effect on brain cells and damp down electrical activity, preventing the excessive build-up that causes epileptic seizures.

2. The most common cause of seizures is epilepsy, which occurs as a result of brain disease or injury. In epileptics, a seizure may be triggered by an outside stimulus such as a flashing light, seizures can also result from the toxic effects of certain drugs and, in young children; seizures may be caused by a high temperature; there are several types of Epilepsy:

a) Generalized epilepsy: In this form of epilepsy, there is widespread disturbance of electrical activity in the brain, and loss of consciousness occurs at the outset, in its simplest form, a momentary loss of consciousness occurs during which the sufferer may stare into space, this is called an absence seizure, and mainly affects children; Seizures do not occur, another form of generalized epilepsy causes a brief jerk of a limb (myoclonus).

b) Tonic-Clonic (grand mal) seizure, which is characterized by loss of consciousness and seizures that may last for a few minutes.

c) Partial (focal) epilepsy: This type of epilepsy is caused by an electrical disturbance in only one part of the brain. The result is a disturbance of function, such as an abnormal sensation or movement of a limb, without loss of consciousness. Known as a simple partial seizure, this may precede a more serious attack associated with loss of consciousness (complex partial seizure), which may in turn progress to a generalized convulsive seizure.

d) Status epilepticus: Repeated attacks without full recovery between, or a single attack lasting more than 10 minutes, occur in this form of epilepsy; Emergency treatment is required.

Notes:

1. Example of some antiepileptic drugs available: Carbamazepine, Gabapentin, Lamotrigine, Levetiracetam, Phenytoin, Pregabalin, Topiramate and Valproate.

Other examples include **Benzodiazepines** as (Diazepam, Lorazepam, and Clonazepam), and **Barbiturates** as (Phenobarbital, Primidone) → **see above section 1.**
- **AEDs suppress seizures; but do NOT CURE epilepsy.**
- Other indications for some AEDs are: neuropathic pain, migraine prophylaxis, trigeminal neuralgia, bipolar disorder, and anxiety disorder

2. The choice of an AED depends on the **seizure type, potential for drug interactions and side effects, cost and physician familiarity with the drug**.
- If one drug is not effective, a different one will be tried.
- Occasionally, it is necessary to take a combination of drugs.

3. Usually, **therapy is initiated at low dose and gradually increased** over 3 or 4 weeks to an effective dose.

4. Adverse effects of AEDs: Two types of adverse effects occur with AEDs, dose-related and idiosyncratic:
- **a.** For many AEDs, common **dose-related adverse effects** include **sedation**, **ataxia**, and **diplopia** (If a patient has a job that requires mental alertness, it is best to choose an AED that is less likely to cause sedation (lamotrigine).
- **b. Idiosyncratic adverse effects** will almost always result in the AED being discontinued. Rash, hepatotoxicity, and hematologic toxicities are the most common idiosyncratic reactions seen with AEDs.

5. **Antiepileptic hypersensitivity syndrome** is a rare but potentially fatal syndrome associated with some antiepileptic drugs (carbamazepine, Lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, Primidone, and Rufinamide); rarely cross-sensitivity occurs between some of these antiepileptic drugs.
   a. The symptoms usually start between 1 and 8 weeks of exposure; fever, rash, and lymphadenopathy are most commonly seen.
   b. Other systemic signs include liver dysfunction, hematological, renal, and pulmonary abnormalities, vasculitis, and multi-organ failure.

6. **One chronic adverse effect that is of concern is osteoporosis**; Carbamazepine, phenytoin, Phenobarbital, and valproate have all been shown to decrease bone mineral density, even after only 6 months of treatment; **Patients taking these drugs for longer than 6 months should take supplemental calcium and vitamin D** [8].

7. **Sexual dysfunction** was reported in 30%–60% of patient with epilepsy.
   - Sexual dysfunction has been reported with carbamazepine, phenobarbital, phenytoin, Pregabalin, Topiramate, and Zonisamide.
   - But Improved sexual functioning has been reported with lamotrigine and oxcarbazepine.

8. **Regarding suicide with AEDs**, the ones most associated with depression and suicidality are Levetiracetam, Perampanel, phenobarbital, Primidone, Tiagabine, Topiramate, and Vigabatrin.
   - Thus; When starting or switching AEDs, patients should be advised to report any changes in mood and suicidal ideation.

9. AEDs are associated with many **different drug interactions**:
   a. **Phenobarbital, phenytoin, and carbamazepine are potent inducers of various CYP-450 isoenzymes,** increasing the clearance of other drugs metabolized through these pathways.
   b. **Valproic acid inhibits many hepatic enzyme systems**.
   c. **Felbamate** and **Topiramate** can act as inducers with some isoforms and inhibitors with others.

10. **A febrile seizure** (fever fit or febrile convulsion) is an epileptic seizure associated with a high body temperature but without any serious underlying health issue. They most commonly occur in children between the ages of 6 months and 5 years. Most seizures are less than five minutes in duration and the child is completely back to normal within 16 minutes of the event.
    a. Antipyretic medication (**Paracetamol**) is commonly used (rectally or I.V.) to reduce fever and prevent further convulsions.
    b. Some physicians prefer to use **Diazepam** (amp.) rectally.

Scientific name	Dosage form	Trade name	concentration
Carbamazepine	Tab	Tegretol® , Taver® , Tegral®	200 mg
	Tab ER	Tegretol CR®	200 mg , 400 mg
	Oral Susp.		100 mg/5 ml
	Supp.		125 mg , 250 mg
Eslicarbazepine	Tab	Zebinix® , Aptiom®	200 mg , 400 mg , 800 mg
Oxcarbazepine	Tab	Trileptal®	150 mg , 300 mg , 600 mg
	Oral Susp.		300 mg/5 ml
Valproic acid	Cap	Depakene® , Depacon®	125 mg , 250 mg , 500 mg
	Syrup		250 mg/5 ml
	Inj.		100 mg/ml
Divalproex	Tab	Depakote®	250 mg , 500 mg
Stiripentol	Cap	Diacomit	250 mg , 500 mg
Ethosuximide	Cap	Zarontin® , Petnidan®	250 mg
	Syrup	Meside®	250 mg/5 ml

Scientific name	Dosage form	Trade name	concentration
Ezogabine	Tab	Potiga®	200 mg , 300 mg , 400 mg
Retigabine	Tab	Trobalt®	100 mg , 200 mg , 300 mg
Tiagabine	Tab	Gabitril®	2 mg , 4 mg , 12 mg
Rufinamide	Tab	Inovelon®, Banzel®	100 mg , 200 mg , 400 mg
Felbamate	Tab	Felbatol®	400 mg , 600 mg
	Oral Susp.		600 mg/5 ml
Lamotrigine	Tab	Lamictal®	25 mg , 50 mg , 100 mg
Brivaracetam	Tab	Briviact®	10 , 25 , 50 , 75 mg , 100 mg
Levetiracetam	Tab	Keppra®, EPIXX®	250 mg , 500 mg , 750 mg
	Oral Solu.		100 mg/ml
	Infusion Solu.		100 mg/ml (5 ml vial)
Phenytoin	Tab , Cap	Epanutin®	100 mg , 200 mg
	Inj. (Amp)		50 mg/ml
Fosphenytoin	Inj. (Amp)	Cerebyx®	50 mg/ml
Lacosamide	Tab	Vimpat®	100 mg , 150 mg , 200 mg
	Infusion Solu.		10 mg/ml (200 mg vial)
Methsuximide	Cap	Celontin®	150 mg , 300 mg
Topiramate	Tab	Topamax®	25 mg , 50 mg , 100 mg
Vigabatrin	Tab	Sabril®	500 mg
Zonisamide	Cap	Zonegran®	25 mg , 50 mg , 100 mg
Gabapentin	Cap	Neurontin® , Gabamed®	100 mg , 300 mg , 400 mg
	Tab		600 mg , 800 mg
Pregabalin	Cap	Lyrica®	50 mg , 75 mg , 150 mg
	Cap SR		200 mg , 225 mg , 300 mg
Perampanel *	Tab	Fycompa®	2 mg , 4 mg , 8 mg , 12 mg
Cannabidiol **	Oral Solu.	Epidiolex®	100 mg/ml
Cenobamate	Tab	Xcopri®	25 , 50 , 100 , 150 , 200 mg

* **Perampanel** is an AMPA antagonist, uses as adjunctive therapy for treatment of partial-onset seizures with/without secondary generalized seizures, **has risks for serious neuro-psychiatric events.**

** **Cannabidiol** is approved by (FDA) for treatment of epilepsy associated with Lennox–Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.

Notes:

1. **Carbamazepine** is also **mood-stabilizing** drug used primarily in the treatment of epilepsy and bipolar disorder, as well as trigeminal neuralgia; It is also used off-label for a variety of indications, including attention-deficit hyperactivity disorder (ADHD), **(Carbamazepine Stabilizes inactivated state of sodium channels, thereby making neurons less excitable).**
   - Can cause **hyponatremia, Aplastic anemia**
   - Can **cause Folate deficiency**, thus give **folic acid** as supplementation with it.
   - It **may cause an increase in seizures**.
2. **Valproic acid** is also **mood-stabilizing** and also used to treat **migraine headaches.**
3. **Divalproex** consists of a compound of **sodium valproate** and **Valproic acid** in a 1:1 molar relationship in an enteric coated form.
4. **Lamotrigine** is one of a small number of FDA-approved therapies **for seizures associated with Lennox-Gastaut syndrome,** also seems to act as an effective **mood stabilizer.**
5. **Levetiracetam** has potential benefits for other psychiatric and neurologic conditions such as Tourette syndrome, autism, bipolar disorder and anxiety disorder, as well as Alzheimer's disease, However, **its most serious adverse effects are behavioral** (aggression, agitation, anger, anxiety, apathy, depersonalization, hostility, hyperkinesis, irritability, nervousness, neurosis, and personality disorder) and its benefit-risk ratio in these conditions is not well understood.

6. **Phenytoin** is very old anticonvulsant, may **cause gingival hyperplasia** (cause the gums to grow over the teeth), this side effect led **Phenytoin to be used topically for wound healing**.
   - See chapter 14, section 21 for more info.
   - **Phenytoin should not be given I.M.** as it causes tissue necrosis, given only as I.V infusion.
   - **Fosphenytoin** is a pro drug, that is converted to Phenytoin; it can be given as I.M. inj.
7. **Topiramate** is used to **treat epilepsy in children and adults**, for seizures associated with **Lennox-Gastaut syndrome**, this drug is **also widely used to treat migraines** due to the effect it has on the blood vessels in the brain; It is used as a **preventative for atypical migraine and Cluster headaches**, also used for **alcoholism, smoking cessation and in combination with phentermine for weight loss.**
   - Maintain adequate fluid intake due to **kidney stone risk with Topiramate**.
   - Monitor closely for decreased sweating and increased body temperature.
8. **Vigabatrin** is an antiepileptic drug that inhibits the catabolism of gamma-amino butyric acid (GABA) by irreversibly inhibiting GABA transaminase; It is an analog of GABA, but it is not a receptor agonist.
   - Only used for **refractory complex partial seizures** and **infantile spasms.**
   - **Causes permanent vision loss in infants, children, and adults** and includes progressive and permanent bilateral concentric visual field constriction in >30% of patients and ranges in severity from mild to severe, including tunnel vision to within 10 degrees of visual fixation, and can result in disability
   - **May damage the central retina and decrease visual acuity.**
   - Vision loss onset is unpredictable and can occur within weeks of starting treatment, or sooner, or at any time during treatment (even after months or years), and possibly after Vigabatrin is discontinued
   - **Vision testing is required at baseline and then at least every 3 months** (unless patient is formally exempt), but cannot reliably prevent vision damage.
   - **The retinal toxicity of Vigabatrin can be attributed to a taurine depletion.**
9. **Ethosuximide is useful only for absence seizures.**
10. **Lamotrigine** occasionally causes Rash; and thus, must be titrated slowly to avoid a rash.
    - when adding Lamotrigine to Valproic acid; the dose of Lamotrigine should be reduced or titrated to avoid the skin rashes, which is very serious and may progress to a life-threatening reaction.
    - Estrogen-containing oral contraceptives increase lamotrigine clearance; therefore, twice the amount of lamotrigine may be necessary.
11. **Lacosamide** may **cause PR interval prolongation or first-degree atrioventricular block;** thus, its preferred not to use in patients with cardiac problems.
    - **Has euphoretic effect;** a Controlled substance schedule V.
12. **Zonisamide** is also indicated for **Weight Loss,** maintain fluid intake due to risk of kidney stone formation, discontinue treatment if significant sustained increase in creatinine occurs.
    - Combination with Topiramate or Acetazolamide increase the risk of metabolic acidosis.
13. **Gabapentin** is a GABA analogue; structurally related to neurotransmitter GABA, but has no effect on GABA binding, uptake, or degradation; **mechanism for analgesic and anticonvulsant activity unknown.**
    - Used to relieve neuropathic pain; may help with menopausal symptoms, effective treatment for migraine prophylaxis [unlicensed]; Helps with itching due to renal failure, known as **uremic pruritus,** useful anxiety with bipolar disorder and restless leg syndrome.
14. **Pregabalin** is a GABA analogue, appears to be as effective as **Gabapentin** for neuropathic pain; but costs more; Used in:
    - Diabetic Peripheral Neuropathic, Post-herpetic Neuralgia, Neuropathic Pain with Spinal Cord Injury, Fibromyalgia, perioperative pain; It appears to have anxiolytic effects similar to benzodiazepines, and is licensed for the treatment of generalized anxiety disorder.

4.5-Drugs used in Parkinsonism

1. In Parkinson's disease, the progressive degeneration of pigmented neurons in the substantia nigra leads to a **deficiency of the neurotransmitter dopamine**, the resulting neurochemical imbalance in the basal ganglia causes the characteristic signs and symptoms of the illness.
   - Parkinsonism is caused by an imbalance of chemicals in the brain; **the effect of acetylcholine is increased by a reduction in the action of dopamine.**
   - Drugs to treat Parkinsonism **restore the balance between dopamine and acetylcholine;** They fall into two main groups: those that reduce the effect of acetylcholine and those that boost the effect of dopamine**.**
2. The primary objective of drug therapy **is to enhance dopaminergic activity within the damaged areas of the basal ganglia**, and this is achieved in various ways (see table below).
3. Currently available drugs **offer temporary relief** from the symptoms of the disorder, **but they do not arrest or reverse the neuronal degeneration caused by the disease.**
   - That's due the degeneration of brain cells in Parkinson's disease cannot be halted.
4. No treatment has been unequivocally shown to prevent progression of Parkinson disease; therefore, treatment is based on symptoms.
5. In patients who need the initiation of dopaminergic treatment, either levodopa or a dopamine agonist can be used. The choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with dopamine agonists) for each individual patient.

Pharmacological rationales for enhancing dopaminergic transmission in the basal ganglia

Approach	Rationale	Drug group and examples
Reduce cholinergic activity	Balance diminished dopaminergic activity	Antimuscarinic, e.g. trihexyphenidyl (benzhexol), procyclidine
Inhibit neuronal dopamine re-uptake	Maximize remaining dopaminergic activity	Amantadine
Stimulate dopamine receptors	Mimic dopamine	Dopamine agonist: • Ergot derived: cabergoline, pergolide, lisuride, bromocriptine • Non-ergot derived: ropinirole, rotigotine, pramipexole • Other: apomorphine
Supply dopamine precursor	Increase dopamine level in basal ganglia	Levodopa
Reduce peripheral destruction of precursor	Increase levodopa penetration into brain	Decarboxylase inhibitor, e.g. carbidopa, benserazide COMT-inhibitor: entacapone, tolcapone
Reduce central destruction of dopamine	Increase dopamine half-life in brain	COMT-inhibitor: tolcapone MAO-B inhibitor, e.g. selegiline. rasagiline

MAO-B, monoamine oxidase-B; COMT, catechol-O-methyl transferase.

Notes:

1. Ergot-derived dopamine-receptor agonists (bromocriptine, cabergoline, and pergolide), have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions.
2. **Apomorphine** is a potent dopamine-receptor agonist that is sometimes helpful in advanced disease for patients experiencing unpredictable 'off' periods with levodopa treatment.

Scientific name	D. form	Trade name	concentration
Dopamine agonists			
Bromocriptine	Tab	Parlodel® , Cycloset®	2.5 mg , 5 mg , 10 mg
Cabergoline	Tab	Dostinex® , Cabaser®	0.5 mg , 1 mg
Ropinirole	Tab	Requip®	0.5 mg , 1 mg , 2 mg
	Tab MR	Requip XL®	4 mg , 8 mg
Pramipexole	Tab , Tab ER	Mirapex®, Sifrol®, Pexola® Mirapex ER®	0.125 mg , 0.25 mg , 0.5 mg 1 mg , 1.5 mg , 3 mg
	Tab PR	Motorax®	0.52 mg , 1.05 mg , 2.1 mg
Pergolide	Tab	Pergo®	50 mcg , 250 mcg
Rotigotine	Skin patch	Neupro®	1 mg , 2 , 4 , 8 mg (per 24 hr.)
Apomorphine	Inj.	APO-go®	10 mg/ml
Levodopa derivatives			
Levodopa + Carbidopa	Tab	Sinemet®, Isicom® Parcopa®	(100 mg + 25 mg) Sinamet®, (250 mg + 25 mg) Isicom®,
	Tab MR	Caramet CR®	200 mg + 50 mg
	Intestinal Gel *	Duodopa®	20 mg + 5 mg
Levodopa + Benserazide	Tab , Cap	Madopar®	(50 mg + 12.5 mg), (100 mg + 25 mg)
Levodopa + Carbidopa + Entacapone	Tab	Stalevo®, Corbilta®	(150 mg + 37.5 mg + 200 mg) (100 mg + 25 mg + 200 mg)
Monoamine-oxidase-B inhibitors			
Selegiline *	Tab , Cap	Eldepryl® , Jumex®	1.25 mg (Tab), 5 mg (tab, Cap)
Rasagiline	Tab	Azilect®	0.5 mg , 1 mg
Safinamide	Tab	Xadago®	50 mg , 100 mg
Catechol-O-methyl transferase (COMT) inhibitors			
Entacapone	Tab	Comtan® , Comtess®	200 mg
Tolcapone	Tab	Tasmar®	100 mg
Antimuscarinics			
Benztropine	Tab	Cogentin®	0.5 mg , 1 mg , 2 mg
	Inj. Solu.		1 mg/ml
Benzhexol (or) Trihexyphenidyl	Tab, Elixir	Parkizol®, Trihex® Artane®	2 mg , 5 mg (Tab) 0.4 mg (Elixir)
Procyclidine	Tab	Kemadrin® , Arpicolin®	5 mg
Other drugs			
Biperiden	Tab	Akineton®, Dekinet®	2 mg
Piribedil	Tab	Trivastal®	50 mg
Amantadine	Tab , Cap	Symmetrel®	100 mg

*** Selegiline = Deprenyl,** they are the same drug.

Notes:

1. **Levodopa** is a metabolic **precursor of Dopamine**; it restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine.
   Dopamine itself does not cross the blood-brain barrier, but **Levodopa is actively transported into the CNS and is converted to dopamine in the brain.**
   - **a.** It Has a short half-life (1-2 hours), and should be taken on empty stomach.
   - **b.** It causes a **brownish urine** and **saliva**.

2. **Carbidopa and Benserazide,** are Dopa-decarboxylase inhibitor, **they diminish the metabolism of levodopa** in the gastrointestinal tract and peripheral tissues**,** thereby increasing the availability of levodopa to the CNS; **Also, they lower the dose of levodopa needed by 4 to 5-fold** and thus **decreases the severity of side effects from peripherally formed dopamine.**
    a. **Side effects** of this combination include: **Anorexia, nausea, and vomiting** occur because of stimulation of the chemoreceptor trigger zone of the medulla
        - (Don't give B_6 for the treatment of vomiting in this case, B_6 increases the peripheral breakdown of levodopa and diminishes its effectiveness, thus use another antiemetic).
    b. **Other side effects:** Visual and auditory hallucinations, Tachycardia, Hypotension.
    c. **Benserazide** is not approved for use in the US.
    d. These combinations are also used for the **treatment of restless legs syndrome.**

3. **Levodopa derivatives** has a **wearing-off effect**; (wearing off occurs when patients experience recurrence of symptoms before the next dose of medication).
    - **Possible options to solve such problem include:** the drug needs to be given more frequently, or the addition of the COMT inhibitor Entacapone, or the MAO-B inhibitor Rasagiline, or a dopamine agonist (ex: Pramipexole, Ropinirole)

4. Another complication of **Levodopa derivatives therapy is dyskinesia** (an involuntary chorea form movement (too much movement); involving the neck, trunk, and extremities lower and upper; **Possible options to solve such problem include:** The use of lower individual doses of L-dopa (with an increase in dosage frequency) or addition of **Amantadine** [3].

5. **Monoamine-Oxidase-B inhibitors** are used in conjunction with levodopa to reduce (end-of-dose) deterioration in advanced Parkinson's disease.
    a. **Selegiline** is metabolized to **Methamphetamine and Amphetamine**, which have stimulating properties that may produce insomnia and restlessness.
    b. **Rasagiline** is an **irreversible and selective** inhibitor of brain monoamine oxidase Type-B**, has 5 times the potency of Selegiline.**
        - It's not metabolized into Methamphetamine and Amphetamine.
        - **Ciprofloxacin** can double the concentration of **Rasagiline** (through CYP1A2).

6. **COMT inhibitors** prevent the peripheral breakdown of levodopa, by inhibiting Catechol-O-methyl transferase, allowing more **levodopa** to reach the brain.
    a. **Used only in conjunction with carbidopa/L-dopa**; (not used as monotherapy).
    b. **Tolcapone** is associated with fulminating hepatic necrosis, therefore; it should be used along with appropriate hepatic function monitoring.
    c. **Entacapone** does not exhibit the above liver toxicity and has largely replaced **Tolcapone.**
    d. Both are not affected by food.
    e. Entacapone may cause urine discoloration.

7. Both **Bromocriptine** and **Cabergoline** are dopamine receptor agonist on D_2 receptors. Both have a direct inhibitory effect on pituitary lactotroph (prolactin) cells, thereby inhibiting prolactin release → **used in Hyperprolactinemia.**
    a. With **Bromocriptine** in patients with peripheral vascular disease, a **worsening of the vasospasm occurs**, and in patients with peptic ulcer, there is **a worsening of the ulcer**. Also, it has the potential to cause pulmonary and retroperitoneal fibrosis.
    b. **Bromocriptine is also FDA approved for the treatment of Diabetics type 2 (DM).**
    c. **Cabergoline** have a high affinity for D2 receptors, more than **Bromocriptine.**
    d. **Bromocriptine** and **Cabergoline** are sometimes used as a **lactation suppressant**, and this is **not (FDA) approved.**
    e. **Cabergoline** has been found to raise a man's chances of sustaining multiple orgasms during sex, (enhance Erection and libido), But don't try this at home, **it's not (FDA) approved.**

8. **Amantadine** which is an **(antiviral)** was accidentally discovered that it has an anti-Parkinsonism action.
    a. Amantadine has been found to **have antidyskinesia effects.**
    b. It's no longer recommended for treatment of influenza in the USA.
    c. It is also used for post-herpetic neuralgia.
    d. **If dopamine release is already at a maximum; then Amantadine has no effect.**
    e. It May cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth.
9. **Piribedil** is an antiparkinsonian agent and Piperazine derivative which acts as a D_2 and D_3 receptor agonist. It also has α2-adrenergic antagonist properties.
    a. Also used in the treatment of pathological **cognitive deficits in the elderly** (impaired attention, motivation, memory, etc.)
    b. Used as adjunctive treatment of **intermittent claudication** due to peripheral vascular disease (PVD) of the lower limbs, it also showed a positive effect in restless legs syndrome.
10. **Antimuscarinic drugs** exert their anti-Parkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency; Antimuscarinic drugs can be useful in drug induced Parkinsonism, but they are generally not used in idiopathic Parkinson's disease because they are less effective than dopaminergic drugs and they are associated with cognitive impairment.
    a. **Benzhexol** in a high dose have a direct central inhibition effect on the cerebral motor centers, **it's abused due to a short acting mood-elevating and euphoretic effect.** (It's called by the local addicts "the miracle tab", "abu-Tabrah").
    b. **Procyclidine** overdose can **cause sleeplessness** that can last up to or more than 24 hours, it also has a **euphoretic effect** (abused by many addicts).

4.6-Drugs used in Nausea and Vertigo

1. **Antiemetics should be prescribed only when the cause of vomiting is known because otherwise, they may delay diagnosis, particularly in children; Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin or antiepileptic overdose.**
2. **See also Anti-Emetics in chapter 2;** (The drugs mentioned in this section acts on the vomiting trigger zone (deactivates the vomiting center) in the brain, they are used mainly for drug-induced emesis or chemotherapy induced emesis).
3. 5HT3-receptor antagonists (like **Ondansetron**) are of value in the management of **nausea and vomiting in patients receiving cytotoxics and in postoperative N/V.**
4. **Dexamethasone** has antiemetic effects and it is used in **vomiting associated with cancer chemotherapy**, it can be used alone or with metoclopramide, Prochlorperazine, lorazepam, or a 5HT3 antagonist.
5. **Antihistamines are also used as Antiemetics, especially those with anticholinergic effect, as (**diphenhydramine, Doxylamine, hydroxyzine, meclizine, Cyclizine, promethazine).
    - **Scopolamine, meclizine, Cyclizine, are very useful in motion sickness** but are ineffective against substances that act directly on the chemoreceptor trigger zone.
6. **Droperidol and Haloperidol** act by blocking dopamine receptors. They are moderately effective Antiemetics. (**Haloperidol is also used as antipsychotics)**
7. **Lorazepam and Alprazolam has a low antiemetic effect.**

8. **Aprepitant** belongs to a new family of antiemetic agents. It targets the neurokinin receptor in the brain and blocks the actions of the natural substance. **It is only indicated for highly or moderately emetogenic chemotherapy regimens.**
9. **Betahistine** is an **analogue of histamine** and is licensed **for vertigo tinnitus, and hearing loss associated with Meniere's disease**; (**Meniere's disease** is a disorder of the inner ear that can affect hearing and balance to a varying degree. It is characterized by episodes of vertigo, low-pitched tinnitus, and hearing loss).
   - **Betahistine** dilates the blood vessels within the inner ear which can relieve pressure from excess fluid and act on the smooth muscle.

A) 5HT3-receptor antagonists

Scientific name	Dosage form	Trade name	concentration
Ondansetron	Tab	Zofran® , Zuplenz®	4 mg , 8 mg
	Oral Solu.	No-Vomit®	4 mg/5 ml
	Inj. Solu. (Amp)		2 mg/ml
	Supp.		16 mg
Palonosetron	Inj. Solu.	Aloxi®	50 mcg/ml
	Cap		500 mcg
Dolasetron	Tab	Anzemet®	50 mg , 100 mg
	Inj. Solu.		20 mg/ml
Granisetron	Tab	Granisol® , Kytril®	1 mg
	Patch	Sancuso®	3 mg (each 24 hours)
	Inj. Solu. , Amp	Kytril® , Grani-Denk®	0.1 mg/ml , 1 mg/ml

Notes:

1. 5HT3-receptor antagonists **are not effective against motion sickness.**
2. **Ondansetron** is used off-label to treat morning sickness and hyperemesis gravidarum of pregnancy. (Pregnancy risk factor = B); **Ondansetron** may have value in the treatment of schizophrenia, also useful in treating antipsychotic-induced tardive dyskinesia in people with schizophrenia.

B) Butyrophenones

Scientific name	Dosage	Trade name	concentration
Haloperidol	Tab	Haldol® , Peridol®	0.5 mg & 1 mg & 2 mg & 5 mg
	Amp	Haldol Lactate®	5 mg/ml
	Depot Inj.	Haldol Deconate®	50 mg/ml & 100 mg/ml
Droperidol	Inj. Solu.	Inapsine® , Droleptan® , Dridol®	2.5 mg/ml

C) Cannabinoids

Scientific name	Dosage form	Trade name	concentration
Dronabinol *	Cap	Marinol®	2.5 mg , 5 mg , 10 mg
Nabilone	Cap	Cesamet®	1 mg

*** Dronabinol** is also used to **treat loss of appetite**, treat weight loss and the 1st drug approved for the **treatment of sleep Apnea.**

D) Miscellaneous agents

Scientific name	Dosage form	Trade name	concentration
Aprepitant	Cap	Emend®	40 mg , 80 mg , 125 mg
	Inj. Powder		150 mg/vial
Fosaprepitant *	Inj. Powder	Ivemend®	150 mg/vial
Rolapitant	Tab	Varubi®	90 mg
Trimethobenzamide	Cap	Tigan®	300 mg
Betahistine	Tab	Betaserc®	8 mg , 16 mg

*** Fosaprepitant** is a pro-drug of **Aprepitant.**

*** Rolapitant** is FDA approved for the **prevention** of **chemotherapy-related N/V.**

4.7- Drugs for Dementia (Anti-Alzheimer)

1. In **Dementia**, there is a deterioration memory, judgment, language and communication. **Alzheimer's disease is the most common cause of dementia and accounts for over half of all patients; about one-third of dementia cases are due to vascular disease**.
   - **Dementia** can be sudden and irreversible, due to a stroke or head injury.
   - It **can also develop gradually** and may be a feature of disorders such as poor circulation in the brain, multiple sclerosis and Alzheimer's disease.
2. In healthy people, **Acetylcholinesterase** (an enzyme in the brain) breaks down the neurotransmitter **Acetylcholine**, balancing its levels and limiting its effects; **In Alzheimer's disease, there is a deficiency of acetylcholine**.
   - So, we use a group of drugs called **Acetylcholinesterase inhibitors;** that blocks the action of the enzyme acetylcholinesterase, **raising brain levels of Acetylcholine**, and thus increasing alertness and slowing the rate of deterioration.
   - **Donepezil**, **Galantamine**, **Tacrine** and **Rivastigmine** are the main **(central) Acetylcholinesterase inhibitors**; All have produced modest improvement in mild to moderate disease state.
3. **Acetylcholinesterase inhibitors** can **cause unwanted cholinergic side-effects**, **including:** (nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps), all of which are predicted by the actions of the drugs to enhance cholinergic neurotransmission, unlike the others, **Tacrine is associated with hepatotoxicity.**
   - Thus; **drug treatment is started at a low dose and increased gradually** to minimize side effects and any improvements should begin to appear in about three weeks.
   - Assessment is repeated at six-monthly intervals to decide if the treatment is beneficial.
4. **Rivastigmine** is a **unique cholinesterase inhibitor** with both **Acetylcholinesterase** and **Butyrylcholinesterase** inhibitory activity.
   - **Butyrylcholinesterase**, also known as pseudocholinesterase; is a nonspecific cholinesterase enzyme, which is similar in activity to **Acetylcholinesterase.**
   - **Thus; Rivastigmine** is **more potent** and **more effective** than **Donepezil** in Dementia.
   - **But** the incidence of adverse events is generally lower for **Donepezil** and higher for **Rivastigmine**, (thus some doctors prefer to use Rivastigmine Patch).
5. There is increasing evidence that memory loss and dementia in Alzheimer's disease are related to **malfunctioning of the signals that pass messages between the nerve cells** in the brain, in particular, there is evidence that excessive activity of a natural body chemical called **glutamate contributes to the symptoms of Alzheimer's and the progression of this disease.**
   - **Glutamate** acts on receptors called **NMDA receptors** that are found on nerve cells in the brain, these receptors and nerve cells are involved in transmitting nerve messages in the brain that are important in learning and memory; **Glutamate can damage the nerve cells by excessively stimulating the NMDA receptors.**
6. **Memantine** works by **blocking the NMDA receptors** in the brain; This **blocks the excessive activity of glutamate**, but still allows the normal activation of these receptors that occurs when the brain forms a memory.
   - **Memantine** may improve brain functioning in Alzheimer's disease, and may also block the glutamate activity that could cause further damage to the brain cells.
   - Its licensed for treating moderate to severe Alzheimer's disease.
   - **Memantine is often given in combination with an AChE inhibitor,**
   - **Side effects include:** confusion, agitation, and restlessness.
7. **Other herbal treatments include:**

a) **Gingko Biloba:** was **not effective in prevention or treatment** in randomized controlled trials.
b) **Citicoline:** may **improve cognitive impairment, especially of vascular origin**; it serves as choline source in the metabolic pathways for biosynthesis of Acetylcholine; (for more details see section 9, Nootropics).

8. **Summary of treatment guideline recommendations** of the American Psychiatric Association, American College of Physicians, and American Academy of Family Physicians, 2007–2008:
   - **a.** Initiate an AChE inhibitor in patients with mild to moderate Alzheimer Disease.
   - **b.** No evidence one agent is superior to others
   - **c.** Titrate to recommended maintenance dose as tolerated.
   - **d.** Increase to maximum dose if tolerated and maintenance dose no longer effective, but clinically meaningful improvement unlikely
   - **e.** In moderate to severe disease, may use an AChE inhibitor, Memantine, or both as a combination; but Slight or no benefit with combination therapy in systematic reviews.
   - **f.** Studies find no benefit of Memantine in mild Alzheimer Disease.

Scientific name	Dosage form	Trade name	concentration
Donepezil	Tab	Aricept®	5 mg , 10 mg
Galantamine	Tab , Tab ER	Razadyne® , Reminyl®	4 mg , 8 mg , 12 mg
Rivastigmine	Cap	Exelon®	1.5 mg , 3 mg , 6 mg
	Skin Patch		9.5 mg (each 24 hr.)
Tacrine	Cap	Cognex®	10 mg , 20 mg , 30 mg
Memantine *	Tab	Ebixa® , Namenda® , Demax®	5 mg , 10 mg
	Cap ER		7 mg , 14 mg , 21 mg
	Oral Solu.		2 mg/ml
Memantine + Donepezil	Tab	Namzaric® , Carrier Plus®	(20 mg + 5 mg) , (20 mg + 10 mg)

*** Memantine** was used first as an anti-diabetic agent at its discovery.

4.8- CNS Stimulants

1. A person's state of mental alertness varies throughout the day and is under the control of chemicals in the brain, some of which are depressant, causing drowsiness, and others that are stimulant, heightening awareness.
2. It is thought that an increase in the activity of the depressant chemicals may be responsible for a condition called **Narcolepsy**, which is a tendency to fall asleep during the day for no obvious reason; In this case, the nervous system stimulants are administered to increase wakefulness.
   - These drugs include the amphetamines (usually dexamphetamine), the related drug methylphenidate, and Modafinil.
   - Amphetamines are used less often these days because of the risk of dependence.
3. A common home remedy for increasing alertness is caffeine, a mild stimulant that is present in coffee, tea, and cola and Red-bull
4. The level of wakefulness is controlled by a part of the brain stem called the reticular activating system (RAS); Activity in this area depends on the balance between chemicals, some of which are excitatory (including norepinephrine), and some inhibitory, such as gamma aminobutyric acid (GABA).
5. This Section describes a group of drugs that act primarily to stimulate the central nervous system (CNS); The psychomotor stimulants, cause excitement and euphoria, decrease feelings of fatigue and increase motor activity; **As a group the CNS stimulants have diverse clinical uses and are important as drugs of abuse**. (This group is widely abused by addicts).
6. **Stimulants are used both individually and clinically** for therapeutic purposes in the treatment of a number of indications, including the following:
   1. **To counteract lethargy and fatigue** throughout the day while at work or while doing other activities.
   2. **To reduce sleepiness** and to keep the person awake when necessary, as well as to **treat narcolepsy.**

3. **To decrease appetite and promote weight loss**, as well as to treat obesity.
4. Occasionally, they are also used off label to **treat clinical depression**, more particularly, non-typical depression and treatment-resistant depression.
5. **To improve concentration and focus** while at work or school, especially for those with attentional disorders such as **ADHD (attention deficit hyperactivity disorder).**
   - It seems a weird and strange to **use a CNS stimulant to treat a hyperactivity disorder (ADHD)**; but stimulants in ADHD cause a negative response (i.e. decrease abnormal hyperactivity).
6. **To treat Autism in children** (although safer options are available, as **Risperidone** and **Aripiprazole,** which are FDA approved for Autism).

Scientific name	Dosage	Trade name	concentration
Armrodafinil	Tab	Nuvigil®	50 mg , 150 mg
Atomoxetine	Cap	Strattera®	10 mg , 25 mg , 40 mg , 60 mg
Caffeine	Comes in Combination in analgesics, pain killers, stimulant combination		
Dexmethylphenidate	Tab	Focalin®	2.5 mg , 5 mg , 10 mg
	Cap	Focalin XR®	15 mg , 20 mg , 25 mg
Dextroamphetamin	Tab , Cap	Dexedrine® , Liquadd®	5 mg , 10 mg
Diethylpropion	Tab	Tenuate®	25 mg , 75 mg
lisdexamfetamine	Cap	Vyvanse® , Elvanse®	20 mg , 30 mg , 40 mg , 50 mg
Methamphetamine	Tab	Desoxyn®	5 mg
Methylphenidate	Tab	Ritalin® , Concerta®	5 mg , 10 mg , 20 mg
	Cap	Ritalin SR®	20 mg , 30 mg , 40 mg
	Skin Patch	Metadate®	----------
	Oral Solu.		5 mg/5 ml
Modafinil	Tab	Provigil®, Modalert®	100 mg , 200 mg
Phendimetrazine	Tab , Cap	Bontril®	35 mg (tab) , 105 mg (cap)
Phentermine	Tab , Cap	Adipex P® , Suprenza®	15 mg , 30 mg

4.9- Nootropics

1. These drugs improve mental functions such as cognition, memory, attention, and concentration, **they enhance attentional control and memory**, and Nootropics are **cognitive enhancers** that are neuroprotective.

Scientific name	Dosage form	Trade name	concentration
Cerebrolysin	Amp , Vial	Cerebrolysin®	1 ml , 5 , 10 , 30 ml
Piracetam	Tab	Nootropil®	800 mg , 1200 mg
	Oral Solution		
Vincamine	Cap	Oxybral®	30 mg
Vinpocetine	Cap	Cavintona® , Cavintona Advanced®	10 mg , 20 mg
Idebenone	Tab	Geniceral®	30 mg , 45 mg
Meclofenoxate	Amp , Vial	Lucidril®, Luciforte®	250 mg , 500 mg
Sulbutiamine	Tab	Arcalion®	200 mg
Citicoline	Tab	Lira®	500 mg
	Inj. (Amp)	Somazina®	500 mg , 1000 mg
	Oral Solution	Somazina®, Trausan®, Citoneurox®	100 mg/ml
	Sachets		1000 mg/10 ml
Citicoline + B_6 + B_{12}	Sachets	Brain Food®	250mg + 1.4mg + 2mcg
Pyritinol	Oral Solution	Encephabol®	100 ml
	Tab		100 mg , 200 mg

Notes:

1. **Cerebrolysin**, a peptide preparation produced from purified pig brain proteins; it mimics the effects of endogenous neurotrophic factors and activates components of the endogenous defense system within the nervous tissue.
   - Indicated for patients suffering from **dementia, stroke, and traumatic brain injury.**
2. **Piracetam**, a derivative of the neurotransmitter (GABA), **has neuroprotective** and **anticonvulsant properties,** and **improves neuroplasticity.** At a vascular level, it appears to reduce erythrocyte adhesion to vascular endothelium, hinder vasospasm, and facilitate microcirculation; This diverse range of physiological effects is consistent with its use in a range of clinical indications, its efficacy is documented in **cognitive disorders and dementia, vertigo, cortical myoclonus, dyslexia, and sickle cell anemia;** Although it's still **not FDA approved.**
3. **Vincamine** is a **Peripheral Vasodilator** that acts by increasing cerebral blood circulation.
   - **Vinpocetine** is a synthetic derivative of **Vincamine**; may lead to improved attention, focus, and memory.
4. **Idebenone** is indicated for the Treatment of mild and moderate cognitive alterations in patients with Alzheimer or vascular dementia.
5. **Sulbutiamine** is a synthetic derivative of thiamine (Vit. B1), it is used to treat symptoms of weakness or fatigue, it is also sold as a dietary supplement; it may enhance memory, focus, mood and Endurance.
6. **Meclofenoxate** is a **cholinergic nootropic** used as a dietary supplement and drug in the treatment of symptoms of **senile dementia and Alzheimer's disease.**
   a. In elderly patients, **Meclofenoxate** has been found clinically to **improve memory**, have a mentally stimulating effect, and **improve general cognition**.
   b. Also increases cellular membrane phospholipids.
7. **Citicoline** supplements help improve focus and mental energy and may possibly be useful in the treatment of attention deficit disorder.
   a. it inhibits apoptosis associated with cerebral ischemia and several models of neurodegeneration, it is able to potentiate neuroplasticity and is a natural precursor of phospholipid synthesis, chiefly phosphatidylcholine or rather serves as choline source in the metabolic pathways for biosynthesis of acetylcholine.
   b. used for treatment in cases of **head trauma, stroke, neurodegenerative disease**
   c. **Improves visual function** in patients with glaucoma, amblyopia, and non-arteritic ischemic optic neuropathy.
   d. **Citicoline** reduces oxidative stress; it also prevents excessive inflammatory response in the brain by inhibiting the release of free fatty acids and decreasing blood–brain barrier breakdown.
8. **Pyritinol** is semi-natural water-soluble analog of vitamin B_6 (Pyridoxine), it is approved for "symptomatic **treatment of chronically impaired brain function in dementia syndromes** and for supportive treatment of sequelae of craniocerebral trauma.

4.10- Herbals and Supplements for Cognitive function

This section describes the herbals and supplements that is used for the enhancement of cognition, memory and brain boost; many of them are also Nootropics.

1. **Ginkgo Biloba** has been repeatedly evaluated for its ability to reduce anxiety, stress and other symptoms associated with Alzheimer's disease and cognitive decline associated with aging.
   - It cannot be concluded that **Ginkgo** treats Alzheimer's and other forms of dementia, but it might help in some cases; The chances of it helping seem to increase when used alongside conventional treatment; also, Some research shows that **Ginkgo** may improve mental performance in healthy people, but the data is inconsistent.
   - **Ginkgo** may improve symptoms of sexual dysfunction due to its impact on blood flow. However, research has not proven it to be effective.
2. **Ginseng** may improve thinking processes and cognition; although its well-known for its effectiveness in the treatment of erectile dysfunction.
3. **5-Hydroxytryptophan (5-HTP)** is an amino acid that the body naturally produces; it's used by the body to produce serotonin, a chemical messenger that sends signals between the nerve cells (Low serotonin levels are associated with depression, anxiety, sleep disorders, weight gain and other health problems), thus increasing the body's production of serotonin may have various benefits including cognitive ones.
4. **L-Arginine** which enhances blood circulation, by increasing the amount of nitric oxide in the body, they stimulate blood vessels to become larger (thus also used by bodybuilders); This improves blood flow, and increasing blood supply to the brain, which could help in cognition.
5. **Coenzyme Q10** (CoQ10) has been shown to protect brain cells from oxidative damage and reduce the action of harmful compounds that can lead to brain disease.
6. **Lecithin** is used for treating memory disorders such as dementia and Alzheimer's disease; its converted into acetylcholine, a substance that transmits nerve impulses.
7. **Alpha-Lipoic acid (ALA)** is a synthetic version of Lipoic acid, which helps cells make energy. It has antioxidant properties and may reduce inflammation.
   - It may protect brain cells from conditions such as stroke, multiple sclerosis, and Alzheimer's disease; Preclinical studies also indicate that ALA or a combination of ALA and regular exercise may improve certain aspects of learning and memory; However, no clinical studies suggest that ALA can prevent dementia or improve cognition.
8. **St John's Wort**, or called (Hypericum perforatum) may counteract stress-induced memory impairment; it's also considered an antidepressant and anti-anxiety agent, it effects multiple neurotransmitters in a non-competitive synergistic manner, and may have nootropic potential.
   - It has a high drug-drug interaction profile; thus, France has banned the use of St. John's Wort in products. In other countries it is only available with a prescription.

Trade name	D. form	Scientific name(s)	concentration
Neuro-All®	Tab	Ginkgo Biloba + Vit. B_1 + Vit. B_6 + Vit. B_{12}	50mg + 200mg + 50mg + 1mg
Ginkgo Ceutica®	Tab	Ginkgo Biloba + Ginseng	80 mg + 150 mg
Neurozan®	Tab	Ginkgo Biloba + 5-HTP + L-Arginine + L-Glutamine + L-Glutathione + Co-Q10 + Phosphatidylcholine + Phosphatidylserine + Beta-carotene + Vitamin D + Vitamin E + Vitamin C + Vit.B_1 + Vit.B_2 + Vit.B_3 + Vit.B_6 + Vit.B_{12} + Folic Acid + Pantothenic acid + Minerals	120 mg + 20 mg + 40 mg + 10 mg + 5 mg + 10 mg + 10 mg + 10 mg + 2 mg + 25 mcg + 36 mg + 80 mg + 25mg+3mg+32mg+10mg + 400 mcg + 36 mg

Active Memory®	Cap	Lecithin + Vit. E + Folic acid + Vit. B_1 + Vit. B_2 + Vit. B_6 + Vit. B_{12} + Niacin	1000 mg + 30 mg + 400 mcg + 4.2mg+4.8mg+4.8mg+6mcg + 27 mg
Mentat®	Syrup	Herbal combination	100 ml
Neurobooster®	Cap	Coenzyme Q10 + Alpha-Lipoic Acid + Acetyl-L-Carnitine	1000 mg blend (per 2 caps)
Memo Up®	Oral Drop	Ginkgo Biloba + Gotu Kola + Eleutherococcus Senticosus + Foti root extract	60 ml blend
Think-Rite®	Cap	Ginkgo Biloba + Acetyl-L-Carnitine + Phosphatidylserine Complex + St. John's Wort + Bacopin + L-Glutamine + Vinpocetine + DMAE Bitartrate	50 mg + 50 mg + 125 mg + 250 mg + 100 mg + 150 mg + 2 mg + 50 mg
Memo-B®	Oral Solu.	Fructoplant of blueberry berries + Brewer's yeast + Royal jelly + Schisandra berries dry extract + Astragalus root dry extract + Vit. B_1 + Vit. B_3 + Vit. B_6 + CoQ10	2.4 gm (per 20 ml) + 200 mg + 100 mg + 200 mg + 200 mg + 1.7mg + 24mg + 2mg +10mg
Speak®	Cap	D-alpha Tocopherol + Gamma Tocopherol + Vitamin K + Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) + Gamma-linolenic acid	500 IU + 200 mg + 2.3 mg + 725 mg + 275 mg + 60 mg

References

1- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition.
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Russell J Greene, Norman D Harris. Pathology and Therapeutics for Pharmacists: A basis for clinical pharmacy practice third edition, 2012 by pharmaceutical press.
4- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition.
5- ACCP Updates in Therapeutics® 2018: Pharmacotherapy Preparatory Review
6- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th ed.
7- Canadian pharmacists association, Therapeutic choices. 2014.
8- Marie A. Chisholm-Burns, Pharmacotherapy Principles & Practice Copyright © 2014
9- Comprehensive Pharmacy Review for NAPLEX 8th Ed

INFECTIONS

Chapter Five: Infections

Part One: Introduction

Part Two:

5.1- Antibacterial drugs

1. Penicillins
2. Cephalosporins
3. Carbapenems
4. Other Beta-lactams
5. Tetracyclines
6. Aminoglycosides
7. Macrolides
8. Quinolones
9. Urinary tract Antiseptics
10. Lincosamides
11. Sulfonamides, Trimethoprim
12. Antimycobacterials (anti-TB)
13. Drugs used to treat Leprosy
14. Metronidazole, Tinidazole and their relatives
15. **Other Antibacterials:**
    - **a.** Glycopeptides
    - **b.** Quinupristin/Dalfopristin
    - **c.** Tedizolid
    - **d.** Linezolid
    - **e.** Nifuroxazide
    - **f.** Rifaximin
    - **g.** Chloramphenicol
    - **h.** Thiophenicol, Colistimethate, Lefamulin, Daptomycin
16. **Topical antibiotics**

5.2- Antifungal drugs

1. Systemic antifungals
2. Topical antifungals
3. Vaginal Antifungals

5.3- Antiviral drugs

1. Herpes simplex and varicella–zoster infections
2. Cytomegalovirus (CMV) infection
3. Influenza Virus infection
4. Viral Hepatitis infections
5. Respiratory syncytial virus
6. human immunodeficiency virus (HIV)

5.4- Anthelmintics (drugs used for worms)

5.5- Antiprotozoal drugs

1. Amebicides
2. Drugs for Toxoplasmosis
3. Drugs for Leishmaniasis
4. Drugs for Trypanosomiasis
5. Drugs for Balantidiasis and Cryptosporidiosis
6. Drugs for Pneumocystis Pneumonia
7. Drugs for Trichomoniasis
8. Drugs for Malaria

Chapter Five: Infections

Part One:

1. Introduction:

1. The human body provides a suitable environment for the growth of many types of microorganism (MO), including **bacteria**, **viruses**, **fungi**, **yeasts**, and **protozoa**; It may also become the host for animal parasites such as **insects**, **worms**, and **flukes**.
2. Microorganisms (microbes) exist all around us (in the air we breathe, on the mucous membranes of our mouth and nose, on our skin, and in our intestines – but we are protected, most of the time, by our immunological defences); microbes can be transmitted from person to person in many ways: direct contact, inhalation of infected air, and consumption of contaminated food or water.
3. **Not all microorganisms cause disease**; many types of bacteria exist on the skin surface or in the bowel without causing ill effects
    - Normally, the immune system protects the body from infection; Invading microbes are killed before they can multiply in sufficient numbers to cause serious disease.

2. Types of Infecting Organism

A) Bacterium: consists of a single cell with a protective wall, some bacteria are aerobic (requiring oxygen) and are therefore more likely to infect surface areas such as the skin or respiratory tract, Others are anaerobic and multiply in oxygen-free surroundings, as the bowel or deep wounds.
- Bacteria can cause symptoms of disease in two principal ways: by releasing toxins that harm body cells and by provoking an inflammatory response in the infected tissues.

B) Viruses: are smaller than bacteria and consist simply of a core of genetic material surrounded by a protein coat; it can multiply only in a living cell, by using the host tissue's replicating material.

C) Fungi: group of living organisms which are classified in their own kingdom; This means they are not animals, plants, or bacteria. Unlike bacteria, which have simple prokaryotic cells, fungi have complex eukaryotic cells like animals and plants.
- In humans, fungal infections occur when an invading fungus takes over an area of the body and is too much for the immune system to handle.

D) Protozoa: are single-celled parasites and are slightly bigger than bacteria, many protozoa live in the human intestine and are harmless; other types cause malaria, sleeping sickness, dysentery.

E) Parasites: Invasion by parasites that live on the body (as **lice**) or in the body (as **tapeworms**) is known as infestation, it's associated with tropical climates, poor standards of hygiene.

3. What can go wrong

1. Infectious diseases occur when the body is invaded by microbes, this may be caused by the body having little or no natural immunity to the invading organism, or the number of invading microbes being too great for the body's immune system to overcome.
2. Serious infections can occur when the immune system does not function properly or when a disease weakens or destroys the immune system, as occurs in patients taking high doses of corticosteroids or Immunosuppresants.
    - Some parts of the human body are more susceptible to infection than others; respiratory tract infections are relatively common, whereas bone and muscle infections are rare.
    - Some symptoms are the result of damage to body tissues by the infection, or by toxins released by the microbes. In other cases, the symptoms result from the body's defence mechanisms.
    - Most bacterial and viral infections cause fever; Bacterial infections may also result in inflammation and pus in the affected area.

5.1-Antibacterial drugs

1. **Before selecting an antibacterial you must first consider two factors: the patient and the known or likely causative organism.**
2. Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking an oral contraceptive.

3. **Before starting any anti-infective therapy,** the following precepts should be considered:
   - **Viral infections should not be treated with Antibacterials**, however, Antibacterials may be used to treat secondary bacterial infection (e.g. bacterial pneumonia secondary to influenza).
   - Samples should be taken for culture and sensitivity testing; 'blind' antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis.
   - Knowledge of prevalent organisms and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available. Generally, **narrow-spectrum Antibacterials are preferred to broad-spectrum Antibacterials** unless there is a clear clinical indication (e.g. life-threatening sepsis).
   - The dose of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection.
   - The prescribing of the 'standard' dose in serious infections may result in failure of treatment or even death of the patient; therefore, **it is important to prescribe a dose appropriate to the condition.**
   - **An inadequate dose may also increase the likelihood of antibacterial resistance**, On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored.
   - The route of administration of an antibacterial often depends on the severity of the infection, **Life-threatening infections require intravenous therapy**, Antibacterials that are well absorbed may be given by mouth even for some serious infections, Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate.
   - Whenever possible, **painful intramuscular injections should be avoided in children.**
   - Duration of therapy depends on the nature of the infection and the response to treatment, **Courses should not be unduly prolonged because they encourage resistance**, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or osteomyelitis it may be necessary to treat for prolonged periods. Conversely a single dose of an antibacterial may cure uncomplicated urinary-tract infections.
   - The prescription for an antibacterial should **specify the duration of treatment or the date when treatment is to be reviewed.**

4. **There is a term called (superinfection)** that is generally defined as a **second infection superimposed on an earlier one**, especially by a different microbial agent that is resistant to the treatment used against the first infection, an example of this is the overgrowth of endogenous **Clostridium difficile** which occurs following treatment with a **broad-spectrum antibiotic.**
   - **In virology, the definition is slightly different:** Superinfection is the process by which a cell that has previously been infected by one virus gets co-infected with a different strain of the virus, or another virus, at a later point in time, **Viral superinfections may be resistant to the antiviral drug or drugs that were being used to treat the original infection.** Viral superinfections may also be less susceptible to the host's immune response.

- **Classes of Antibiotics include: Penicillins** (First introduced in the 1940s), **Cephalosporins**, **Carbapenems**, **Macrolides, Tetracyclines**, **Aminoglycoside**s, **Lincosamides**, **Quinolones** and **Sulfonamides.**

The table below shows common drugs in each class of antibiotic used to treat infections in different parts of the body. (It is not intended as a guide to prescribing.)

ANTIBIOTIC	SITE OF INFECTION: Ear, nose, throat, and mouth	Respiratory tract	Skin and soft tissue	Gastrointestinal tract	Eye	Kidney and urinary tract	Brain and nervous system	Heart and blood	Bones and joints	Genital tract
Penicillins										
Amoxicillin	●	●	●			●		●	●	
Ampicillin	●	●	●			●	●		●	
Benzylpenicillin	●	●	●				●	●		●
Co-amoxiclav	●	●	●			●				
Flucloxacillin	●		●					●	●	
Phenoxymethylpenicillin	●	●	●							
Cephalosporins										
Cefaclor	●	●				●				
Cefalexin		●	●			●				
Cefotaxime		●		●			●	●		
Macrolides										
Azithromycin	●	●	●							●
Clarithromycin	●	●	●	●						
Erythromycin	●	●	●	●	●				●	●
Tetracyclines										
Doxycycline	●	●	●			●				●
Oxytetracycline	●	●	●							
Tetracycline	●	●	●		●	●				●
Aminoglycosides										
Amikacin		●	●	●		●	●		●	
Gentamicin		●	●	●	●	●	●	●	●	
Neomycin			●	●						
Streptomycin		●						●		
Tobramycin		●	●	●		●	●		●	
Sulphonamide										
Co-trimoxazole		●				●				
Other drugs										
Chloramphenicol	●				●		●			
Ciprofloxacin		●		●		●				●
Clindamycin		●	●	●					●	
Colistin		●								
Dapsone			●							
Fusidic acid			●		●			●	●	
Levofloxacin	●	●	●			●				
Linezolid		●	●							
Metronidazole	●		●	●				●	●	●
Nalidixic acid						●				
Nitrofurantoin						●				
Teicoplanin			●					●	●	
Trimethoprim		●	●			●				
Vancomycin			●					●	●	

5.1.1- Penicillins (Bactericidal antibiotics)

1. The Penicillins are **bactericidal** and act by **interfering with bacterial cell wall synthesis,** they diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed, they are **classified as**:

	Penicillin groups	Examples
1	**Natural penicillin's**	Benzyl penicillin and Phenoxymethylpenicillin
2	**Penicillinase-resistant penicillin's**	Flucloxacillin, Cloxacillin
3	**Broad-spectrum penicillin's**	Amoxicillin, Ampicillin
4	**Antipseudomonal penicillin's**	Piperacillin, Ticarcillin

2. The most **important side-effect** of the penicillin's is **hypersensitivity** which causes rashes and anaphylaxis and can be fatal, other includes: diarrhea and headache.

How to do Penicillin Allergy skin Test
Dissolve 1 vial of penicillin (Amoxicillin or Ampicillin) in 5 ml of Distal water for injection, then take 10 units from the vial (by insulin syringe) and complete the volume to 100 units by Distal water, then inject 10 units only as intradermal injection, Then wait and observe for about 15 – 30 minutes, a skin reaction will conform that the patient has a Penicillin allergy.

3. Ampicillin, Flucloxacillin and Cloxacillin must be given on an empty stomach (1 hr. before food or 2 hrs. after food) while **Amoxicillin maybe taken without regard to meal**.

4. Co-Amoxiclave consists of amoxicillin with the **beta-lactamase inhibitor (clavulanic acid)**; **Clavulanic acid inactivates beta-lactamases**, making the combination active against beta-lactamase-producing bacteria that are resistant to Amoxicillin.

5. Various combinations between **(Amoxicillin** and **Clavulanic acid)** are presents:

Combinations (mg)	Dosage form	Notes
156 (125 +31) , 312 (250 + 62)	suspension	
457 (400 + 57) , 642.9 (600 + 42.9)	suspension	Given **twice daily** (every 12 hours)
375 (250 + 125) , 625 (500 + 125)	Tablet	
1000 (875 +125)	Tablet	Given twice daily (every 12 hours)
600 (500 + 100) , 1200 (1000 + 200)	Injection	**For intravenous injection only**

Comes in many trade names, include: (Augmentin®, Augmenta®, Cloclav®, Co-Amox®, etc.)

6. For the eradication of **H. pylori** (a bacterium that causes ulcer), Amoxicillin is given with Clarithromycin and a proton pump inhibitor; usual doses of **amoxicillin for the eradication of H. pylori is 1 g twice daily;** (for more details see chapter 2, section 2, PPIs).

Scientific name	D. form	Trade name	concentration
Procaine benzyl penicillin	Vial	Procaine benzyl	0.4 , 0.6 , 0.8 , 1.2 mega gram
Amoxicillin	Cap , Vial	Amoxil , Neomox®	250 mg , 500 mg , 1000 mg
	Susp.	Neomox®, Glomox®	250 mg/5 ml , 125 mg/5 ml
	Sachets	Amoxil Sachets SF®	3 gm per sachet
Amoxicillin + Flucloxacillin	Cap	Flumox®	250 mg , 500 mg
Amoxicillin + Sulbactam	Vial	BiomoxSalb®	(0.5 gm + 0.25 gm)
Ampicillin + Cloxacillin	Cap	Ampiclox®	250 mg + 250 mg
	Vial	Ampiclox®	250 mg + 250 mg
Ampicillin + Sulbactam	Vial	Unasyn®, BioSalb®	(0.5gm+0.25gm), (1gm+0.5gm)
Ampicillin	Susp.	Ampicillin®	250 mg/5 ml
Ampicillin	Cap	Ampicillin®	250 mg , 500 mg
Piperacillin + Tazobactam	Vial	Tazocin® , Tazopip®	2.25 gm , 4.5 gm
Ticarcillin + Clavulanic acid	Vial	Timentin®	3.2 gm
Flucloxacillin	Cap	Fluxa®	500 mg

**** Ampicillins (including Amoxicillin)** when mixed with water has **stability of 1 hour ONLY, thus discard any solution remaining in the vial after 1 hour.**

5.1.2- Cephalosporins (Bactericidal antibiotics)

The pharmacology of the Cephalosporins is similar to that of the Penicillins, Cephalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed.

1. **Classification**

	Cephalo Groups	Examples
1	**First-generation**	**Cephalexin and Cefadroxil**
2	**Second -generation**	**Cefuroxime**
3	**Third-generation**	**Cefotaxime, Ceftazidime, ceftriaxone, Cefpodoxime**
4	**Fourth-generation**	**Cefepime**
5	**Fifth -generation**	**Ceftraroline**

2. In general, the activity against gram negative bacteria is increase and the activity against gram positive bacteria is decrease when we move from first to third generation Cephalosporins.

3. **Some important properties** for specific agents:

Drug	Properties
Ceftriaxone	It has a **long half-life** (may be given **once daily**), **safe in hepatic failure.**
Cefotaxime	Safe in renal failure.
Ceftazidime	Has **good activity against pseudomonas**, **safe in renal and hepatic failure**
Cefixime	**Oral** third Marketed generation cephalosporin (in fact it's a 2nd gen.)
Cefpodoxime	**Oral** third-generation cephalosporin (must be given **after food).**

4. The principal side-effect of the Cephalosporins **is hypersensitivity** and **about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the Cephalosporins**, other includes: diarrhea and headache and arrhythmias.
   Patients with a history of immediate hypersensitivity to penicillin <u>should not</u> receive a cephalosporin (relative contraindication).
   - Antibiotic-associated colitis may occur with the use of broad-spectrum Cephalosporins, particularly second and third-generation Cephalosporins.

5. **IMPORTANT: regarding Cefotaxime, and Ceftriaxone:**
   When given by an intravenous injection these drugs should be **given over at least 2–4 minutes** (arrhythmias following rapid injection reported); **There have been cases of death recorded due to the rapid I.V. inj. of Cefotaxime, and Ceftriaxone.**
   - **A newer recommendation states that (Cefotaxime, Ceftriaxone) must be given in at least 100 mL I.V. infusion ONLY; although 10 ml is sometimes enough.**
   - Some new studies found that **Ceftriaxone causes PARF** (pediatric acute renal failure), by forming urine stone that precipitate in the renal tubules causing PARF.
   - **Ceftriaxone is contraindicated in babies below 28 days** because it can displace bilirubin leading to **bilirubin encephalopathy** in these patients.
   - **Ceftriaxone** when mixed with water has stability of **24 hr.**, while **Cefotaxime** has a **12 hr**.
   - **Ceftriaxone, Cefoperazone are metabolized by liver,** so they are used safely in renal failure, **while Cefotaxime is metabolized by kidney,** so it's used safely in liver failure.
   - **It's a fatal mistake to combine ceftriaxone with Ca^{+} containing fluids in the same IV route,** high risk of fatal particulate precipitation in lungs and kidneys, separate by at least 48 hr., or use alternatives as **Cefotaxime, Cefoperazone**. (Does not cause precipitations).

Scientific name	Dosage form	Trade name	concentration
1st Generation Cephalosporins			
Cephalexin	Cap	Keflex®, Cephalonin®	250 mg & 500 mg
	Susp.	Acaflex®	250 mg/5 ml
Cefadroxil	Tab	Cefadrox®, Duricef®	1000 mg
Cefalothin	Vial	Keflen®	1 gm
Cefazolin	Vial	Cefazo®	0.5 gm , 1 gm

2nd Generation Cephalosporins			
Cefaclor	Cap	Ceclor® , Cloracef Forte®	250 mg & 500 mg
	Susp.	Cloracef®	250 mg/5 ml , 375 mg/5 ml
Cefotetan	Vial	Cefotetan®	1 gm , 2 gm
Cefoxitin	Vial	Cefoxitin®	1 gm , 2 gm
Cefprozil	Tab	Cefzil®	250 mg & 500 mg
	Susp.		250 mg/5 ml , 125 mg/5 ml
Cefuroxime	Tab	Zinnat®, Zamor® , Zinacef®	250 mg , 500 mg
	Susp.		250 mg/5 ml , 125 mg/5 ml
	Inj. Powder	Ceftin®	225 mg , 750 mg , 1.5 gm

** **Cefuroxime** is the only cephalosporin that can be given both orally and as injection, other Cephalosporins are **either given orally OR as injection. (One route only).**

3rd Generation Cephalosporins			
Cefotaxime	Vial	Claforan® , Cefotac®	0.25 gm , 0.5 gm , 1 gm
Ceftriaxone	Vial	Rocephin® , Mesporin® , Novocef®	0.25 gm , 0.5 gm , 1 gm
Ceftriaxone + Sulbactam	Vial	Philbacxone®	1 gm + 0.5 gm
Ceftazidime	Vial	Fortaz® , Tazicef®, Tottizim®	0.5 gm , 1 gm
Ceftazidime + Avibactam	Vail	Avycaz®	2 gm/0.5 gm
Cefoperazone	Vial	Cefobid®, Ceprazo®, Magnamycin®	0.25 gm , 0.5 gm , 1 gm
Cefoperazone + Sulbactam	Vial	Cef Novo® , Cefortal® , Cefobid S®	(1 gm + 0.5 gm) & (1 gm + 1 gm) & (2 gm + 1gm)
Ceftizoxime	Vial	Cefizox®	0.5 gm , 1 gm
Cefdinir *	Cap	Omnicef®	300 mg
Cefditoren	Tab	Spectracef®	200 mg , 400 mg
Ceftibuten	Cap	Cedax®	400 mg
Cefixime *	Cap	Suprax® , Cefix®	200 mg , 400 mg
	Susp.		100 mg/5 ml , 200 mg/5 ml
	Granules		50 mg/Sachet
Cefpodoxime	Tab	Orelox® , Vantin®, Zakon®, Infex®	100 mg , 200 mg
	Susp.	Cefpodox®	50 mg/5 ml , 100 mg/5 ml
Cefpodoxime + Clavulanic Acid	Tab, Susp.	Infex Plus®	(200 mg + 125 mg) Tab (100 mg + 62.5)/5 ml Susp
4th Generation Cephalosporins			
Cefepime	Infusion	Maxipime® , Maxcef® , Cepimax®	1 gm/50 ml , 2 gm/100 ml
	Vial		0.5 gm , 1 gm , 2 gm
Cefpirome	Vial	Cefrom®, Keiten®, Broact®	1 gm , 2 gm
Cefluprenam	Infusion	----------	1 gm/50 ml
Cefozopran	Infusion	----------	1 gm/50 ml
Cefquinome	Infusion	----------	1 gm/50 ml
5th Generation Cephalosporins			
Ceftraroline	Vial	Teflaro®, Zinforo®	400 mg , 600 mg
Ceftobiprole	Infusion	Zevtera®	500 mg
Cefiderocol	Vial	Fetroja®	1 gm
Ceftolozane + Tazobactam	Vial	Zerbaxa®	1 gm/0.5 gm

***** Both **Cefixime (Suprax®)** and **Cefdinir (Omnicef®)** are considered as a 2nd generation cephalosporin (by their chemical structure), but are intentionally marketed as a 3rd generation cephalosporin, mainly to increase their sells.

5.1.3- Carbapenems (Bactericidal antibiotics)

1. The **Carbapenems** are beta-lactam Antibacterials with a broad-spectrum of activity which includes many Gram positive and Gram-negative bacteria, and anaerobes.
   - **Imipenem** and **Meropenem** have **good activity against Pseudomonas aeruginosa**, the Carbapenems **are not active against methicillin-resistant Staphylococcus aureus and Enterococcus faecium.**
2. **Imipenem** is partially inactivated in the kidney by enzymatic activity and is therefore **administered in combination with Cilastatin**, a specific enzyme inhibitor, which blocks its renal metabolism. (**Cilastatin is not required with the others,** because these are not sensitive to renal enzyme; which is dipeptidase).
3. Most physicians prescribe **Meropenem 500 mg or 1 gm every 12 hours; and that's wrong**; its half-life is only 1 hour and its serum level will totally disappear after 5-7 hour; **thus, it should be given every 8 hours; (Meropenem dose should not exceed 2 gm every 8 hr.).**
   - **Imipenem** is given twice daily or 4 times a day according to the severity.
   - **Ertapenem** is given 1 gm **once daily**.
4. **Side-effects** of Carbapenems are similar to those of other beta-lactam antibiotics; **neurotoxicity has been observed at very high dosage**, in renal failure, or in patients with CNS disease.
   - **High levels of Imipenem may provoke seizures,** but **Meropenem is possibly less** likely to do so, **Doripenem** has not demonstrated any potential to cause seizures.
   - Patients who are allergic to penicillin or Cephalosporins may suffer cross-sensitivity reactions during Carbapenems therapy.

Scientific name	D. form	Trade name	concentration
Imipenem + Cilastatin	Vial	Primaxin®, Tenam®	(250 mg + 250) , (500 mg + 500 mg)
Imipenem + Cilastatin + Relebactam *	Vial	Recarbrio®	500 mg + 500 mg + 250 mg
Meropenem	Vial	Meronem®, Merrem®	500 mg , 1 gm
Doripenem	Vial	Doribax®	500 mg
Tebipenem	Vial	Orapenem®	500 mg , 1 gm
Ertapenem	Vial	Invanz®	1 gm
Meropenem + Vaborbactam *	Vial	Vabomere®	1 gm + 1 gm

* **Relebactam** and **Vaborbactam** are β-lactamase inhibitors.

5.1.4- Other Beta-lactams Antibacterials

These include: **Aztreonam** and **Pivmecillinam**

1- **Aztreonam** is a monocyclic beta-lactam (monobactam) antibiotic with an antibacterial spectrum **limited to Gram-negative aerobic** bacteria including Pseudomonas aeruginosa, Neisseria meningitides, and Hemophilus influenza; **it should not be used alone for 'blind' treatment since it is not active against Gram-positive organisms.**
   - It resembles the **aminoglycosides** in its efficacy against many gram-negative organisms but **does not cause nephrotoxicity or ototoxicity.**
   - Other advantages of this drug include its ability to preserve the body's normal gram-positive and anaerobic flora, activity against many gentamicin-resistant organisms, and **lack of cross-allergenicity with penicillin.**

2- **Pivmecillinam** has significant activity against many Gram-negative bacteria including Escherichia coli, Klebsiella, Enterobacter, and salmonellae; **It is not active against Pseudomonas aeruginosa or enterococci.**

Scientific name	D. form	Trade name	concentration
Pivmecillinam	Tab	Selexid®	200 mg
Aztreonam	Vial	Azactam®	1 gm , 2 gm
	Inhaler powder	Cayston®	75 mg/vial

5.1.5- Tetracyclines (Bacteriostatic antibiotics)

Tetracyclines are a group of broad-spectrum antibiotics whose general usefulness has been reduced with the onset of antibiotic resistance. Despite this, they remain the treatment of choice for some specific indications.

1. **Important: Oral administration:**
   A- Tetracyclines must be given on an empty stomach (This means an hour before food or 2 hours after food) while Doxycycline is given during meals.
   B- Capsules and tablets **should be swallowed whole with plenty of fluid while sitting or standing;** (because they may **cause esophageal irritation**).
2. **Deposition of tetracycline's in growing bone and teeth** (by binding to calcium) causes staining, **thus they are contraindicated in children under 12 years, or to pregnant or breast-feeding women**.
3. **Other side effects include:** dysphagia, and esophageal irritation, GI disturbance, dizziness, nausea and vomiting, photo-toxicity (they increase the risk of sunburn under exposure to light from the sun or other sources).
4. **About Doxycycline:**
   - **Doxycycline** has longer duration than tetracycline and may be **given once or twice daily**.
   - **Common indications for doxycycline** include: **genital Chlamydia**, **acne**, and in **brucellosis** (in combination with rifampicin).
   - Also given in the treatment of recurrent **Aphthous ulceration**, or as an adjunct to **gingival scaling** and **root planning for periodontitis**.
   - Also used for **Lyme disease**.
   - It is used in **prophylaxis against malaria**, it should not be used alone for initial treatment of malaria, even when the parasite is doxycycline-sensitive.
5. **Minocycline** have **immunomodulatory, anti-inflammatory,** or **chondroprotective effects**; thought to be a potent inhibitor of metalloproteinase, which are active in rheumatoid arthritis joint destruction, thus; it's used off-label in the treatment of **Rheumatoid Arthritis.**
6. **Tigecycline** is a glycylcycline antibacterial structurally **related to the Tetracyclines**; side effects similar to those of the Tetracyclines can potentially occur, **Tigecycline** is active against Gram-positive and Gram-negative bacteria including tetracycline-resistant organisms.

Scientific name	Dosage form	Trade name	concentration
***Tetracycline** **	Cap	Hostacycline® , Sumycin® , Samacycline®	250 mg , 500 mg
Doxycycline	Cap , Tab	Vibramycin® , Doxidar®	100 mg
	MR Cap	Efracea®	40 mg
Demeclocycline	Tab	Declomycin®	150 mg , 300 mg
Lymecycline	Cap	Tetralysal®	408 mg
Minocycline	Cap , Tab	Dynacin® , Minocin®	50 mg , 100 mg
	MR Cap	Minocin MR®	100 mg
	Vial	Solodyn®	100 mg
Oxytetracycline	Tab	Oxymycin®, Terramycin®	250 mg
Tigecycline	Vial (I.V.)	Tygacil®	50 mg
Eravacycline	Vial	Xerava®	50 mg
Omadacycline **	Tab , Vial	Nuzyra®	150 mg (tab), 100 mg (vial)
Sarecycline **	Tab	Seysara®	60 mg , 100 mg , 150 mg

* **Tetracycline** is also available as skin cream, eye ointment.

** **Omadacycline** is a new broad-spectrum antibiotic; its FDA approved for the treatment of community-acquired bacterial pneumonia and acute skin and skin structure infections.

** **Sarecycline** is approved by the FDA for the treatment of moderate to severe acne vulgaris.

5.1.6- Aminoglycosides (Bactericidal antibiotics)

1. These include: **Amikacin, gentamicin, neomycin, streptomycin, and tobramycin**.
2. The **aminoglycosides** are **not absorbed from the gut** and must therefore be given **by injection for systemic infections** (1). Except for Neomycin which is given orally for local effect.
   - **Neomycin is too toxic for parenteral administration** and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure.
3. The important **side-effects** are **ototoxicity, and nephrotoxicity**; **They are dose related; Their relative ototoxicity is as follows:**
   Streptomycin = kanamycin > Amikacin > gentamicin > tobramycin > Netilmicin.
   - **Gentamicin and streptomycin** cause primarily vestibular damage (manifested by tinnitus, vertigo, and ataxia). Such damage may be bilateral and irreversible.
   - **Amikacin, kanamycin, and neomycin** cause mainly auditory damage (hearing loss).
   - **Tobramycin** can result in both vestibular and auditory damage.
   - Ototoxicity and nephrotoxicity **occur most commonly in the elderly.**
4. **Streptomycin** is used mainly for **tuberculosis** (2nd line drug) and for **brucellosis**.
5. **The aminoglycosides synergize** (increased effect dramatically) **with the β-lactam antibiotics (Penicillins, Cephalosporins, Carbapenems),** because of the latter's action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacteria.
6. **Whenever possible; treatment should not exceed 7 days with aminoglycosides.**
7. **Once daily administration** of aminoglycosides is more convenient, provides adequate serum concentrations, and in many cases has largely superseded multiple daily dose regimens (given in 2–3 divided doses during the 24 hours).
8. **Aminoglycosides may impair neuromuscular transmission, thus:**
   - **C.I.** in patients with **myasthenia gravis.**
   - **Large doses** given during **surgery** have been responsible for a **transient myasthenic syndrome** in patients with normal neuromuscular function.
9. **Aminoglycoside** should be avoided in patients with a creatinine clearance less than 20 mL/Min, also **dosage adjustment is needed in patients with renal disease.**
10. There is an increased **risk of auditory or vestibular nerve damage in the infant** when **Aminoglycosides are used in the second and third trimesters of pregnancy.**

Scientific name	Dosage form	Trade name	concentration
Gentamicin	Amp	Garamycin®, Cidomycin®	80 mg/2 ml , 20 mg/2 ml
Amikacin	Vial (Solu.)	Amikin®	100 mg/2 ml , 500 mg/2 ml
Neomycin	Tab , Powder	Myciguent® , Mycifradin®	500 mg
Streptomycin	Vial (powder)	Streptomycin®	1 gm
Tobramycin	Inj. Solu.	Nebcin®	10 mg/ml , 40 mg/ml
	Inhalation Sol.	Bramitob®, Tobi®	75 mg/ml , 60 mg/ml
Kanamycin	Inj. Solu.	Kantrex®	500 mg/2 ml
Netilmicin	Amp	Netromycin®	10 mg , 25 mg , 50 mg
Plazomicin	Vial (Solu.)	Zemdri®	500 mg/10 ml

Notes:

1. **Gentamicin** is also found as skin cream/ointment, Eye drop/ointment.
2. **Neomycin** is also found in combination of skin creams/Oint., Ear drops/Oint., Eye drops.
   - **Neomycin is not absorbed into the blood stream**; it's usually used with **lactulose** in the **treatment of hepatic encephalopathy.**
3. **Tobramycin** is also found as eye drop or in combination of eye drops.

5.1.7- Macrolides (Bacteriostatic antibiotics)

1. The Macrolides have an antibacterial spectrum that is similar but not identical to that of penicillin; these include Erythromycin, Azithromycin and Clarithromycin, **they are the 1st choice as an alternative to penicillin in individuals allergic to β-lactam antibiotics.**
2. About **Erythromycin**: it is given 4 times daily.
   - **Has a prokinetic effect**, it improves gastric emptying and symptoms from delayed gastric emptying.
   - **I.V. administration** is associated with a **high incidence of thrombophlebitis**; however, the incidence of thrombophlebitis reported with I.V. administration of Azithromycin is less than 1%; **Erythromycin** can cause fatal levels of digoxin, Terfenadine, and theophylline leading to QT prolongation and sudden death. (3)
3. About **Azithromycin:** it's given once daily.
   - **Azithromycin** is **slightly less activity than erythromycin** against Gram-positive bacteria, but enhanced activity against some Gram-negative organisms.
   - It has a **long half-life,** and once daily dosage is recommended.
   - **Azithromycin capsules** must be given on an empty stomach (an hour before food or 2 hours after food) while **Azithromycin tablet and Susp.** are given without regard to meal.
   - Can **cause irregular heart activity and result in a fatal heart rhythm** (QT prolongation); it's already been banned in some countries especially for pediatrics.
4. About **Clarithromycin**: it's given twice per day.
   - **Clarithromycin** has **slightly greater activity** than the parent compound.
   - **Clarithromycin** is one of the **components of triple therapy for eradication of H. Pylori** (a bacterium that cause ulcer).
   - **Co-administration with Cabergoline is C.I.; its causes severe Vasospasm.**
5. **Side effects of Macrolides include:** Epigastric distress, Cholestatic jaundice, Ototoxicity, (Transient deafness)
   - **Macrolides** should be **used with caution in patients with a predisposition to QT interval prolongation** (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval). (also see notes below)
   - **Macrolides** may aggravate myasthenia gravis.

Scientific name	Dosage form	Trade name	concentration
Azithromycin	Tab , Cap	Zithromax® , Zithrocan®	250 mg , 500 mg
	Susp.	Azi-Once®, Azro®	100 mg/5 ml
	Inj. Powder		500 mg
Clarithromycin	Tab	Biaxin®	500 mg
	Susp.		125 mg/5 ml , 250 mg/5 ml
Erythromycin *	Tab	E-Mycin®	200 mg , 250 mg , 500 mg
	Susp.	Erythrodar®	125 mg/5 ml , 200 mg/5 ml
	Inj. Powder		500 mg , 1 gm
Telithromycin	Tab	Ketek®	400 mg
Roxithromycin	Tab	Roxithin® , Biaxsig®	150 mg , 300 mg
Miocamycin	Tab, Susp.	Miocamen®	600 mg (tab), 200 mg/5 ml
Josamycin	Tab	Josaxin	500 mg
Spiramycin	Tab	Rovamycin® , Rovac®	1.5 & 3 million I.U
	Cap		250 mg , 500 mg , 1 gm
	Inj.		500 mg , 1 gm
	Supp.		250 mg , 500 mg
Fidaxomicin	Tab	Dificid®	200
Troleandomycin	Cap	Tao®, Triocetin®	250 mg , 500 mg

*** Erythromycin** is also formulated as skin gel/cream, mainly used for acne.

** **Fidaxomicin** is related to **Macrolides** (Macrocycles), it's **bactericidal** against C. Difficile.

Extra Notes:

1. **Roxithromycin** is not available in the USA, but available in Australia, Europe; it **possesses an antimalarial activity**, and currently undergoing clinical trials for the **treatment of male-pattern hair loss**.
2. **Spiramycin** is **still considered as an experimental drug in the USA,** but can sometimes be obtained by special permission from the FDA **for toxoplasmosis** in the first trimester of pregnancy, **however it has been used in Europe since the year 2000, where it is mostly marketed to dentists for mouth infections.**
    - **Spiramycin** comes with **Metronidazole** in a combination known as **Rodogyl®** tab, which contains (Metronidazole 125 mg; Spiramycin 750,000 I.U.).
3. **Fidaxomicin** is non-systemic, meaning it is minimally absorbed into the bloodstream, it has **demonstrated selective eradication of pathogenic Clostridium Difficile** with minimal disruption to the multiple species of bacteria that make up the normal, healthy intestinal flora.

5.1.8- Quinolones (Bactericidal antibiotics)

1. These include **Nalidixic acid, Norfloxacin, Ciprofloxacin, Gatifloxacin, Ofloxacin, Levofloxacin, Moxifloxacin**.
2. **About Nalidixic acid:**
    - It is used mainly in the treatment of **lower urinary-tract infections in pediatrics**, **(but it should be avoided in infants less than 3 months old**).
    - Withdrawn from USA and no longer used there.
3. About **Ciprofloxacin:** given twice daily
    - It is the drug of choice for **Typhoid fever**.
    - Should not be taken with **Dairy products** (interfere with the absorption).
4. **Norfloxacin** should be taken on an empty stomach.
5. **About Levofloxacin:** given once daily
    - Cause a rare but serious adverse reaction such as **spontaneous tendon ruptures and irreversible peripheral neuropathy.**
    - **Contraindicated** in patients with **epilepsy or other seizure disorders;** as it's a GABA antagonist which cause imbalance between stimulation/inhibition, thus cause convulsions.
6. About **Moxifloxacin:** given once daily
    - It has been associated with QT interval prolongation and **life-threatening hepatotoxicity**.
    - **Not active** against **Pseudomonas Aeruginosa** or **Methicillin-resistant Staphylococcus Aureus (MRSA).**
7. **Disadvantage of the quinolones:**
    a) Cause **acute hemolytic anemia** when taken by individuals with Glucose 6-phosphate dehydrogenase **(G6PD) deficiency**, or any hemolytic anemia (thalassemia).
    b) Cause **Glycemic reactions** including **hypoglycemia** (within 3 days) and **hyperglycemia** (Within 4-10 days) can occur in ~1% of patients on oral hypoglycemic or insulin.
    c) Concurrent use with **(NSAIDs)** may increase the risk of CNS stimulation **(seizures).**
    d) May produce **prolonged QT interval** (cause accumulation of K inside the cardiac muscles) when administered with antiarrhythmic agents; (**Gemifloxacin, Moxifloxacin**) should be avoided in patients with known prolongation of the QTC interval, with uncorrected hypocalcemia, or who are receiving class IA or class III antiarrhythmic drugs.
8. They are **generally not recommended** for use in **children under 18 years, adolescents, and pregnant or breast-feeding** women because of their propensity to cause **joint erosions and dwarfism**, **Although FDA has licensed ciprofloxacin** in ages **below 18 ONLY** in: Complicated urinary tract infections (UTI), Pyelonephritis and Post-exposure treatment for inhalation anthrax.

Scientific name	Dosage form	Trade name	concentration
1st generation Fluoroquinolones			
Nalidixic acid	Cap	Neggram® , Naldexin®	500 mg
	Susp.	Negramon®	300 mg/5 ml
Norfloxacin	Tab	Noroxin® , Utenor®	400 mg
2nd generation Fluoroquinolones			
Ciprofloxacin	Tab	Cipro® , Ciprodar®	250 mg , 500 mg , 750 mg
	Tab ER	Bactiflox®	500 mg , 1000 mg
	Infusion Solu.		200 mg , 400 mg
Ofloxacin	Tab	Floxin®	200 mg , 300 mg , 400 mg
Lomefloxacin	Tab	Maxaquine® , Okacin®	400 mg
3rd generation Fluoroquinolones			
Levofloxacin	Tab	Levaquin® , Tavacin®	250 mg , 500 mg , 750 mg
	Inj. Solu.	Tavanic®	500 mg/20 ml , 750 mg/30 ml
Sparfloxacin	Tab	Zagam®	100 mg , 200 mg , 400 mg
Grepafloxacin	Tab	Raxar®	200 mg
4th generation Fluoroquinolones			
Moxifloxacin	Tab	Avelox® , Maxim® , Moxai®	400 mg
	Inj. Solu.	Avelox®	400 mg/250 ml
Gemifloxacin	Tab	Factive®	320 mg
Trovafloxacin	Tab	Trovan® , Turvel®	100 mg , 200 mg
Gatifloxacin	Tab	Tequin®	200 mg , 400 mg
	Inj. Solu.		400 mg/40 ml
Delafloxacin	Tab , Vial	Baxdela®	450 mg (tab) , 300 mg (vial)

Extra Notes:

1. **Gatifloxacin** has been associated with a higher incidence of dysglycemia, **it was withdrawn from the Markets in March 2006** due it can cause life threatening side effects including serious diabetes, hallucinations, liver damage and purpura, **Gatifloxacin** is currently available only **as an ophthalmic solution.**
2. **Lomefloxacin** Brand Company **discontinued its manufacturer in 2008**, due it forms a magnesium chelate with itself during long shelf storage; The chelate is formed between the 2-carbonyl groups of two separate Lomefloxacin molecules, **(It destroys itself)**, But generic formulas are still available.
3. **Sparfloxacin** is limited in use due it has a controversial safety profile, as (Prolonged QT interval, Torsade's de pointes, Seizures); **it is no longer available in the USA.**
4. **Grepafloxacin** was withdrawn worldwide from markets in 1999, due to its side effect of lengthening the QT interval, leading to cardiac events and sudden death.
5. **Delafloxacin** was approved by FDA in 2017 used to treat acute skin and skin structure infections.

Some Quinolones are formulated as ophthalmic solutions as:

Scientific name	Dosage form	Trade name	concentration
Ciprofloxacin	Eye drop/Oint.	Ciprodar® , Ciloxan®	0.3% (both)
Ofloxacin	Eye drop	Ocuflox®	0.3%
Norfloxacin	Eye drop	Chibroxin®, Apiflox®	0.3%
Lomefloxacin	Eye drop	Okacin®	0.3%
Levofloxacin	Eye drop	Iquix® , Quixin® , Vefloxin®	0.5%
Moxifloxacin	Eye drop/Oint.	Vigamox®, Moxeza®, Moxicip®	0.5%
Besifloxacin	Eye drop	Basivance®	0.6% (5 ml)
Gatifloxacin	Eye drop	Zymar® , Tequin® , Zymaxid®	0.3% , 0.5%

5.1.9- Urinary Tract Antiseptics (Nitrofurantoin, Methenamine, Fosfomycin)

These agents tend to concentrate in the renal tubules and bladder, **these agents exert local antibacterial effects**; most do not achieve blood levels high enough to treat systemic infections.

1. **Nitrofurantoin** (bacteriostatic) is used in the treatment and **prophylaxis urinary-tract infections** (UTI), **not recommended for the treatment of pyelonephritis and prostatitis.**
   - **a.** It is given orally, 2 or 3 times daily, **with food or milk**.
   - **b.** Any prophylactic dose of antibiotic for UTI should be given at bedtime.
   - **c.** May cause a **brownish discoloration of the urine**.
   - **d.** Should **not be taken with an Alkaline effervescent** (which is usually given to treat kidney stones); due its only active in acidic environment.
   - **e. Has Pregnancy Category B (safe),** it's one of the few drugs commonly used in pregnancy to treat UTIs, **but Contraindicated in pregnancy at term or ≥ 38 weeks pregnant due to the potential risk of hemolytic anemia in the newborn.**
   - **f. Also contraindicated** in patients with glucose-6-phosphate dehydrogenase deficiency **(G6PD) or any type of hemolytic anemia** because of risk of **intravascular hemolysis** resulting in more severe anemia.
2. **Methenamine** (bactericidal) decomposes at an acidic pH of 5.5 or less in the urine, thus **producing formaldehyde**, which acts locally and is toxic to most bacteria.
   - **a.** Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant its action; thus; used to treat lower UTIs but is **not effective in upper UTIs.**
   - **b. Contraindicated** with **Sulfonamides (co-trimoxazole).**
3. **Fosfomycin** (bactericidal) **used only for UTI and prostatitis,** pregnancy Category (B).
   - **a.** It's used (off-label) in combination with **tobramycin** to treat **lung infections** in patients with **cystic fibrosis; It's not recommended for children and pediatrics.**
   - **b.** Dosed as **3 gm once for uncomplicated UTI,** and 3 gm every 2 days for 3 doses in complicated UTI, and **3 gm every 3 days for 21 days in prostatitis**.

Scientific name	Dosage form	Trade name	concentration
Nitrofurantoin	Cap	Macrobid® , Uvamin®	50 mg , 75 mg , 100 mg
	Oral Susp.	Furadantin®, Urodantin®	25 mg/5 ml
Methenamine	Tab	Hiprex® , Urex®	500 mg , 1 gm
Fosfomycin	Sachets	Monurol® , Berny®	3 gm

5.1.10-Lincosamides (Lincomycin and Clindamycin) (Bacteriostatic)

1. Active against **Gram-positive cocci, and also against many anaerobes**, the main indication for the use of Lincosamides is now in the treatment of **severe anaerobic infections**.
2. **Clindamycin is much better absorbed from the GIT than Lincomycin,** they both penetrate well **into bone** and have been used successfully in **osteomyelitis**.
   - **Clindamycin** also exhibits some activity against parasitic protozoa, and has been used in toxoplasmosis and malaria.
3. The capsules should be **taken with a glass of water**.
4. **Clindamycin** have also been **used topically in the treatment of acne vulgaris**.
5. **Patients should discontinue immediately and contact doctor if diarrhea develops**, (**Lincosamides** are reported to produce diarrhea, in some patient's severe antibiotic-associated or pseudomembranous colitis may develop during therapy or up to several weeks after it, and has proved fatal).

Scientific name	Dosage form	Trade name	concentration
Lincomycin	Cap	Lincocin® , Lincodar®	250 mg , 500 mg
	Vial (Solu.)		300 mg/2 ml , 600 mg/2 ml
Clindamycin	Cap	Cleocin® , Clindamycin®	75 mg , 150 mg
	Inj. Solu. (Amp)		150 mg/ml (600 mg/4 ml)
	Vag. Cream/Supp.	Clindamax®	2% (cream) , 100 mg (Supp.)

5.1.11- Sulfonamides and Trimethoprim (Bacteriostatic)

1. **Sulfamethoxazole** and **Trimethoprim** are used in combination (as **co-trimoxazole**) because of their **synergistic activity**; Trimethoprim is also used alone particularly in the treatment of infections of the urinary and respiratory tracts.
   - A report showed **increase sudden death** in patients over 60 years who is **taking Co-trimoxazole with ARBs or ACEIs**; so, avoid this combination always.
2. **Sulfamethoxazole** is from a family called **(Sulfonamides)** or **the Sulpha drugs,** the same family of **sulfasalazine** that is used for the IBD**, Sulfonamides** are inhibitors of folate synthesis.
3. This group should **not be given to infants below 6 weeks of age because of the risk of kernicterus**, **also Should not be given to pregnant at term or nursing Mother (it passes throw the placenta and excreted in the milk)**
   - **They Cause kernicterus**; because sulfa drugs displace bilirubin from binding sites on serum albumin, the bilirubin is then free to pass into the CNS, because the baby's blood brain barrier is not fully developed
4. This group **should be avoided by people with G6PD deficiency or any type of hemolytic anemia**, causes blood dyscrasias, Granulocytopenia and thrombocytopenia.
5. **Other side effects include: Crystalluria and hematuria** that possibly leading **to urinary tract obstruction**; (Adequate fluid intake and urine alkalization can prevent or minimize this risk), also **cause Hypersensitivity reactions** (rashes, angioedema, and Stevens-Johnson syndrome).

A) Sulfonamides

Scientific name	Dosage form	Trade name	concentration
Mafenide *	Cream, Topical Solu.	Sulfamylon®	----------
Silver sulfadiazine	Cream	Silvadene®	1%
Sulfisoxazole	Tab , Susp	Gantrisin®	500 mg , 500 mg/ml
Sulfadiazine **	Tab	Lantrisul® , Neotrizine®	500 mg
Sulfadoxine	Tab	Sulfaxine®	500 mg
Sulfasalazine	***See chapter 2 , Section 9 , Drugs for IBD***		

*** Mafenide** and **Silver sulfadiazine** are usually used in burns treatment as topical antibiotics.
** **Sulfadiazine** is also used for the treatment of toxoplasmosis.

B) Folate reduction inhibitors (Trimethoprim, Pyrimethamine)

Scientific name	Dosage form	Trade name	concentration
Trimethoprim	Tab	----------	100 mg
Pyrimethamine *	Tab	Daraprim®	25 mg

*** Pyrimethamine** is also an anti-malarial; mainly is used for the treatment of toxoplasmosis, it also comes in combination with **Sulfadoxine.**

C) Combinations

Scientific name	Dosage form	Trade name	concentration
Sulfamethoxazole + Trimethoprim	Tab	Bactrim®, Septrim®, Cotrim®	(80 mg + 400 mg) & (160 mg + 800 mg)
	Oral Solu.		(80 mg + 400 mg)/5 ml
Sulfisoxazole + Erythromycin	Oral Susp.	Pediazole®	(600 mg + 200 mg)/5 ml
Pyrimethamine + Sulfadoxine	Tab	Fansidar®	25 mg + 500 mg

*** Fansidar®** it is no longer recommended as a routine preventative, **but only to treat serious malaria infections** or to prevent them in areas where other drugs may not work; **it's also given for the treatment of Toxoplasmosis.**

5.1.12- Antimycobacterials (drugs used for Tuberculosis)

1. **Tuberculosis** is an infectious bacterial disease **acquired by inhaling the tuberculosis bacilli that are present in the spray of a sneeze or cough from an actively infected person**, it may also, rarely, be acquired from infected unpasteurized cow's milk; The disease usually starts in a lung and takes one of two forms: primary or reactivated infection.
   - In 90-95% of those with a primary infection, the body's immune system suppresses the infection but does not kill the bacilli, they remain alive but dormant and may cause the reactivated form of the disease, after they are reactivated, the tuberculosis bacilli may spread via the lymphatic system and bloodstream throughout the body.
2. **Tuberculosis is treated in two phases:** an initial phase using 4 drugs and a continuation phase using 2 drugs:
   - **Initial Phase:** The treatment of choice for the initial phase is the **daily use of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol,** these drugs **should be continued for 2 months.**
   - **Continuation phase:** treatment is continued for a further **4 months with Isoniazid and Rifampicin,** Longer treatment duration is necessary for meningitis, HIV patients.
3. **For Latent Infection:**
   1. **Isoniazid** 300 mg daily in adults is the preferred treatment generally given for 9 months
   2. **Rifampicin** 600 mg daily for 4 months, can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid.
   3. **Rifabutin** 300 mg daily, may be substituted for rifampin for patients at high risk of drug interactions.
4. **Special Populations:**

- **TB Meningitis: Isoniazid, Pyrazinamide, Ethionamide,** and **Cycloserine penetrate the cerebrospinal fluid readily,** patients with CNS TB are often treated for **longer periods (9–12 months).** With the addition of **Dexamethasone injection** (used for three days only).
- **Extra pulmonary TB:** Can be treated with same regimens but typically **treated for 9 months**.
- **Children TB:** Extend treatment **to 9 months**; Pediatric doses of drugs should be used.
- **Pregnant Women:** The usual treatment of pregnant women is **Isoniazid, Rifampicin and Ethambutol for 9 months.**

5. **Common TB medications:**

Drug	Usual dose per day	Common side effect
Isoniazid	300 mg	Hepatitis, Peripheral neuritis, psychotic episodes, vertigo
Rifampicin	600 mg	Flu-like symptoms, acute renal failure, shock
Ethambutol	According to Kg: 800 mg (40–55 kg) 1,200 mg (56–75 kg) 1,600 mg (76–90 kg)	Optic neuritis, red/green color blindness, Peripheral neuritis and thrombocytopenia. And uric acid retention.
Pyrazinamide	According to Kg: 1,000 mg (40–55 kg) 1,500 mg (56–75 kg) 2,000 mg (76–90 kg)	hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice And uric acid retention.

1. **Rifampicin** (also Called **Rifampin** in USA) is used mainly for **Tuberculosis** (in combination with other Antituberculosis drugs) and in **Brucellosis** (in combination with **Doxycycline** for 6 weeks), also used for **Leprosy.**
   - It must be taken **30 to 60 minutes before food**.
   - **Rifampicin causes a harmless orange-red discoloration** of the urine, feces, sweat, saliva, sputum, tears, and other body fluids.

2. **Isoniazid** is a synthetic analog of pyridoxine, **a common side effect of Isoniazid is Peripheral neuritis** (manifesting as paresthesias of the hands and feet), appears to be due to a relative pyridoxine deficiency, most of the toxic reactions are corrected by supplementation of 25 to 50 mg per day of Pyridoxine (vitamin B_6).

Scientific name	Dosage form	Trade name	concentration
1st line treatment drugs			
Rifampicin	Cap	Rifadin® , Rimactane®	150 mg , 300 mg
	Inj. Powder		600 mg
Isoniazid	Tab	Nydrazid®	50 mg , 100 mg
	Inj. Solu.		25 mg/ml , 100 mg/ml
Ethambutol	Tab	Myambutol®	100 mg , 400 mg
Pyrazinamide	Tab	Zinamide®	500 mg
Rifabutin	Cap	Mycobutin®	150 mg
Rifapentine	Tab	Priftin®	150 mg
2nd line treatment drugs			
Amino salicylic acid	Granules	Paser®	4 gm/packet
Capreomycin	Inj. Powder	Capastat®	1 gm/vial
Clofazimine	Cap	Lamprene®	50 mg
Cycloserine	Cap	Seromycin®	250 mg
Ethionamide	Tab	Trecator®	250 mg
Bedaquiline	Tab	Sirturo®	100 mg
Pretomanid	Tab	----------	200 mg

Extra Notes:

1. **Aminoglycosides, Fluoroquinolones, Macrolides** maybe used as 2ndary line treatments.
2. **Rifampin, Rifabutin, and Rifapentine** are all considered to be **(Rifamycins)**, a group of structurally similar macrocyclic antibiotics, which are first-line drugs for tuberculosis.
3. **Capreomycin** Adverse effects include nephrotoxicity and 8th cranial auditory vestibular nerve toxicity; **this drug should not be given with streptomycin** or other drugs that may damage the auditory vestibular nerve. Patients on this drug will often require audiology tests.
4. **Clofazimine** has a marked anti-inflammatory effect and is **given to control the leprosy.**
5. **Cycloserine** is also being tested as an adjuvant to exposure therapy for anxiety disorders (e.g. phobias), depression, obsessive-compulsive disorder and schizophrenia, it has been experimentally **used for treatment of Gaucher's disease.**
6. **Bedaquiline** (approved 2013) is indicated for the **multidrug-resistant TB** in adults 18 years and older when other alterations are not available.
    a. **Bedaquiline has a black-box warning for arrhythmias,** as it may induce long QT syndrome by blocking the hERG channel.

Combination products for Tuberculosis:

Trade name	Dosage form	Scientific name(s)	concentration
Rifamate®	Cap	Rifampicin + Isoniazid	300 mg + 150 mg
Bunex®, Coxrid®	Tab	Ethambutol + Isoniazid	400 mg + 150 mg
Rifater®	Tab	Rifampicin + Isoniazid + Pyrazinamide	120 mg + 50 mg + 300 mg
Bunex E®, Actuate 3®	Tab	Ethambutol + Isoniazid + Rifampicin	275 mg + 75 mg + 150 mg
Zucox 4® Actuate 4®	Tab	Ethambutol + Isoniazid + Pyrazinamide + Rifampicin	275 mg + 75 mg + 400 mg + 150 mg

*** Combination products increase patient complaints, but it's usually <u>costs more</u> than each individual drug alone combined with another.**

Tuberculosis Prevention

A vaccine prepared from an artificially weakened strain of cattle tuberculosis bacteria can provide immunity from tuberculosis by provoking the development of natural resistance to the disease.

- **The BCG (Bacille Calmette-Guérin) vaccine** is a form of tuberculosis bacillus that provokes the body's immune response but does not cause the illness because it is not infectious.
- The vaccine is usually injected into the upper arm; A small pustule usually appears 6 to 12 weeks later, by which time the person can be considered immune.

5.1.13- Drugs used to treat Leprosy

1. **Leprosy (Called in the USA: Hansen's disease)** is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract; **skin lesions are the primary external sign, (Caused by Mycobacterium leprae)**.
2. If left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs and eyes, **leprosy does not cause body parts to fall off**, although they can become numb or diseased as a result of secondary infections; these occur as a result of the body's defenses being compromised by the primary disease.
3. Secondary infections, in turn, can result in tissue loss causing fingers and toes to become shortened and deformed, as cartilage is absorbed into the body.
4. The World Health Organization (WHO) recommends the **triple-drug regimen** of **Dapsone** (bacteriostatic), **Clofazimine** (bactericidal), and **Rifampin** for 6 to 24 months.

Scientific name	Dosage form	Trade name	concentration
Dapsone	Tab	Dapsone®	25 mg , 100 mg
	Topical Gel	Aczone®	5%, 7.5% (30, 60 gm tube)
Clofazimine	Cap	Lamprene®	50 mg
Rifampicin	Cap	Rifadin®	150 mg , 300 mg
	Inj. Powder		600 mg

Notes:

1. **Dapsone causes hemolysis**, especially in patients with **(G6PD) or in any other type of hemolytic anemia,** also causes Methemoglobinemia and peripheral neuropathy.
    a. **Dapsone is the drug of choice for treating leprosy.**
    b. **Dapsone Topical Gel** is used for the treatment of **Acne**.
    c. **Maybe used for the treatment of toxoplasmosis.**
    d. **Dapsone may develop erythema nodosum leprosum** (a serious and severe skin complication of leprosy); The latter is treated with corticosteroids or thalidomide.
2. **Clofazimine** has an **anti-inflammatory** activity; thus, **erythema nodosum leprosum does not develop, but Patients may develop a red-brown discoloration of the skin.**
    a. Urine, sweat, and other body fluids may be discolored.
    b. Should be taken with food only.

Clinical Tip

Increasing bacterial resistance against current antibiotics and lack of new molecules to combat bacterial resistance are key challenges to global health. There is, therefore, a continuing need to develop new antibiotics. **Teixobactin**, a cyclic undecapeptide, displays excellent antibacterial activities against a range of pathogenic bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA) and Mycobacterium tuberculosis. Interestingly, it operates by multiple modes of actions and is bactericidal toward S. aureus without detectable resistance; This unique combination of wide Gram-positive activity coupled with its inability to elicit resistance make it a very attractive molecule for antimicrobial therapeutic development.

5.1.14- Metronidazole, Tinidazole and relatives (Bactericidal)

1. They are active against **anaerobic bacteria** and **protozoa** (Entamoeba histolytica, Giardia lamblia); **Tinidazole is similar to metronidazole but has a longer duration of action**.
   - **Metronidazole** when used orally is **effective** for the treatment of **Clostridium difficile infection.**
   - **Topical metronidazole** is used in the treatment of **Acne** and **Rosacea**.
   - It also (topically) reduces the odor produced by anaerobic bacteria in fungating tumors.
2. **Metronidazole** and **Tinidazole** tablets are taken **with or after food**.
   - They can **produce nausea and an unpleasant metallic taste**.
   - The **patient may experience headaches** if used metronidazole or Tinidazole for the first time, (you may give Paracetamol for this case).
   - **Metronidazole** and **Tinidazole are contraindicated in the 1st trimester of pregnancy, after that it's OK to use them.**
   - **Not recommended for nursing mother.**
   - **Tinidazole** may be given as a **single dose of 2 gm** (4 tablets) for some infections including (Amebiasis, Giardiasis, Trichomoniasis and Bacterial Vaginosis).
   - In clinical studies; **Tinidazole is more effective than Metronidazole.**
3. **Secnidazole** offers the advantage of **once daily dose**, (its half-life is 19-27 hours).
   - **Drug of choice for patients with hepatic Amebiasis.**
   - Can be used for Amebiasis, Giardiasis, Trichomoniasis and Bacterial Vaginosis; with less risk of drug resistance
4. **Ornidazole** offers the advantages of both **once daily dose**, and a **higher efficacy against anaerobic bacterium;** although it's not FDA approved yet.
   - **In Europe** it's used to treat infections of the stomach, intestine, urinary tract and genital area, also used to prevent possible infections during a surgical procedure.
   - It has also been investigated for **use in Crohn's disease after bowel resection.**
5. **When given with alcohol, metronidazole and Tinidazole may provoke a disulfiram-like reaction** (occurs as abdominal cramps, nausea, vomiting, severe headache, psychotic reaction, nervousness, flushing of the skin, tachycardia and shortness of breath).
   - **This is actually used clinically to treat alcohol addiction**; they give metronidazole to the addict, and each time he drinks alcohol he will have a disulfiram-like reaction, without knowing that metronidazole did this to him; he is then forced to stop drinking or he will suffer this painful sensation over and over again each time he drinks.

Scientific name	Dosage form	Trade name	concentration
Metronidazole	Tab	Flagyl®, Flazole®	250 mg , 500 mg
	Syrup	Flagyl®	200 mg/5 ml
	Infusion Solu.		500 mg/100 ml
	Mouth Gel	Metrogyl®	----------
	Vaginal Gel	Vandazole®	0.75% (37.5 mg)
	Vaginal Supp.		500 mg , 1 gm
Tinidazole	Tab	Fasigyn®, Tindamax®	500 mg
Secnidazole	Tab	Flagentyl®, Sindose®	500 mg
	Oral Granules	Solosec®	2 gm
Ornidazole	Tab	Avrazor® , Borneral®	500 mg
	Oral Susp.	Ornida®	125 mg/5 ml
	Vaginal Supp.	Ornidaz®	500 mg
	Gel		10 mg

Combination Products:

Scientific name	D. form	Trade name	concentration
Tinidazole + Norfloxacin	Cap	Tinidol plus®	600 mg + 400 mg
Secnidazole + Itraconazole	Cap	Sporasec® , Itrasec®	166.6 mg + 33.3 mg
Secnidazole + Albendazole	Tab	C Cobistal® , Prothelmint®	1 gm (2 tabs) + 200 mg (2 tabs)
Secnidazole + Fluconazole	Tab	Gynflu®	500 mg + 37.5 mg
	Tab	Gynflu D®	1000 mg + 75 mg
Ornidazole + Ofloxacin	Tab	Bactorax OZ® , Chekmet®	500 mg + 200 mg
	Susp.		(125 mg + 50 mg)/5 ml
Ornidazole + Ciprofloxacin	Tab	Orcipol® , Repixol®	500 mg + 500 mg
Ornidazole + Levofloxacin	Tab	Lebact-O®	500 mg + 200 mg
Ornidazole + Gatifloxacin	Tab	Diragyl®	500 mg + 200 mg
	Susp.	Asoget OZ®	30 ml , 60 ml
Ornidazole + Cefixime	Tab	Cefit-OZ®	500 mg + 200 mg

5.1.15-Other Antibacterials (3-4)

A) Glycopeptides: (Bactericidal)

These include: **Vancomycin, Telavancin, Dalbavancin, Oritavancin** and **Teicoplanin**: which are **active against aerobic and anaerobic Gram-positive** bacteria including multi-resistant staphylococci.

- **Vancomycin** is not absorbed after oral administration. (not active against Gram -ve)
  - **a.** It has a long duration of action and can therefore be **given every 12 hours.**
  - **b. Vancomycin given by mouth** for 10–14 days is effective in the treatment of Clostridium difficile infection.
  - **c. Side effects of Vancomycin** include: fever, chills, and/or phlebitis at the infusion site. **Flushing ("red man syndrome") and shock result from histamine release associated with a rapid infusion.**
  - **d.** If an infusion-related reaction occurs, slow the infusion rate to administer Vancomycin over 2 hours, increase the dilution volume, and/or pre-treat with an antihistamine 1 hour prior to administration.
- **Telavancin** cause taste disturbances, nausea, vomiting, insomnia, and foamy urine.
  - **a. Causes Nephrotoxicity:** New onset or worsening renal impairment has occurred; monitor renal function in all patients
  - **b. Avoided in pregnancy,** it showed teratogenic effects in animal studies.
- **Teicoplanin** is indicated in potentially serious Gram-positive infections.
  - **a. Given once daily,** has a very long half-life (45-70 hrs.)
  - **b.** Associated with a **lower incidence of nephrotoxicity than vancomycin.**
  - **c.** Causes Thrombocytopenia.
  - **d. Teicoplanin should not be used during pregnancy.**
- **Dalbavancin** is given by 2-dose regimen of 1000 mg I.V. followed 1 week later by 500 mg I.V. (should be infused I.V. over 30 min.), **Oritavancin** is given as a single 1200 mg dose administered I.V. over 3 hours; both have a **very long half-life** (about 6-11 days), which supports once weekly I.V. dosing (single or double dose only).

Scientific name	Dosage form	Trade name	concentration
Vancomycin	Vial (powder)	Vancocin®	500 mg , 1 gm
Telavancin	Vial (powder)	Vibativ®	250 mg , 750 mg
Teicoplanin	Vial (powder)	Targocid®	200 mg , 400 mg
Dalbavancin	Vial (powder)	Dalvance®, Xydalba®	500 mg
Oritavancin	Vial (powder)	Orbactiv®	400 mg

B) Quinupristin/Dalfopristin: mixture of two streptogramins in a ratio of 30% to 70%, they synergistically interrupt protein synthesis; **The combination drug is (bactericidal) and has a long post-antibiotic effect,** mixed and administered only in 5% D5W solution, insoluble in NS 0.9%.

- Adverse effects include: Arthralgia and myalgia, Hyperbilirubinemia.
- Mild to life-threatening pseudomembranous colitis has been reported.

Scientific name	Dosage form	Trade name	concentration
Quinupristin + Dalfopristin	Inj. powder	Synercid®	(150 mg + 350 mg)/10 ml

C) Tedizolid: it's an oxazolidinone-class antibiotic, used for the treatment of acute bacterial skin and skin structure infections, it is 4-16-fold more potent against staphylococci and enterococci compared to **Linezolid** (see below).

- The recommended dosage for treatment is 200 mg once daily for six days.

Scientific name	Dosage form	Trade name	concentration
Tedizolid	Tab	Sivextro®	200 mg
	Vial (powder)		200 mg/vial

D) Linezolid: used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics, it's also used to treat tuberculosis.

- **Linezolid** is **bacteriostatic** against Enterococci and Staphylococci, and **bactericidal** against Streptococci.
- **Common adverse effects** of short-term use include headache, diarrhea, and nausea. Long-term use, however, has been associated with serious adverse effects; **linezolid can cause bone marrow suppression and low platelet counts**, particularly when used for more than two weeks; **Irreversible peripheral neuropathies and optic neuritis (causing blindness) is associated with greater than 28 days of use.**
- Inhibit MAO activity, and can precipitate serotonin syndrome in patients concomitantly taking SSRIs, the condition was reversible when the drug was suspended.

Scientific name	Dosage form	Trade name	concentration
Linezolid	Tab	Zyvox®	600 mg
	Infusion Solu.		2 mg/ml

E) Nifuroxazide: oral nitrofuran antibiotic, used to treat colitis and diarrhea; has a spectrum which covers: Shigella, Escherichia coli, Salmonella, Staphylococci, Klebsiella, Yersinia.

Scientific name	Dosage form	Trade name	concentration
Nifuroxazide	Cap	Ercefuryl® , Diax®	200mg
	Oral Susp.	Diax® , Antinal®	220 mg/5 ml

F) Rifaximin: is used in **the treatment of traveler's diarrhea**, **Irritable bowel syndrome**, and used for the **prophylaxis of hepatic encephalopathy**.

- Maybe combined with **Lactulose for hepatic encephalopathy.**
- Also used for **irritable bowel syndrome (IBS)** diarrhea predominant type.
- Can be taken with or without food.

Scientific name	Dosage form	Trade name	concentration
Rifaximin	Tab	Xifaxan® , ColiDur®	200 mg , 550 mg

G) Chloramphenicol, Thiophenicol, Colistimethate, Lefamulin and **Daptomycin:**

- **Daptomycin is bactericidal,** inactivated by pulmonary surfactants; thus, it should **never** be used in the **treatment of pneumonia.**
  - **a.** Activity similar to Vancomycin.
  - **b. Side effects include:** constipation, nausea, headache, myalgias and insomnia.
  - **c. Discontinue Statins when giving Daptomycin** (it causes myopathy, rhabdomyolysis).

- **Chloramphenicol (bacteriostatic)** is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.
    a. Causes bone marrow suppression, Hemolytic anemia, Aplastic anemia**.**
    b. Causes Gray baby syndrome when given to newborn infants **(leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis).**
    c. It's used these days only as topical preparations as eye drop/Oint.
- **Thiophenicol (bacteriostatic)** is Chloramphenicol analog that have an **advantage of not causing Aplastic anemia**, some drug references consider it as a **veterinary antibiotic**, but it's approved for human use in Italy and Argentina.
- **Colistimethate** has **bactericidal** activity against aerobic gram-negative micro-organisms**;** it is particularly indicated when the infection is caused by sensitive strains of **Pseudomonas aeruginosa;** either by I.V. injection or by inhalation of the powder in the vial content.
- **Lefamulin (bactericidal),** approved in 10/2019 by the FDA; it is used to treat adults with community-acquired bacterial pneumonia.

Scientific name	Dosage form	Trade name	concentration
Daptomycin	Vial (powder)	Cubicin®	500 mg
Chloramphenicol*	Cap	Biomicin®	250 mg
	Inj. (vial)	Chloromycetin®	1000 mg
	Eye drop/Oint.	Phenicol® , Optrex®	1%
Thiophenicol	Inj. (vial)	Thiophenicol®	750 mg
Colistimethate	Inj. (I.V. or Inhale)	Xylistin®	1 million IU
Lefamulin	Tab	Xenleta®	600 mg
	I.V. Solu.		150 mg/15 ml

*** The Manufacture of <u>oral</u> chloramphenicol was stopped in the USA in 1991.**

5.1.16- Topical antibiotics

These include:

1. **Fusidic acid:** (bacteriostatic), the only indication for their use is in infections caused by penicillin-resistant staphylococci; It's also used in the treatment of burns.
    a. Occasionally used as a treatment for acne.
    b. Comes in combination with **hydrocortisone** or **betamethasone**.
2. **Bacitracin:** (bacteriostatic), **used only** for the prevention of superficial skin infections caused by the susceptible bacteria. (Not substantially absorbed from intact or denuded skin, wounds, or mucous membranes).
3. **Mupirocin:** used for furuncle, impetigo, open wounds, do not apply to eyes; do not apply topical to mucous membranes.
4. **Nadifloxacin** is a **topical fluoroquinolone antibiotic** for the treatment of **acne vulgaris**; It is also used to treat bacterial skin infections, it also showed potent antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA).
5. **Mafenide** and **Silver sulfadiazine** (see Sulfonamides above); **Usually used for burns.**
6. **Retapamulin:** for treatment of bacterial skin infections **such as impetigo**
7. **Fusafungine:** for the treatment of nasal and throat infection; **It also possesses anti-inflammatory properties.**
8. **Retapamulin** was approved by the FDA for the treatment of bacterial skin infections such as impetigo in adults and children older than nine months.

Scientific name	Dosage form	Trade name	concentration
Fusidic acid	Cream/Oint.	Fucidin®, Fucine®, Fucibact®	2%
	Eye Oint./Drop	Fucithalmic®	1% (5 mg/Tube)
Bacitracin	Oint. / Powder	Baciquent®	500 Unit/gm
Nadifloxacin	Cream	Nadixa®, Magnis®	1%
Mupirocin	Cream/Oint.	Bactroban®, Avoban®	2%
Mafenide	Cream, Topical Solu.	Sulfamylon®	----------
Silver Sulfadiazine	Cream	Silvadene®	1%
Retapamulin	Oint.	Altabax®	1% (5 gm , 10 gm Tubes)
Ozenoxacin	Cream	Xepi®	1%
Fusafungine	Oro/nasal Spray	Locabiotal® , Bioparox®	1% (500 mcg)
Retapamulin	Oint.	Altabax	1%

Note1: Combination products of some topical Antibacterials:

Scientific name(s)	D. Form	Trade name	concentration
Fusidic acid + Betamethasone	Cream	Fucibet® , Fucibact B®	2% + 0.1% (15 gm tube)
Fusidic acid + Hydrocortisone	Cream	Fucidin H®	2% + 1% (15 gm tube)
Polymyxin B + Bacitracin	Cream/Oint	Polysporin®	(10,000 unit + 500 unit) per gm
Neomycin + Polymyxin B + Bacitracin	Cream, Oint.	TAO®	(3.5 mg + 5,000 unit + 400 unit) Per 1 gm
Neomycin + Polymyxin B + Bacitracin + Pramoxine	Oint.	TriBiozene®	(3.5 mg + 10,000 unit + 500 unit + 10 mg) per 1 gm

Note2: Other Antibacterials that can be formulated as skin products include:

- Erythromycin, Gentamycin, Neomycin, Tetracycline, Clindamycin, Metronidazole and Dapsone.

5.2-Antifungal drugs

a. The most common fungal infections are **caused by the tinea group**, these include tinea pedis (athlete's foot), tinea cruris (jock itch) tinea corporis (ringworm), and tinea capitis (scalp ringworm).
- They are spread by direct or indirect contact with infected humans or animals.

b. Problems may also result from the proliferation of a fungus normally present in the body; the most common example is excessive growth of **candida**, a yeast that causes thrush infection of the mouth, vagina, bowel; It can infect other organs if spread through the body via the bloodstream.
- Overgrowth of candida may occur in people taking antibiotics or oral contraceptives, in pregnant women, or in those with diabetes or immune system disorders.

1. Antifungals are classified as:
- **A) Systemic antifungals:** as (Amphotericin B, Griseofulvin, Fluconazole, Itraconazole).
- **B) Topical antifungals:** as (Tolnaftate, Sertaconazole, Ciclopirox).
- **C) Vaginal antifungal:** as (Miconazole, Terconazole, Tioconazole).

2. Or they can be classified on their pharmacological structure as:

Class	**Examples**
Echinocandin antifungals	Nidulafungin, Caspofungin, Micafungin,
Polyene antifungals	Amphotericin B, Nystatin.
Triazole antifungals	Fluconazole, Itraconazole, Posaconazole, Voriconazole
Others	Flucytosine, Griseofulvin

3. The table below shows some indications for some antifungals:

DRUG / INFECTION	Oesophageal thrush	Cryptococcal meningitis	Skin ringworm	Scalp ringworm	Nail infection	Mouth thrush	Vaginal thrush	Candida of the skin	Systemic candida	ADMINISTRATION: Topical	ADMINISTRATION: Injection	ADMINISTRATION: Oral
Amphotericin B	●	●				●			●			●	●
Caspofungin	●								●			●	
Clotrimazole			●	●			●	●			●		
Fluconazole	●	●					●	●	●			●	●
Flucytosine	●	●							●			●	●
Griseofulvin			●	●	●								●
Ketoconazole	●		●	●	●		●	●			●		
Miconazole			●			●	●	●			●		●
Nystatin	●					●	●	●			●		●
Terbinafine			●	●	●								●
Voriconazole	●						●		●			●	●

4. Some systemic antifungals are also available as topical products, also systemic antifungals maybe used for vaginal infections.

5. **Fluconazole** is used 150 mg as a **single oral dose for vaginal candidiasis**, while for **recurrent vulvovaginal candidiasis**: Initially 150 mg every 72 hours for 3 doses, then 150 mg once weekly for 6 months.

6. **Itraconazole, Fluconazole and ketoconazole must be given after food**.

7. The use of **ketoconazole may be restricted from the oral use due to the risk of hepatotoxicity** (reported very rarely); also **ketoconazole has anti-androgenic effects causing Gynecomastia, decreased libido, impotence, oligospermia, and decreased testosterone levels in men, and menstrual irregularities in women,** result from the blocking of Androgen and adrenal steroid synthesis, leading to decreased testosterone and cortisol production.
- Ketoconazole is topically effective for **treatment of seborrheic dermatitis** and **dandruff.**
- **2% Ketoconazole shampoo** was found to **improve hair density and the size** and proportion of anagen follicles in **androgenetic alopecia (AGA)** and used in combination with finasteride, to have an additive effect for AGA.

A) Systemic antifungals:

Scientific name	Dosage form	Trade name	concentration
Amphotericin B	Vial (powder)	Ambisome®	50 mg
Flucytosine	Cap	Ancobon® , 5-FC®	250 mg , 500 mg
Caspofungin	Inj. powder	Cancidas®	50 mg , 70 mg
Anidulafungin	Inj. powder	Eraxis®	50 mg
Micafungin	Inj. powder	Mycamine®	50 mg , 100 mg
***Fluconazole** **	Cap	Diflucan®	150 mg
	Inj. Solu.		2 mg/ml
***Itraconazole** **	Cap	Sporanox®, Inox®, Omnel®	100 mg
***Ketoconazole** **	Tab	Nizoral® , Ketonaz®	200 mg
	Shampoo	Nizoral shampoo®	1% , 2%
Posaconazole *	Tab	Noxafil®	100 mg
	Oral Susp.		40 mg/ml (105 ml)
***Voriconazole** **	Tab	Vfend®, Voricona-Denk®	50 mg , 200 mg
	Inj. powder		200 mg
Isavuconazole * (Isavuconazonium)	Cap	Cresemba®	100 mg
	Vial (powder)		200 mg
Terbinafine	Tab	Lamisil®, Lamifin®, Terbisil®	250 mg
Griseofulvin	Tab	Grifulvin®	500 mg , 750 mg
	Oral Susp.		125 mg/5 ml
Nystatin	Tab	Mycostatin®	500,000 Units
	Oral Susp.		100,000 Units
	Oral Drop		100,000 Units

*** Items are called Azoles.**

**** Voriconazole** is 300 times more potent than **Ketoconazole,** it's also very high in price.

Combination Products:

Scientific name	D. form	Trade name	concentration
Itraconazole + Secnidazole	Cap	Sporasec® , Itrasec®	33.3 mg + 166.6 mg
Fluconazole + Secnidazole	Tab	Gynflu®	37.5 mg + 500 mg
		Gynflu D®	75 mg + 1000 mg
Fluconazole + Tinidazole	Tab	Azostat®	150 mg + 1 gm

Notes:

1. **Amphotericin B (Fungistatic, Fungicidal)** depending on the type of organism; it is the drug of choice for the treatment of life-threatening systemic mycoses.
   - **a.** Act by decreasing Ergosterol content of the fungal membrane.
   - **b.** **Amphotericin B has a low therapeutic index,** causes: (Fever and chills, renal impairment, Hypotension, Anemia, Neurologic effects, Thrombophlebitis), which all can be reduced by formulating Amphotericin B as Lipid soluble formula.
     - Premedication with a corticosteroid or an antipyretic help to prevent Fever & chills.
     - A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation.
     - Adding heparin to the infusion can alleviate thrombophlebitis.
   - **c.** **Amphotericin B** is also used in the treatment of the protozoal infection Leishmaniasis.
   - **d.** Can be used **as a Topical preparation** to eradicate cutaneous and mucocutaneous candidiasis.
   - **e.** **Amphotericin B** parenteral use should be **mixed only in dextrose 5% in water (D5W)** and should be **protected from light.**
   - **f.** Sometimes used in combination with **Flucytosine (5-FC) for synergistic effect.**

2. **Flucytosine (5-FC)** causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression, reversible hepatic dysfunction, gastrointestinal disturbances.
   - Used in combination with Amphotericin B (it increases cell permeability, allowing more Flucytosine to penetrate the cell, thus leading to a synergistic effect).
3. **Echinocandins** which include **(Caspofungin, Anidulafungin, and Micafungin)** interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β (1, 3)-D-glucan, leading to lysis and cell death, **available for IV administration** once daily; Micafungin does not require a loading dose, others do.
   a. **Caspofungin** is the first approved member of the Echinocandins class of antifungal drugs.
   b. **Anidulafungin** significantly differs from other antifungals in that it undergoes chemical degradation to inactive forms at body pH and temperature; Because it does not rely on enzymatic degradation or hepatic or renal excretion, **the drug is safe to use in patients with any degree of hepatic or renal impairment.**
   c. Echinocandin antifungals are only active against Aspergillus spp. and Candida spp.
4. **Azoles** Include: (**Fluconazole, Itraconazole, ketoconazole, Voriconazole, Posaconazole) all are Fungistatic.** (They disrupt fungal membrane structure and function, which inhibits fungal cell growth); **All are teratogenic, and should not be used in pregnancy.**
   a. **Fluconazole** may rarely cause serious liver disease.
   b. To increase efficacy of Fluconazole for topical fungal infections; the patient should be advised to sweat (do exercise); due the fact that Fluconazole is concentrated in the sweat.
   c. **Itraconazole** has a **-ve inotropic effect;** should not be taken by patients with evidence of ventricular dysfunction, such as **congestive heart failure (CHF) or a history of CHF.**
   d. **Voriconazole** is associated with visual and auditory hallucinations, (blurred vision).
   e. **Posaconazole** (approved 2008) must be administered with a high fat meal.
   f. **All Azoles must be taken after food.**
5. **Griseofulvin is contra-indicated in pregnancy, and women should not become pregnant during, or within 1 month of stopping therapy;** Also, **men should avoid fathering a child during and for at least 6 months after administration**.
   a. Griseofulvin is a **fungistatic**; it is effective in Tinea infections of the skin, hair, and nails (including athlete's foot, jock itch, and ringworm).
   b. Absorption of Griseofulvin from the GIT is enhanced by reducing the particle size or when given **with a fatty meal** (should be given with or after meals).
   c. It possesses a **vasodilator activity** and may be used in Raynaud disease, and also it may be used to **treat gout.**
6. **Nystatin** is used for oral, oropharyngeal, and perioral infections by **local application** in the mouth; (will be discussed later in chapter 13), and it may be given orally for the treatment of intestinal candidiasis.
   a. **Nystatin** is not absorbed orally (or poorly absorbed), and act by direct contact to the fungal cells, thus its preferred in pediatric patients and in neonates.
   b. **Nystatin** comes in combination with many skin products/vaginal products.

B) Topical antifungals:

Duration of therapy is dependent on the site of the infection and may extend to a number of months; (2 to 8 weeks for infections of the hair and skin, up to 6 months for infections of the fingernails, and 12 months or more for infections of the toe nails).

1. **Miconazole** is also used for oral, oropharyngeal, and perioral infections by local application in the mouth, **Topical Miconazole is highly effective** in vulvovaginal candidiasis, ringworm, and other skin infections, and it has **some activity against Gram positive bacteria**.
2. **Clotrimazole** is an **Azole** antifungal agent
   - The cream, lotion, or solution is used to treat dermatophytoses, superficial mycoses, and cutaneous candidiasis.
   - Intravaginal dosage forms are useful in treating vulvovaginal candidiasis.
   - The lozenges, which are administered five times per day, are useful in treating oropharyngeal candidiasis.

3. **Terbinafine (Fungicidal)** is indicated is used to treat dermatophytoses, superficial mycoses, and cutaneous candidiasis, it's also used to treat fungal infections of the toe nails and fingernails.

4. **Sertaconazole**, an imidazole topical antifungal; has a low **antibacterial activity**, and moderate **anti-inflammatory** and **antipruritic effects.**
   - It has a Significantly lower relapse rate than other antifungal drugs.

5. **Amphotericin B** is available as a 3% cream or lotion or an oral suspension that is not absorbed through the GI tract, (usually prepared in the pharmacy).
   - Used for oropharyngeal candidiasis, cutaneous and mucocutaneous candida infections, or as a local irrigant for the bladder and intrapleural or intraperitoneal areas.

6. **Gentian violet** is a **dye that possesses the ability to kill fungi, yeasts**, and some gram-positive bacteria, may cause irritation or sensitivity reactions or possibly ulceration of the mucous membranes, if the solution is swallowed, esophagitis, laryngitis, or tracheitis may occur.

Scientific name	Dosage form	Trade name	concentration
Butenafine	Cream	Lotrimin®, Mentax®	1%
Ciclopirox	Cream, Lotion, Gel	Loprox®, Penlac®	0.77%
	Shampoo		1%
	Nail Lacquer		8%
Clotrimazole	Cream, Lotion	Canesten® , Gynomizole® , Mycelex®	1%
	Lozenges		10 mg
Econazole	Cream	Gyno-Pevaryl® , Ecostatin®, Spectazole®	1%
Efinaconazole	Cream, Topical Solu. Gel, Nail Lacquer	Topazole®, Jublia®	10%
Amorolfine	Nail Lacquer	Loceryl®	5% (50 mg/ml)
Ketoconazole	Cream, Gel, Foam	Nizoral® , Ketonaz®	2%
	Shampoo		1% , 2%
Luliconazole	Cream	Luzu® , Lulican®	1%
Miconazole	Cream	Desenex®, Fungoid®, Daktarin®	2%
Naftifine	Cream, Gel	Naftin®	1% , 2%
Nystatin	Cream, Oint	Pediaderm®, Mycostatin®	100,000 Units/gm
Oxiconazole	Cream, Lotion	Oxistat®, Tinox®	1%
Sertaconazole	Cream	Ertaczo®, Dermofix®, Onabet®	2%
	Topical Spray		2% (15 ml)
	Shampoo		20 mg/gm
Eberconazole	Cream	Ebernet®	1%
Sulconazole	Cream, Lotion	Exelderm®	1%
Isoconazole	Cream	Travocort® , Travogen®	1%
Tioconazole	Cream	Trosyd®	1%
Butoconazole	Cream	Gynazole-1®	2%
Terconazole	Cream	Terazole® , Zazole®	0.4% , 0.8%
Terbinafine	Cream, Lotion	Lamisil®, Lamifin®, Terbisil®	1%
Tolnaftate	Cream, Powder, Solu.	Tinactin®, Aftate®, Tolnalin®	1%
Bifonazole	Cream	Mycospor®	1%
Tavaborole	Topical Solu.	Kerydin®	0.5% (43.5 mg/ml)
Efinaconazole	Topical Solu.	Jublia®	10%

C) Vaginal Antifungals

1. Duration of therapy ranges from short courses of 1 to 14 days according to the preparation used; treatment can be repeated if initial course fails to control symptoms or if symptoms recur, all internal preparations **should be administered at night**.
   - this give the drug time to be absorbed, and eliminate the possibility of accidental loss which is more likely to occur if the person is mobile or moving.

2. **Vaginal Antifungal** preparations may damage birth-control devices such as condoms and diaphragms, leading to inadequate protection. Consider alternative methods of birth control.

Scientific name	Dosage form	Trade name	concentration
Clotrimazole	Vag. Cream	Canestene®, Gyne-Mycelex®	1% , 2%
	Vag. Tab	Canestene®	100 mg , 200 mg
Butoconazole	Vag. Cream	Femstat®	2%
Fenticonazole	Vag. Cream	Gynoxin®	2%
	Vag. Cap		200 mg , 600 mg
***Miconazole** *	Vag. Cream	Gyno-Daktarin®, Mycoheal®	2% , 4%
	Vag. Supp.	Gyno-Mikazole®	200 mg , 400 mg
***Nystatin** *	Vag. Tab	Monicure®	100,000 Units
Terconazole	Vag. Cream/Supp.	Terazole®	0.4% , 0.8%
Tioconazole	Vag. Oint.	Vagistat®, Topazole V®	6.5%
	Vag. Cream	Topzole V®	2% (20 gm cream)
Sertaconazole	Vag. Cap	Dermofix Ovule®	2%
Econazole	Vag. Supp.	Ecorex®	150 mg

*** Miconazole** and **Nystatin** comes in many combination products of vaginal creams and Supps.
Note: See also Chapter 7, section 2, for more details on vaginal infections and Gynecological combinations.

Clinical Tip

Some antibiotics have a non-antibacterial use; such as:

- **Erythromycin** (as prokinetic) in Gastroparesis.
- **Isoniazid** in Multiple Sclerosis.
- **Rifampicin** in Cholestatic Jaundice.
- **Rifaximin** in IBS (irritable bowel syndrome).
- **Dapsone** gel in Acne

5.3-Antiviral drugs

First: Herpes Simplex and Varicella–Zoster infections

1. **Herpes viruses (HSV)** are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections, drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase, except for **Foscarnet** and **Fomivirsen**.
   a. **Herpes infection has 2 serotypes,** HSV-1 usually affects the mouth, lips and the eye, other areas of the skin may also be infected, especially in immunodeficiency, Genital infection is most often associated with HSV-2 and also HSV-1.
   b. **Varicella-zoster infection (Chickenpox)** is more severe in adolescents and adults than in children; **antiviral treatment** started within 24 hours of the onset of rash may reduce the duration and severity of symptoms.
      - Treatment also include **antipyretics, calamine lotion** and **antihistamines.**
   c. In **herpes zoster (shingles)** systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding.
      - **Accompanied by Chronic pain** which persists after the rash has healed (**Post herpetic neuralgia**) requires specific management (usually given **Gabapentin** or **Pregabalin**).
2. The most common Antiviral drug used for **Herpes simplex and varicella–zoster infections is Acyclovir,** usually **given 5 times daily** (every 4 hours for 5 times).
   - **Acyclovir** is active against **herpes viruses** but does not eradicate them.
   - **Topical Acyclovir** is applied directly on herpes lesions in recurrent **herpes labialis** (cold sores); it is **not recommended for use on genital herpes** lesions due to poor efficacy.
   - **Acyclovir IV administration** may cause dose-dependent renal impairment, crystalline nephropathy, neurological effects (e.g., lethargy, confusion, tremors, agitation, seizures, coma), hypotension, rash, itching, and phlebitis at the injection site.

Second: Cytomegalovirus (CMV) infection

CMV infections are frequently associated with the **salivary glands causing flu-like symptoms,** CMV infection is typically unnoticed in healthy people, but can be life-threatening for the immunocompromised, such as HIV-infected, organ transplant recipients, newborn infants.

- Symptomatic CMV disease can affect almost every organ of the body, resulting in fever of unknown origin, pneumonia, hepatitis, encephalitis, myelitis, colitis, uveitis, retinitis, and neuropathy; In patients with HIV infection, CMV involves the entire GI tract. Retinitis is the most common manifestation of CMV disease in patients who are HIV positive.

Antivirals for Herpes simplex, Varicella Zoster and Herpes Zoster

Scientific name	Dosage form	Trade name	concentration
Acyclovir	Tab	Zovirax® , Veramed®	200 mg , 400 mg , 800 mg
	Susp.		200 mg/5 ml
	Vial (powder)		250 mg , 500 mg , 1 gm
	Cream/Oint.	Sitavig®	5%
	Eye Oint		1%
Famciclovir	Tab	Famvir®	125 mg , 250 mg , 500 mg
Penciclovir	Cream	Fenlips® , Denavir®	10 mg/gm (2 gm tube)
Docosanol	Cream	Abreva®	10%
Tromantadine	Gel	Viru-Merz®	1% (5 gm tube)
Trifluridine	Eye Drop	Viroptic®	1% (7.5 ml drop)
Valacyclovir	Tab	Valterx®	500 mg , 1 gm
Inosine Pranobex	Tab	Imunovir®	500 mg
Tecovirimat *	Cap	Tpoxx®	200 mg

* **Tecovirimat** is indicated for the treatment of human smallpox disease caused by **Variola** virus.

Antivirals for CMV			
Ganciclovir	Cap	Cytovene®, Cymevene®	250 mg , 500 mg
	Vial (I.V.)	Cymevene®	500 mg
	Eye gel	Zirgan® , Vitrasert®	0.15% (5 gm)
Cidofovir	Inj. Solu.	Vistide®	75 mg/ml
Foscarnet sodium	Inj. Solu.	Foscavir®	24 mg/ml (250 ml vial)
Fomivirsen	Intravitreal inj.	Vitravene®	6.6 mg
Letermovir	Tab	Prevymis®	240 mg , 480 mg
Valganciclovir	Tab	Valcyte®	450 mg
	Oral solution		250 mg/5 ml

1. **Cidofovir** is used for the treatment (but not the cure) of CMV retinitis.
   a. **Causes acute renal failure** leading to dialysis or death.
   b. It is **carcinogenic and teratogenic.**
2. **Ganciclovir** is related to **Acyclovir** but it is more active against cytomegalovirus (CMV); it is also much more toxic (myelosuppression) than Acyclovir.
   - It has a black box warning concerning increased potential for neutropenia, anemia, and thrombocytopenia; It is also **teratogenic, carcinogenic, and mutagenic**, Adverse effects commonly include: fever, rash, and GI disturbances; Phlebitis, pain may occur at the site of infusion.

Third: Influenza Virus infections:

Influenza is one of the most common infectious diseases, is a highly contagious airborne disease that occurs in seasonal epidemics and manifests as an acute febrile illness with variable degrees of systemic symptoms, ranging from **mild fatigue to respiratory failure and death.**

- Onset of illness can **occur suddenly** over the course of a day, or it can progress more slowly over the course of several days. Typical signs and symptoms include the following (Cough, Fever, Sore throat, Myalgias, severe fatigue and weakness, Tachycardia, Red-watery eyes).
- There are 3 antiviral drugs are approved for chemoprophylaxis and treatment of influenza: **Oseltamivir, Zanamivir** and **Peramivir.**
- **Amantadine** can be used for Influenza, but it's not recommended these days, (it's used mainly as an anti-Parkinson's), **Rimantadine** is active against Influenza A only.

Antivirals for Influenza			
Scientific name	Dosage form	Trade name	concentration
Oseltamivir	Cap	Tamiflu®	30 mg , 45 mg , 75 mg
	Susp.		75 mg/5 ml
Zanamivir	Inhale Powder	Relenza®	5 mg (20 Units)
Peramivir	I.V. Solu.	Rapivab®	200 mg/20 ml
Laninamivir	Inhale Powder	Inavir	20 mg , 40 mg (single inhale)
Baloxavir Marboxil	Tab	Xofluza®	40 mg , 80 mg
Amantadine	Tab , cap	Symmetrel®	100 mg
Rimantadine	Tab	Rymanta®	100 mg

1. **Oseltamivir** is active against both Influenza A and B; It is one of the preferred agents for use against the 2009 H1N1 strain of influenza.
   a. It is also approved for the prophylaxis of influenza infections in patients 1 year of age and older, **BUT** the influenza virus vaccine is still the gold standard for prophylaxis.
   b. The most common adverse effects are nausea and vomiting, delirium; Some recent studies showed that there is **no difference** between **Oseltamivir** and **Placebo** in the management of Influenza.
2. **Zanamivir** is used for prevention or treatment of Avian and Swine (H1N1) influenza; the use of **Zanamivir** is not recommended in patients with a history of asthma or chronic obstructive pulmonary disease, owing to the risk of bronchospasm and acute decline in lung function.
3. **Baloxavir**, is an antiviral medication for treatment of influenza A and influenza B, **has an advantage that it is taken as a single dose** by mouth; it targets the endonuclease function of the viral PA polymerase subunit and prevents the transcription of viral mRNA.

Forth: Viral Hepatitis:

Viral hepatitis is liver inflammation due to a viral infection; it may present in acute (recent infection, relatively rapid onset) or chronic forms. The most common causes of viral hepatitis are the five unrelated hepatotropic viruses (A, B, C, D and E).

A. Hepatitis A:

HAV infection usually produces a self-limited disease and acute viral infection, with a low fatality rate, and confers lifelong immunity, it's primarily occurs through transmission by the fecal-oral route, person-to-person, or by ingestion of contaminated food or water.

- HAV does not lead to chronic infections.
- Management of HAV infection is primarily supportive, Steroid use is not recommended.
- Two inactivated virus vaccines are currently licensed by FDA (**Havrix®** and **Vaqta®**).
- A single dose of IG of 0.02 mL/kg is given I.M. for post-exposure prophylaxis or short term (≤5 months) pre-exposure prophylaxis. For lengthy stays, a single dose of 0.06 mL/kg is used, HAV vaccine may also be given with IG.

B. Hepatitis B:

HBV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, Transmission of HBV occurs sexually, parenterally, and parentally.

- Two products are available for prevention of HBV infection: **HBV vaccine**; which provides active immunity, and **HBV Ig**; which provides temporary passive immunity.
- Drug therapy is used to suppress viral replication by immune mediating or antiviral effects: **Interferon-α2b** (IFN-α2b), **Lamivudine**, **Telbivudine**, **Adefovir**, **Entecavir**, **Pegylated IFN-α2a** (PEG-IFN), and **Tenofovir.**
- Treatment for a minimum of **12 months** is associated with greater sustained virologic response rates than treatment for **4 to 6 months**.
- Conventional **IFN therapy** has been virtually replaced with **PEG-IFN**, because of the ease of administration (once-weekly injections), fewer side effects, and improved efficacy.
- **Lamivudine** (100 mg daily given orally) **in combination with PEG-IFN** resulted in greater HBV DNA suppression.

C. Hepatitis C:

1. **HCV** is the most common blood-borne pathogen, it's a lethal infection leading to chronicity and carcinogenicity with **no available product for prevention and prophylaxis yet.**
   - During the initial infection people often have mild or no symptoms, occasionally a **fever, dark urine, abdominal pain, and yellow tinged skin occurs.**
   - Over many years however, it often leads to liver disease and occasionally cirrhosis, in some cases, those with cirrhosis will develop complications such as liver failure, liver cancer, or dilated blood vessels in the esophagus and stomach.
2. HCV is most often acquired through injection drug use, may occur by sexual contact; hemodialysis; or perinatal exposure.
   - An estimated 20% of patients with chronic HCV infection will develop cirrhosis, and half of those patients will progress to decompensated cirrhosis or hepatocellular carcinoma.
   - The current standard of care for chronic HCV patients is **combination therapy of a once-weekly injection of PEG-IFN and a daily oral dose of Ribavirin.**
   - **Ribavirin** adverse effects include hemolytic anemia (black box warning) and GI upset, **Ribavirin** is teratogenic; its use is **contraindicated in pregnancy.**
   - **PEG-IFN monotherapy** can cure recent HCV infection in about 90% of the patients.
3. There is a **new generation** of drugs - direct acting antiviral (DAA)- approved for HCV that have a **cure rate up to 95%,** although their price is high, include: (Sofosbuvir, Ledipasvir, Velpatasvir).
   - Their initial recommended **treatment depends on the type of hepatitis C virus (HCV genotype)** and whether or not a person has cirrhosis.
   - The **treatment regimen is 12 weeks** of therapy.
   - **Treatment during the first six months is the most effective period.**
   - Adverse effects with these treatments were common, with half of people getting **flu like symptoms** and a third experiencing **emotional problems.**

4. **Successful treatment does not give any protection against another hepatitis C infection**; the patient can still catch it again and get re-infected.
   - Usually cure rate is about 95%, but if the treatment does not work, it may be repeated, extended, or a different combination of medicines may be tried.

5. **Note:** The recommended **treatment regimen in HCV depends upon the genotype** as below:

Drug Combination Regimen		Indication(s)
1.	Sofosbuvir + Ledipasvir (with or without ribavirin)	Genotype 1, 4, 5, 6 infection
2.	Sofosbuvir + Velpatasvir (with or without ribavirin)	All 6 genotypes
3.	Sofosbuvir + Daclatasvir (with or without ribavirin)	Genotype 1, 3, 4 infection
4.	Sofosbuvir + Simeprevir (with or without ribavirin)	Genotype 1, 4 infection
5.	Sofosbuvir + Velpatasvir + Voxilaprevir	All 6 genotypes
6.	Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir (with or without ribavirin)	Genotype 1 infection only
7.	Ombitasvir + Paritaprevir + Ritonavir (with ribavirin)	Genotype 4 infection only
8.	Grazoprevir + Elbasvir (with or without ribavirin)	Genotypes 1, 4 infection
9.	Glecaprevir + Pibrentasvir (with or without ribavirin)	All 6 genotypes

Drugs Available for Hepatitis			
Scientific name	Dosage form	Trade name	concentration
Adefovir dipivoxil	Tab	Hepsera®	10 mg
Ribavirin	Tab , Cap	Rebetol® , Virazole®	200 mg , 400 mg , 600 mg
	Inhale Solu.		6 gm per vial
Entecavir	Tab	Baraclude®	0.5 mg , 1 mg
Telbivudine	Tab	Sebivo® , Tyzeka®	600 mg
Lamivudine	Tab	Zeffix® , Epivir®	100 mg , 150 mg , 300 mg
Boceprevir	Cap	Victrelis®	200 mg
Sofosbuvir	Tab	Sovaldi®	400 mg
Telaprevir	Tab	Incivo®	375 mg
Tenofovir	Tab	Viread®	150 mg , 200 mg , 300 mg
Simeprevir	Cap	Olysio®	150 mg
Daclatasvir	Tab	Daklinza®	30 mg , 60 mg

Combination Products (Double products)			
Sofosbuvir + Ledipasvir	Tab	Harvoni®, Ledifos ® Hetrosofir Plus®	400 mg + 90 mg
Sofosbuvir + Velpatasvir	Tab	Epclusa®, Velasof®	400 mg + 100 mg
Sofosbuvir + Simeprevir	Tab	Olysova®	400 mg + 150 mg
Sofosbuvir + Daclatasvir	Tab	Sovodak®	400 mg + 60 mg
Elbasvir + Grazoprevir	Tab	Zepatier®	50 mg + 100 mg
Glecaprevir + Pibrentasvir	Tab	Mavyret®	100 mg + 40 mg

Combination Products (Triple & Quadrant products)			
Sofosbuvir + Velpatasvir + Voxilaprevir	Tab	Vosevi®	400 mg + 100 mg + 100 mg
Ombitasvir + Paritaprevir + Ritonavir	Tab	Technivie® , Qurevo®	12.5 mg + 75 mg + 50 mg
Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir	Tab	Veikira XR®, Viekira Pak®	8.33 mg + 50 mg + 33.33 mg + 200 mg
Pegylated interferons			
Peg-Interferon Alfa-2a	Vial	Pegasys®	180 mcg/ml (single use)
	Prefilled Inj.		180 mcg/0.5 ml (single use)
Peg-Interferon Alfa-2b	Inj. Powder	Sylatron®	444 mcg/vial , 888 mcg/vial
	Prefilled Inj.	PEG Intron®	80 mcg , 120 mcg , 180 mcg

D. Hepatitis D:

HDV is transmitted through percutaneous or mucosal contact with infectious blood, it is an incomplete virus that requires the helper function of HBV to replicate and only occurs in people infected with HBV.

- There is no vaccine for HDV.
- Treatment by **Pegylated Interferon-Alfa.**

E. Hepatitis E:

HEV is spread by the fecal–oral route, HEV usually results in a self-limited, acute illness.

- Hepatitis E **usually resolves on its own**, treatment is supportive (rest, fluids).

Fifth: Respiratory syncytial virus (RSV)

1. it's a common respiratory virus that usually causes mild, cold-like symptoms, most people recover in a week or two, but RSV can be serious, especially for infants and older adults.
   - RSV is the most common cause of **bronchiolitis**, **pneumonia**, and **middle ear infections** in children younger than 1 year of age.
   - The virus can spread through both direct and indirect contact with secretions from people with the infection.
2. **Ribavirin** is licensed for **administration by inhalation** for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases.
3. **Palivizumab** is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease (e.g. those with chronic lung disease, congenital heart disease)

Scientific name	Dosage form	Trade name	concentration
Palivizumab	Inj. powder	Synagis®	100 mg/ml
Ribavirin	Tab , Cap	Rebetol® , Virazole®	200 mg , 400 mg , 600 mg
	Inhale Solu.		6 gm per vial

Sixth: human immunodeficiency virus (HIV)

a. The disease **AIDS (acquired immune deficiency syndrome)** is caused by infection with the human immunodeficiency virus **(HIV)**, this virus invades certain cells of the immune system, particularly the white blood cells called T-helper lymphocytes (or CD4 cells), which normally activate other immune cells to fight infection.

b. HIV kills T-helper lymphocytes, so that the body cannot fight the virus or subsequent infections, in recent years the number of drugs to treat HIV has increased considerably, as well as knowledge about how best to use them in combination.
- **Current treatment for HIV is not a curative**, but it can keep HIV under control very effectively and prevent it from spreading to others.
- Although, several cases around the world had a 100% cure form HIV (google it).

1. Drugs that act directly against HIV are called **antiretrovirals**; the most common groups work by **interfering with enzymes vital for virus replication.**

a) The first group inhibit an enzyme called **reverse transcriptase**, they are divided according to their chemical structure into **nucleoside inhibitors**, and **non-nucleoside inhibitors.**
- **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)** are analogs of the naturally occurring deoxynucleotides needed to synthesize the viral DNA, and they compete with them for incorporation into the growing viral DNA chain (NRTIs act as a chain terminators).
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** binds directly at an allosteric hydrophobic site adjacent to the active site, inducing a conformational change that results in enzyme inhibition and blocks viral dependent DNA polymerase activity; unlike the NRTIs, NNRTIs neither compete with nucleoside triphosphate nor require phosphorylation to be active.

b) The second group interfere with an enzyme called **protease (protease inhibitors)**.
- They prevent viral replication by selectively binding to viral protease and blocking proteolytic cleavage of protein precursors that are necessary for the production of viral particles.

c) **Entry, or fusion, inhibitors**, interfere with the entry of the virus into the cell.
- HIV attachment to the host cell entails binding of the viral envelope glycoprotein complex to the cellular receptor CD4, this binding induces conformational changes that enable access to the chemokine receptors CCR5, chemokine receptor binding induces further conformational changes leading to fusion of the viral envelope with the host cell membrane and subsequent entry of the viral core into the cellular cytoplasm.

d) **Integrase inhibitors** prevents the virus from injecting its genetic material into cell nucleus.
- Also called Integrase strand transfer inhibitors (INSTIs), works by inhibiting the insertion of viral DNA into the host cell DNA.

e) Other drugs to target the receptor sites the virus relies on for entry into cells; **Chemokine co-receptor antagonists (CCR5 antagonists).**

2. Antiretrovirals are much more effective in combination, treatment usually starts with two nucleoside transcriptase inhibitors plus a non-nucleoside drug or protease inhibitor.

3. The regimens of choice contain **Tenofovir** and **Emtricitabine** combined with either:
- (Efavirenz) or (Ritonavir + Atazanavir) or (Ritonavir + Darunavir) or (Raltegravir).

4. Alternative regimens contain **Abacavir** and **Lamivudine** combined with either:
- (Lopinavir + Ritonavir) or (Ritonavir + Fosamprenavir) or (Nevirapine) or (Rilpivirine).

5. New York state department of health AIDS institute (NYSDOH AI) recommends:
- Tenofovir + (Emtricitabine or Lamivudine) + (Raltegravir or Dolutegravir)

Scientific name	D. form	Trade name	concentration
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)			
Abacavir	Tab	Ziagen®	300 mg
Lamivudine	Tab	Epivir® , Zeffix®	100 mg , 150 mg , 300 mg
Zidovudine	Tab	Retrovir®	300 mg
	Cap		100 mg
	Inj. Solu.		10 mg/ml
Emtricitabine	Cap	Emtriva®	200 mg
Zalcitabine	Tab	Hivid®	0.375 mg , 0.750 mg
Tenofovir (fumarate)	Tab	Viread®	150 mg , 300 mg
Tenofovir (alafenamide)	Tab	Vemlidy®	25 mg
Didanosine	Cap	Videx®	125 mg , 250 mg , 400 mg
Stavudine	Cap	Zerit®	15 mg , 20 mg , 30 mg
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Efavirenz	Tab	Sustiva®	600 mg
	Cap		200 mg
Doravirine	Tab	Pifeltro	100 mg
Etravirine	Tab	Intelence®	100 mg , 200 mg
Nevirapine	Tab, Tab ER	Viramune®	200 mg , 400 mg (ER tab)
Rilpivirine	Tab	Edurant®	25 mg
Delavirdine	Tab	Rescriptor®	100 mg , 200 mg
Protease inhibitors			
Ritonavir	Tab , Cap	Norvir®	100 mg
Atazanavir	Cap	Reyataz®	100 mg , 200 mg , 300 mg
Darunavir	Tab	Prezista®	400 mg , 600 mg , 800 mg
Amprenavir	Cap	Agenerase®	50 mg , 150 mg
	Oral Solu.		15 mg/ml (240 ml solu.)
Fosamprenavir	Tab	Lexiva®	700 mg
Tipranavir	Cap	Aptivus®	250 mg
Nelfinavir	Tab	Viracept®	250 mg , 625 mg
Indinavir	Cap	Crixivan®	200 mg , 400 mg
Saquinavir	Tab	Invirase®	500 mg
Entry inhibitors (Fusion inhibitors)			
Enfuvirtide	Inj. powder	Fuzeon®	90 mg/ml
Ibalizumab	Inj. Solu.	Trogarzo®	200 mg/1.33 ml
Integrase inhibitors			
Dolutegravir	Tab	Tivicay®	50 mg
Elvitegravir	Tab	Vitekta®	150 mg
Raltegravir	Tab	Isentress®	400 mg , 600 mg
Bictegravir	Tab	Bikta®	50 mg
Cabotegravir	(pending FDA approval)		
Chemokine co-receptor antagonists (CCR5 antagonists)			
Maraviroc	Tab	Selzentry®	150 mg , 300 mg

Double Combination Products			
Scientific name	D. form	Trade name	concentration
Abacavir + Lamivudine	Tab	Epzicom®	600 mg + 300 mg
Lamivudine + Zidovudine	Tab	Combivir®	150 mg + 300 mg
Lamivudine + Raltegravir	Tab	Dutrebis®	150 mg + 300 mg
Lamivudine + Tenofovir	Tab	Cimdue® , Temixys®	300 mg + 300 mg
Emtricitabine + Tenofovir	Tab	Truvada® , Descovy®	200 mg + 300 mg
Dolutegravir + Rilpivirine	Tab	Juluca®	50 mg + 25 mg
Dolutegravir + Lamivudine	Tab	Dovato®	50 mg + 300 mg
Atazanavir + Cobicistat *	Tab	Evotaz®	300 mg + 150 mg
Darunavir + Cobicistat *	Tab	Prezcobix®	800 mg + 150 mg
Lopinavir + Ritonavir	Tab	Kaletra®	200 mg + 50 mg

Triple Combination Products			
Abacavir + Lamivudine + Zidovudine	Tab	Trizivir®	300 mg + 150 mg + 300 mg
Abacavir + Dolutegravir + Lamivudine	Tab	Triumeq®	600 mg + 50 mg + 300 mg
Efavirenz + Emtricitabine + Tenofovir	Tab	Atripla®	200 mg + 600 mg + 300 mg
Efavirenz + Lamivudine + Tenofovir	Tab	Symfi®	600 mg + 300 mg + 300 mg
Doravirine + Lamivudine + Tenofovir	Tab	Delstrigo®	100 mg + 300 mg + 300 mg
Emtricitabine + Rilpivirine + Tenofovir	Tab	Complera®, Odefsey®	200 mg + 25 mg + 300 mg
Bictegravir + Emtricitabine + Tenofovir	Tab	Biktarvy®	50 mg + 200 mg + 25 mg

Quadruple Combination Products			
Darunavir + Cobicistat * + Emtricitabine + Tenofovir	Tab	Symtuza®	800 mg + 150 mg + 200 mg + 10 mg
Elvitegravir + Cobicistat * + Emtricitabine + Tenofovir	Tab	Stribild®, Genvoya®	150 mg + 150 mg + 200 mg + 10 mg

* **Cobicistat** is a CYP3A inhibitor, its added as a **pharmacokinetic enhancer** for other HIV treatments.
** **Tenofovir** and **Lamivudine** are also used in the **treatment of hepatitis B virus**.

5.4- Anthelmintics (drugs used for worms)

1. Anthelmintics are drugs that are used to eliminate the many types of worm (**helminths**) that can enter the body and live there as parasites, producing a general weakness in some cases and serious harm in others, most species spend part of their life cycle in another animal, and the infestation is often passed on to humans in food contaminated with the eggs or larvae; in some cases, such as hookworm, larvae enter the body through the skin; Larvae or adult worm may attach themselves to the intestinal wall and feed on the bowel contents; others feed off the intestinal blood supply, causing anemia, worms can also infest the bloodstream or lodge in the muscles or internal organs.
   - Body's **natural defences** against infection are **not effective against most worm infestations.**
   - Doctors may recommend anthelmintic **treatment for the whole family to prevent reinfection.**
   - If worms have invaded tissues and formed cysts, they may have to be **removed surgically.**
   - **Laxatives** are given with some Anthelmintics to hasten expulsion of worms from the bowel.

Types of infestation

1. **Threadworm (enterobiasis):** The most common worm infection in Iraq, especially among young children, the worm lives in the intestine but travels to the anus at night to lay eggs, causing itching; scratching leaves eggs on the fingers, usually under the fingernails; sucking the fingers or eating food with unwashed hands often transfers these eggs to the mouth, keeping the nails short; good hygiene, including washing the hands after using the toilet and before each meal; and an early morning bath to remove the eggs are important in eradicating the infection.
   - Drugs of choice: Mebendazole, all members of the household should be treated simultaneously.
2. **Common roundworm (ascariasis):** The most common worm infection worldwide, it is transmitted to humans in contaminated raw food or in soil, the worms are large, and they infect the intestine, which can be blocked by dense clusters of them.
   - Drugs of choice: Levamisole, Mebendazole
3. **Tropical threadworm (strongyloidiasis):** Occurs in the tropical areas; The larvae from contaminated soil penetrate the skin, pass into the lungs, are swallowed, and pass into the gut.
   - Drugs of choice: Albendazole, Tiabendazole, Ivermectin
4. **Whipworm (trichuriasis)**: Mainly occurs in tropical areas of the world as a result of eating contaminated raw vegetables, the worms infest the intestines
   - Drug of choice: Mebendazole
5. **Hookworm (uncinariasis):** Mainly found in tropical areas, the worm larvae penetrate the skin and pass via the lymphatic system and bloodstream to the lungs; They then travel up the airways, are swallowed, and attach to the intestinal wall, where they feed off the intestinal blood supply.
   - Drug of choice: Mebendazole
6. **Pork roundworm (trichinosis):** Transmitted in infected undercooked pork; Initially, the worms lodge in the intestines, but larvae may invade muscle to form cysts that are often resistant to drug treatment and may require surgery.
   - Drugs of choice: Mebendazole, Tiabendazole
7. **Toxocariasis (visceral larva migrans):** Usually occurs as a result of eating soil or eating with fingers contaminated with dog or cat feces, the eggs hatch in the intestine and may travel to the lungs, liver, kidney, brain, and eyes; Treatment is not always effective.
   - Drugs of choice: Mebendazole, Tiabendazole, Diethylcarbamazine
8. **Creeping eruption (cutaneous larva migrans):** Mainly occurs in tropical areas and coastal areas as a result of skin contact with larvae from cat and dog feces, Infestation is usually confined to the skin.
   - Drugs of choice: Tiabendazole, Ivermectin, Albendazole
9. **Filariasis (including onchocerciasis and loiasis):** Occurs in tropical areas only, it may affect the lymphatic system, blood, eyes, and skin; Infection by this group of worms is spread by the bites of insects that are carriers of worm larvae or eggs.
   - Drugs of choice: Diethylcarbamazine, Ivermectin, Moxidectin.

10. **Flukes, Sheep liver fluke (fascioliasis)**: Infestation usually results from eating watercress grown in contaminated water, it mainly affects the liver and biliary tract, other flukes only found abroad may infect the lungs, intestines, or blood; Drug of choice: Praziquantel, Triclabendazole.
11. **Tapeworms (including beef, pork, fish, and dwarf tapeworms):** Depending on the type, worms may be carried by cattle, pigs, or fish and transmitted to humans in undercooked meat, most types affect the intestines; Larvae tapeworm may form cysts in muscle and other tissues.
    - Drugs of choice: Niclosamide, Praziquantel
12. **Hydatid disease (echinococciasis):** The eggs are transmitted in dog feces, and the larvae may form cysts over many years, commonly in the liver; Surgery is the usual treatment for cysts.
    - Drug of choice: Albendazole
13. **Bilharzia (schistosomiasis):** Occurs in polluted water in tropical areas; The larvae may be swallowed or penetrate the skin and once inside the body, they migrate to the liver; adult worms live in the bladder; Drug of choice: Praziquantel

Notes:

1. The most common Anthelmintic drugs available are **Mebendazole** and **Albendazole.**
2. For the treatment of **Pinworms** (Enterobius vermicularis):
   a. **Mebendazole** is the drug of choice for treating threadworm infection in patients of all ages over 2 years**, it is given as a single dose of 100 mg**; as reinfection is very common, **a second dose (100 mg) should be given after 2 weeks**.
   b. **Albendazole** maybe also given as a **single dose of 400 mg**; as reinfection is very common, **a second dose (400 mg) should be given after 2 weeks**.
3. In the treatment of **Echinococcosis (hydatid disease)**, **Albendazole** is given orally with meals in a dose of **400 mg twice daily for 28 days,** the 28-day course may be repeated after 14 days without treatment **(treatment may need to continue for months or years)**.
4. **Mebendazole** is effective against **Ascaris Lumbricoides** and is generally considered to be the drug of choice; **the usual dose is 100 mg twice daily for 3 days**.

Scientific name	Dosage form	Trade name	concentration
Mebendazole	Tab	Vermox®	100 mg
	Oral Susp.		2% (20 mg/ml) , 30 ml
Albendazole	Tab	Zental®, Albenza®	200 mg , 400 mg
	Oral Susp.		200 mg/5 ml
Levamisole	Tab	Katrex®	40 mg
Tiabendazole	Tab, Susp.	Mintezol®	500 mg (tab) , 500 mg/5 ml
Flubendazole	Tab, Susp.	Fluvermal® , Flub®	100 mg , (20 mg/ml)
Pyrantel pamoate	Cap	Pin Rid®	180 mg
	Oral Susp.	Pin X®	250 mg/5 ml
Diethylcarbamazine	Tab	Hetrazan®	200 mg , 400 mg
Niclosamide	Tab	Yomesan® , Niclon®	500 mg
Ivermectin	Tab	Scav®, Gmtcin®	6 mg , 12 mg
Moxidectin	Tab	----------	2 mg
Praziquantel	Tab	Biltricide®	600 mg
Triclabendazole	Tab	Egaten®	250 mg

1. **About Mebendazole:** [3]
   a. **contraindicated in pregnant women,** also Myelosuppression (neutropenia and thrombocytopenia) can occur with high doses as in (40 to 50 mg/kg/day).
   b. Several studies show Mebendazole exhibits potent antitumor properties, it significantly inhibited cancer cell growth, migration and metastatic formation of adrenocortical carcinoma, both in vitro and in vivo.
   c. From December 2011, it is no longer available from any manufacturer in the USA, and no reason was given publicly for this discontinuation.

2. **About Albendazole:** [3]
   a. **contraindicated in pregnant women**
   b. should be administered with a fatty meal to achieve optimal absorption
   c. Side effects include: Hepatotoxicity, which occurs in 16% of patients; liver function tests every 2 weeks are recommended while taking Albendazole.
3. **Tiabendazole** (or **Thiabendazole –** they are the same drug); is used to treat roundworm hookworm and Toxocariasis.
4. **Pyrantel** causes a spastic paralysis of the helminth, (not death).
5. **Diethylcarbamazine** is used for the treatment of Bancroft's Filariasis, onchocerciasis, ascariasis and loiasis, **but has severe allergic phenomena in conjunction with a skin rash**.
6. **Ivermectin** is often favored over **Diethylcarbamazine** due to its less severe adverse effects.
   a. It's the drug of choice for the treatment of onchocerciasis (river blindness).
   b. Contraindicated in patients with meningitis and in pregnancy.
   c. It can be **used in Scabies** (taken as two doses, 200µg/kg/dose, one week apart)
7. **Moxidectin**, was once used only in animals, but FDA approved its use for **Onchocerciasis** (river blindness) in humans, dosed 8 mg (4 tabs) as a single dose.
8. **Praziquantel** may impair activities that require mental alertness.
   a. Treatment of ocular cysticercosis (in the eye) is contraindicated because parasite destruction within the eyes may cause irreparable lesions.

5.5- Antiprotozoal drugs

Protozoa are single-celled organisms that are present in soil and water, they may be transmitted to or between humans via contaminated food or water, sexual contact, or insect bites.

- There are many types of protozoal infection, each of which causes a different disease, depending on the organism involved; **Trichomoniasis**, **Toxoplasmosis**, **Cryptosporidium**, **Giardiasis**, and **Pneumocystis Pneumonia** are the most common protozoal infections.

First: Amebicides (for the treatment of Amebiasis and Giardiasis)

- **Amebiasis** (caused by Entameba histolytica), or **Amebic dysentery**, is an infection of the bowel (and sometimes the liver and other organs), usually transmitted in contaminated food or water; Its major symptom is violent, sometimes bloody diarrhea, treatment is with Diloxanide, Metronidazole, or Tinidazole.
- **Giardiasis** (caused by Giardia lamblia), or **Lambliasis**, affects the bowel and is usually transmitted in contaminated food or water; but it may also be spread by some types of sexual contact, its major symptoms are generalized ill-health, diarrhea, flatulence, and abdominal pain, treatment is with Mepacrine, metronidazole, or Tinidazole.

1. **Amebicides** include: **Metronidazole, Tinidazole** (discussed previously in section1 part14), **Diloxanide Furoate, Iodoquinol, Nitazoxanide, Paromomycin, Quinacrine (Mepacrine).**

2. **Diloxanide Furoate** is a **luminal Amebicide** acting principally in the bowel lumen and is used in the treatment of intestinal Amebiasis.
   a. Diloxanide is considered second-line agent.
   b. It is given alone in the treatment of asymptomatic cyst passers (patients with E. histolytica cysts in the feces)
   c. Diloxanide is **not effective as single-agent therapy for extra intestinal Amebiasis.**
   d. **Given with an Amebicide** that acts in the tissues, such as metronidazole, in patients with **invasive Amebiasis** [1, 2] and the usual **course is of 10 days**.
   e. **Flatulence** is the most common adverse effect during treatment with Diloxanide Furoate

Scientific name	D. form	Trade name	concentration
Diloxanide Furoate	Tab	Furamide®	250 mg , 500 mg
Iodoquinol	Tab	Yodoxin®	210 mg , 650 mg
Nitazoxanide	Tab	Alinia®	500 mg
	Susp.	Nanazoxid®	100 mg/5 ml
Paromomycin	Cap	Humatin®	250 mg
Quinacrine **Or** Mepacrine	Tab	Calbiochem ®	100 mg
Furazolidone	Tab	Furoxone® , Furazol®	100 mg
	Susp.	Furazon®	50 mg/15 ml

Notes:

1. **Iodoquinol** may produce optic neuritis or atrophy or peripheral neuropathy with high-dose, long-term use.
2. **Nitazoxanide** may cause abdominal pain, diarrhea, vomiting, headache, flatulence, fever, eye discoloration, rhinitis, and discolored urine
3. **Paromomycin is an aminoglycoside antibiotic** indicated for acute and chronic intestinal Amebiasis; **it is not useful for extra-intestinal Amebiasis because it is not absorbed.**
   a. It is also effective against enteric bacteria **Salmonella** and **Shigella.**
   b. Paromomycin may cause nausea, cramping, and diarrhea at high doses (≥ 3g/day).
   c. Inadvertent absorption through ulcerative bowel lesions may result in ototoxicity or renal damage
4. **Quinacrine** (also called **Mepacrine –** they are the same drug) should be administered with extreme caution in patients with psoriasis because it may cause exacerbation of this disease.
5. **Furazolidone** is also used to treat diarrhea and enteritis caused by bacteria or protozoan infections, it has been used to treat traveler's diarrhea, cholera and bacteremic salmonellosis.

Combination products:

Scientific name	Dosage form	Trade name	concentration
Diloxanide Furoate + Metronidazole	Tab	Dilazole® , Di-Nidazole®	(250 mg + 200 mg), (500 mg + 400 mg)
	Susp.		(125 mg + 100 mg) per 5 ml
Diloxanide Furoate + Tinidazole	Tab	Tinidafyl plus®	(250 mg + 300 mg)

Second: Drugs for Toxoplasmosis

Toxoplasmosis (caused by Toxoplasma gondii), is usually spread via cat feces or by eating undercooked meat, although usually symptomless, toxoplasmosis may cause generalized ill-health, mild fever, and eye inflammation.

- Treatment is usually with **Pyrimethamine** with **Sulfadiazine**, or with azithromycin, clarithromycin, or clindamycin/Spiramycin (during pregnancy).

1. Congenital toxoplasmosis is not a problem in women who have Toxoplasma antibody before conception, but **if toxoplasmosis is acquired in pregnancy, it may transfer to the baby, transplacental infection may lead to severe disease in the fetus**.

2. The medications prescribed for acute toxoplasmosis are:
   a) **Pyrimethamine** — an antimalarial medication.
   b) **Sulfadiazine** — an antibiotic used in combination with **Pyrimethamine**
      - Combination therapy is usually **given with folic acid supplements** to reduce the incidence of thrombocytopenia.
      - Combination therapy is most useful in the setting of HIV.

c) **Clindamycin.** (see above, section 1, part 9)
d) **Spiramycin** — an antibiotic used **for pregnant women** to prevent the infection of their children **(reduce the risk of transmission of maternal infection to the fetus)** [1].
e) **Atovaquone** — an antimalarial that has been used to kill Toxoplasma cysts inside AIDS patients, (Clindamycin in combination with Atovaquone, seemed to optimally kill cysts).
f) **Dapsone** — anti-Leprosy drug. (see above, section 1, part 12)

3. Other antibiotics, such as **minocycline**, have seen some use as a salvage therapy.
4. **In people with latent toxoplasmosis, the cysts are immune to these treatments**, as the antibiotics do not reach the bradyzoites in sufficient concentration, thus it's preferable to use **Atovaquone.**

Scientific name	Dosage form	Trade name	concentration
Pyrimethamine	Tab	Daraprim®	25 mg
Sulfadiazine	Tab	Lantrisul® , Neotrizine®	500 mg
Spiramycin	Tab	Rovamycin®	1.5 & 3 million I.U
	Cap		250 mg , 500 mg , 1 gm
	Inj.		500 mg , 1 gm
	Supp.		250 mg , 500 mg
Atovaquone	Tab	Mepron®	250 mg

Notes:

1. **Pyrimethamine** is contraindicated in **Megaloblastic anemia** (it is classified as a **folic acid antagonist**; It works by inhibiting folic acid metabolism and therefore the making of DNA).
   - It was previously used for malaria but is no longer recommended due to resistance.
   - It's also used with Dapsone as a second-line option to prevent Pneumocystis jirovecii pneumonia
2. **Spiramycin is still considered an experimental drug in the USA**, but can sometimes be obtained by special permission from the FDA for toxoplasmosis in the first trimester of pregnancy, **however it has been used in Europe since the year 2000, where it is mostly marketed to dentists for mouth infections.**
3. **Atovaquone** oral absorption significantly increases when administered with food (especially a high-fat meal), **it is also used for:**
   a. For **pneumocystis pneumonia (PCP)**, or **pneumocystosis**, Caused by P. jirovecii.
   b. For **babesia** (protozoan parasites of the blood that causes a hemolytic disease), it is often used in conjunction with oral azithromycin.

Combination Products:

Scientific name(s)	Dosage form	Trade name	concentration
Pyrimethamine + Sulfadoxine	Tab	Fansidar®	25 mg + 500 mg
Spiramycin + Metronidazole	Tab	Rodogyl®	750,000 I.U. + 125 mg
Atovaquone + Proguanil	Tab	Malarone®	250 mg + 100 mg

Third: Drugs for Leishmaniasis (Leishmaniacides)

Leishmaniasis (caused by Leishmania), or called **Kala-azar**, is a mainly tropical and subtropical disease caused by organisms spread through sand fly bites, it affects the mucous membranes of the mouth, nose, and throat and may, in its severe form, invade organs such as the liver.

1- There are three types of Leishmaniasis: cutaneous, mucocutaneous, and visceral.

a) **Cutaneous** is the most common form of Leishmaniasis; which causes skin ulcers.
b) **Mucocutaneous** Leishmaniasis causes ulcers in skin, mouth and nose.
c) **Visceral** is a severe form in which the parasites migrate to the vital organs; causing skin ulcers, fever, low red blood cells and enlarged spleen and liver.

2- Drugs for Leishmaniasis include:

a) **Sodium Stibogluconate**; is used for visceral Leishmaniasis (kala-azar) and for extensive Cutaneous Leishmaniasis; it is given by injection (usually I.M) **20mg/kg/day** for 28 days in visceral Leishmaniasis and for 20 days in cutaneous infection.
   - I.V injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain occur; Injection should be filtered immediately before administration using a filter of 5 microns or less.
   - Serious side effect may include an irregular heartbeat or pancreatitis

b) **Meglumine antimoniate** is a pentavalent antimony compound with properties similar to sodium stibogluconate; it should not be used in people with significant heart, liver, or kidney problems.

c) **Miltefosine, it should not be used in the pregnancy** or in the case of children below 2 years of age.

d) **Pentamidine** and **Amphotericin B** is also used as backup agents in the treatment of Leishmaniasis, **Allopurinol** has also been reported to be effective.

Scientific name	D. Form	Trade name	concentration
Sodium Stibogluconate	Inj. Solu.	Pentostam®	100 mg Sb/ml
Meglumine Antimoniate	Inj. Solu. (amp)	Glucantim®	1.5 gm/5 ml
Miltefosine	Cap	Impavido® , Miltex®	50 mg
Pentamidine	Inj. Powder	Pentam®	300 mg
	Inhale Powder	NebuPent®	300 mg

Notes:

1. **Miltefosine** was originally developed as an antineoplastic (and licensed for topical use), then it was used as an antiprotozoal drug.
   a. **Has antifungal activity,** especially against metronidazole-resistant variants of Trichomonas vaginalis, (a sexually transmitted protozoal disease).
   b. It is also under investigation as a **potential therapy against HIV infection.**
   c. Has exhibited **teratogenicity**, and **should not be administered to pregnant women,** adequate methods of contraception are advised during therapy and **for 5 months after**.

2. **Pentamidine** is active against a variety of protozoal infections, including:
   a. For **Trypanosomiasis.**
   b. For **pneumocystis pneumonia (PCP),** or **pneumocystosis**, Caused by P. jirovecii.
   c. For **babesia** (protozoan parasites of the blood that causes a hemolytic disease).

Side effects of Pentamidine include: Nephrotoxicity, **bronchospasm, and cough** are produced by intravenous or inhaled Pentamidine; **severe hypotension** may occur after a parenteral dose, cardiorespiratory arrest can occur after a single rapid infusion of the drug.

- **Hypoglycemia** may occur with initial administration of drug via the IV, IM, or inhalational route. After the patient has been on the drug for a period, hyperglycemia will result. The effect of the drug may actually induce a reversible insulin-dependent diabetes mellitus.

Fourth: Drugs for Trypanosomiasis

1- There are two types of **Trypanosomiasis:**

a) African Trypanosomiasis (or called **sleeping sickness**)**,** is spread by the **tsetse fly** and causes fever, swollen glands, and drowsiness; the parasite invades the CNS, causing an inflammation of the brain and spinal cord that produces the characteristic lethargy and eventually, continuous sleep.

- **Sleeping sickness** is treated with Pentamidine, Suramin, Eflornithine, or Melarsoprol.

b) South American Trypanosomiasis (or called **Chagas disease**) is spread by **assassin bugs** and causes inflammation, enlargement of internal organs, and infection of the brain, it is caused by T. Cruzi

- **Chagas disease** is treated with Primaquine or Nifurtimox**.**

Scientific name	Dosage form	Trade name	concentration
Benznidazole	Tab	Radanil® , Rochagan®	100 mg
Melarsoprol	Inj. Solu. (I.V)	Arsobal®	180 mg/5 mL
Nifurtimox	Tab	Lampit®	30 mg , 120 mg
Primaquine	Tab	Primaquine®	26.3 mg
Pentamidine	Inj. Powder	Pentam®	300 mg
	Inhale Powder	NebuPent®	300 mg
Suramin	Inj. Powder	Germanin®	1 gm (to get 100 mg/ml)
Eflornithine	Inj. Solu.	Ornidyl®	200 mg/ml

Notes:

1. **Melarsoprol** is a toxic organic compound of arsenic, it is a highly dangerous treatment which is only administered by injection under the supervision of a physician, as it can produce similar effects as arsenic poisoning, it is known to cause a range of side effects including convulsions, fever, loss of consciousness, rashes, bloody stools, nausea, and vomiting. It is fatal in and of itself in around 8% of cases.
2. **Pentamidine** is discussed in details above.
3. **Suramin** adverse reactions include shock and loss of consciousness; acute urticaria; and neurologic problems, including paresthesia, photophobia, palpebral edema (edema of the eyelids), and hyperesthesia of the hands and feet.
4. **Eflornithine** causes Myelosuppression, Seizures occur in about 8% of treated patients.
   - **Available as a topical** product for the treatment of **Hirsutism.**

Fifth: Drugs for Balantidiasis and Cryptosporidiosis

A) Balantidiasis (caused by Balantidium coli) is an infection of the bowel, specifically the colon, that is usually transmitted through contact with infected pigs. Possible symptoms include diarrhea and abdominal pain.

- Treatment of the infection is with tetracycline, metronidazole, Tinidazole or diodohydroxyquinoline.

B) Cryptosporidiosis (caused by Cryptosporidium) affects the bowel (and occasionally the respiratory tract and bile ducts); Cryptosporidiosis is spread through contaminated food or water or by contact with animals or other humans, symptoms include severe diarrhea and abdominal pain.

- there are no specific drugs to treat it, but Paromomycin, azithromycin, or Eflornithine may be effective.

Sixth: Drugs for Pneumocystis Pneumonia

Caused by (Pneumocystis jirovecii), it is a potentially fatal lung infection usually affecting only people with reduced resistance to infection, symptoms include fever, cough, breathlessness, and chest pain; Treatment is with drugs such as Atovaquone, co-trimoxazole, Pentamidine, and Dapsone with trimethoprim.

Seventh: Drugs for Trichomoniasis

Caused by (Trichomonas vaginalis); which most often affects the vagina, causing irritation and an offensive discharge, also can cause infection in men, it may occur in the urethra; It is usually sexually transmitted and Treatment is with Metronidazole or Tinidazole.

Eighth: Drugs for Malaria (Antimalarial Drugs)

1. Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium. The parasite is transmitted to humans through the bite of a female Anopheles mosquito, which thrives in humid, swampy areas.

- Transferred to humans in the saliva of the female mosquito as she penetrates ("bites") the skin, the malaria parasite enters the bloodstream and settles in the liver, where it multiplies asexually; then following its stay in the liver, the parasite (or plasmodium) enters another phase of its life cycle, circulating in the bloodstream, penetrating and destroying red blood cells, and reproducing again.
- If the plasmodia, then transfer back to a female Anopheles mosquito via another "bite", they breed sexually, and are again ready to start a human infection.

2. Malaria is a Disease that is characterized by persistent high fever, orthostatic hypotension, and massive erythrocytosis (an abnormal elevation in the number of red blood cells accompanied by swollen, reddish limbs), which can lead to capillary obstruction and death.

3. Major and common antimalarial drugs include: **Chloroquine, Hydroxychloroquine, Primaquine, Pyrimethamine, Quinine,** and **Mefloquine**, in addition to combination brands.

- They can be classified as follows:

Available Antimalarials	
Drugs used for malaria prophylaxis	**Drugs used for treatment of malaria**
1- Atovaquone + Proguanil 2- Chloroquine phosphate 3- Doxycycline 4- Hydroxychloroquine 5- Mefloquine 6- Primaquine 7- Sulfadoxine + Pyrimethamine	1- Artesunate 2- Artemether + Lumefantrine 3- Atovaquone + Proguanil 4- Chloroquine 5- Clindamycin, Doxycycline 6- Hydroxychloroquine 7- Mefloquine 8- Primaquine 9- Quinidine 10- Quinine

Scientific name	Dosage form	Trade name	concentration
Chloroquine	Tab	Aralen®	250 mg , 500 mg
Hydroxychloroquine	Tab	Plaquenil®	200 mg
Primaquine	Tab	Primaquine®	26.3 mg
Amodiaquine	Tab	ADQ	200 mg
	Oral Susp.		50 mg/5 ml
Halofantrine	Tab	Halfan	250 mg
	Oral Susp.		100 mg/5 ml

Pyrimethamine	Tab	Daraprim®	25 mg
Quinine	Cap	Qualaquin®	324 mg
Mefloquine	Tab	Lariam®	250 mg
Tafenoquine	Tab	Krintafel® , Arakoda®	150 mg , 100 mg
Artemisinin	Tab , Cap	----------	200 mg

Other Antimalarial (rarely used)

Scientific name	Dosage form	Trade name	concentration
Artemether	Tab	Artenam®	50 mg
	Inj. Solu.		100 mg/ml
Artesunate	Inj. Powder	Artesunate®	60 mg/vial
Atovaquone	Tab	Mepron®	250 mg
Proguanil	Tab	Paludrine®	200 mg
Quinidine *	Tab	Quinidex®	200 mg , 300 mg
	Oral Syrup	Quinaglute®	10 mg/ml

*** Quinidine is also an anti-arrhythmic.**

Combination Products for Malaria:

Scientific name(s)	D. form	Trade name	concentration
Pyrimethamine + Sulfadoxine	Tab	Fansidar®	25 mg + 500 mg
Piperaquine + Dihydroartemisinin	Tab	Demoque®	320 mg + 40 mg
Atovaquone + Proguanil	Tab	Malarone®	250 mg + 100 mg
Artemether + Lumefantrine	Tab	Coartem®	20 mg + 120 mg
Artesunate + Amodiaquine	Tab	Camoquin®	200 mg + 600 mg
Artesunate + Mefloquine	Tab	Artequin®	(600 mg + 750 mg) Adult, (300 mg + 375 mg) Child
Sulfamethoxypyrazine + Artesunate + Pyrimethamine	Tab	Asu-Denk®	500 mg + 200 mg + 25 mg

References

1- BNF 82.
2- Sean C. Sweetman, Martindale: The Complete Drug Reference, 38th Edition.
3- Lexi-comp: Drug information handbook, 2022 Ed.
4- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition.
5- ACCP Updates in infectious diseases 2020
6- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th Ed.

ENDOCRINE SYSTEM

Chapter Six: Endocrine System

Part One: Introduction

Part Two:

6.1- Diabetes Mellitus

1. Oral Antidiabetics
2. Insulin's
3. Other anti-diabetic agents
4. Hypoglycemia
5. Hyperglycemic Emergencies

6.2- Thyroid and anti-Thyroid drugs

1. Thyroid hormones
2. Anti-thyroid drugs

6.3- Sex hormones

1. **Female Sex Hormones**
   - **a.** Estrogens
   - **b.** Selective Estrogen Receptor Modulators (SERMs)
   - **c.** Estrogen receptor Antagonists
   - **d.** Anti-Estrogens
   - **e.** Progestogens
     - Progestogens and Estrogens Combinations for CC
     - Progestogens and Estrogens Combinations for HRT
   - **f.** Anti-Progestins and Prostaglandins

6.3- Sex hormones

2. **Male Sex Hormones**
   - **a.** Androgens
   - **b.** Anabolic steroids
   - **c.** Anti-Androgens

3. **Gonadotropins**
   - **a.** Gonadotropin-releasing hormone (GnRH) Analogs
   - **b.** Gonadotropin-releasing hormone (GnRH) Antagonists

6.4- Posterior pituitary hormones

1. Vasopressin, Desmopressin and Oxytocin
2. Vasopressin related drugs: Terlipressin, Conivaptan, Tolvaptan

6.5– Other pituitary hormones

1. Growth Hormone (GH) and its analogs
2. GH inhibiting hormone and its analogs (Octreotide and relatives)
3. Prolactin, Bromocriptine and Cabergoline

6.6- Drugs for Adrenal Gland Disorders

1. Hypersecretory cortisol diseases (Cushing syndrome)
2. Hyperaldosteronism
3. Hyposecretory adrenal disorders

6.7- Bone disorders (Osteoporosis, Osteomalacia)

- **a.** Bisphosphonates
- **b.** Calcium Metabolism Modifiers
- **c.** Vitamin D Analogs

6.8- Calcimimetics

6.9- Other Endocrine drugs

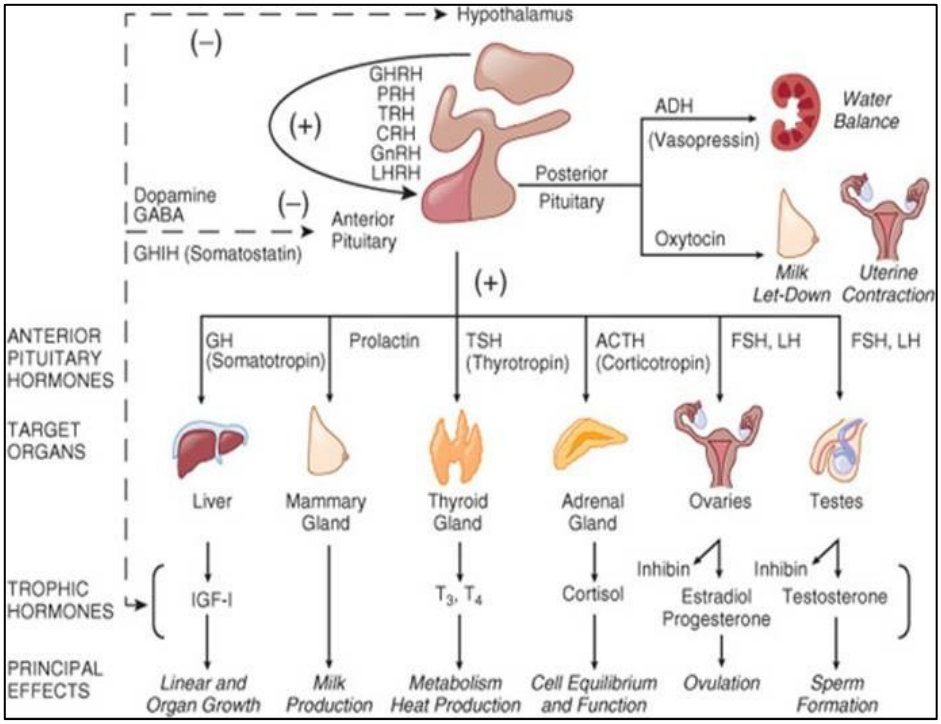
6.10- Rare Drugs used in Rare Metabolic Disorders

Chapter Six: Endocrine system and Hormones

Introduction:

1. The endocrine system is a collection of glands located throughout the body that produce hormones and release them into the bloodstream. Each endocrine gland produces one or more hormones, each of which governs a particular body function, including growth and repair of tissues, sexual development and reproductive function, and the body's response to stress.
   - **The pituitary gland** produces hormones that regulate growth, and sexual and reproductive development, and also stimulate other endocrine glands.
   - **The thyroid gland** regulates metabolism; Hyperthyroidism or hypothyroidism may occur if the thyroid does not function well.
   - **The adrenal glands** produce hormones that regulate the body's mineral and water content and reduce inflammation.
   - **The pancreas** produces insulin to regulate blood glucose levels, and glucagon, which helps the liver and muscles to store glucose.
   - **The kidneys** produce a hormone, erythropoietin, needed for red blood cell production; Patients with kidney failure lack this hormone and become anemic; they may be given Epoetin, a synthetic version of the hormone.
   - **The ovaries** (in women) secrete estrogen and progesterone, responsible for female sexual and physical development.
   - **The testes** (in men) produce testosterone, which controls the development of male sexual and physical characteristics.
2. Most hormones are released continuously from birth, but the amount produced fluctuates with the body's needs, others are produced mainly at certain times – for example, growth hormone is released mainly during childhood and adolescence, while Sex hormones are produced by the testes and ovaries from puberty onwards.
3. Many endocrine glands release their hormones in response to triggering hormones produced by the pituitary gland, this gland releases a variety of pituitary hormones, each of which, in turn, stimulates the appropriate endocrine gland to produce its hormone.
4. A feedback system usually regulates blood hormone levels: if the blood level rises too high, the pituitary responds by reducing the amount of stimulating hormone produced, thereby allowing the blood hormone level to return to normal.

Endocrine disorders, usually resulting in too much or too little of a particular hormone, have a variety of causes. Some are congenital in origin; others may be caused by autoimmune disease (including some forms of diabetes mellitus), malignant or benign tumors, injury, or certain drugs.



Note1: A Partial Listing of the Endocrine Glands

Endocrine Gland	Major Hormones	Primary Target Organs	Primary Effects
Adipose tissue	Leptin	Hypothalamus	Suppresses appetite
Adrenal cortex	Glucocorticoids (mainly cortisol) Mineralocorticoids (mainly aldosterone)	Liver and muscles Kidneys	Glucocorticoids influence glucose metabolism; mineralocorticoids promote Na^+ retention, K^+ excretion
Adrenal medulla	Epinephrine	Heart, bronchioles, and blood vessels	Causes adrenergic stimulation
Heart	Atrial natriuretic hormone	Kidneys	Promotes excretion of Na^+ and water in the urine
Hypothalamus	Releasing and inhibiting hormones	Anterior pituitary	Regulates secretion of anterior pituitary hormones
Small intestine	Secretin and cholecystokinin	Stomach, liver, and pancreas	Inhibits gastric motility and stimulates bile and pancreatic juice secretion
Islets of Langerhans (pancreas)	Insulin Glucagon	Liver, skeletal muscle, and adipose tissue primarily	Insulin promotes cellular uptake of glucose and formation of glycogen and fat; glucagon stimulates hydrolysis of glycogen and fat
Kidneys	Erythropoietin	Bone marrow	Stimulates red blood cell production
Liver	Somatomedins	Cartilage	Stimulates cell division and growth
Ovaries	Estradiol-17β and progesterone	Female reproductive tract and mammary glands	Maintains structure of reproductive tract and promotes secondary sex characteristics
Parathyroid glands	Parathyroid hormone	Bone, small intestine, and kidneys	Increases Ca^{2+} concentration in blood
Pineal gland	Melatonin	Hypothalamus and anterior pituitary	Affects secretion of gonadotrophic hormones
Pituitary, anterior	Trophic hormones	Endocrine glands and other organs	Stimulates growth and development of target organs; stimulates secretion of other hormones
Pituitary, posterior	Antidiuretic hormone Oxytocin	Kidneys and blood vessels Uterus and mammary glands	Antidiuretic hormone promotes water retention and vasoconstriction; oxytocin stimulates contraction of uterus and mammary secretory units, promoting milk ejection
Skin	1,25-Dihydroxyvitamin D_3	Small intestine	Stimulates absorption of Ca^{2+}
Stomach	Gastrin	Stomach	Stimulates acid secretion
Testes	Testosterone	Prostate, seminal vesicles, testes, and other organs	Stimulates secondary sexual development, spermatogenesis, other effects
Thymus	Thymopoietin	Lymph nodes	Stimulates white blood cell production
Thyroid gland	Thyroxine (T_4) and triiodothyronine (T_3); calcitonin	Most organs	Thyroxine and triiodothyronine promote growth and development and stimulate basal rate of cell respiration (basal metabolic rate or BMR); calcitonin may participate in the regulation of blood Ca^{2+} levels

Note2: Conversion of Pre hormones into Biologically Active Derivatives

Endocrine Gland	Prehormone	Active Products	Comments
Skin	Vitamin D_3	1,25-Dihydroxyvitamin D_3	Conversion (through hydroxylation reactions) occurs in the liver and the kidneys.
Testes	Testosterone	Dihydrotestosterone (DHT)	DHT and other 5α-reduced androgens are formed in most androgen-dependent tissue.
		Estradiol-17β (E_2)	E_2 is formed in the brain from testosterone, where it is believed to affect both endocrine function and behavior; small amounts of E_2 are also produced in the testes.
Thyroid	Thyroxine (T_4)	Triiodothyronine (T_3)	Conversion of T_4 to T_3 occurs in almost all tissues.

6.1- Diabetes Mellitus

1. The body obtains most of its energy from glucose, a simple form of sugar made in the intestine from the breakdown of starch and other sugars; **Insulin**, one of the hormones produced in the pancreas, enables body tissues to take up glucose from the blood, either to use it for energy or to store it.
- In diabetes mellitus, there is either a complete lack of insulin or too little is produced, this results in reduced uptake of glucose by the tissues and therefore the glucose level in the blood rises abnormally, a high blood glucose level is known medically as hyperglycemia.
- If diabetes is left untreated, the continuous high blood glucose levels damage various parts of the body, the major problems are caused by reducing the flow of blood, and this can result in heart attacks, blindness, kidney failure, reduced circulation in the legs, and even gangrene.

2. There are two main types of diabetes mellitus:

a) Type 1 (insulin-dependent) diabetes, usually appears in young people, with 50 per cent of cases occurring around the time of puberty.
- The insulin-secreting cells in the pancreas are gradually destroyed, due to either an autoimmune condition (where the body recognizes its pancreas as "foreign" and tries to eliminate it) or a childhood viral infection.
- The decline in insulin production is slow, the condition often appears suddenly, brought on by periods of stress (as infection, puberty) when the body's insulin requirements are high.
- Symptoms of Type 1 diabetes include extreme thirst, increased urination, lethargy, and weight loss. This type of diabetes is fatal if it is left untreated.
- In Type 1 diabetes, insulin treatment is the only treatment option. It has to be continued for the rest of the patient's life.

b) Type 2 diabetes, formerly known as **non-insulin-dependent diabetes mellitus (NIDDM)**, or maturity-onset diabetes, tends to appear at an older age (usually over 40, although it has become increasingly common in younger age groups) and to come on much more gradually – there may be a delay in its diagnosis for several years because of the gradual onset of symptoms.
- In this type of diabetes, the levels of insulin in the blood are usually high; but, the cells of the body are resistant to the effects of insulin and have a reduced glucose uptake despite the high insulin levels, this results in hyperglycemia.
- Obesity is the most common cause of Type 2 diabetes.

3. In both types of diabetes, an alteration in diet is vital, a healthy diet consisting of a low fat, high-fiber, low simple sugar (cakes, sweets) and high complex sugar (pasta, rice, potatoes) intake is advised, in Type 2 diabetes, a reduction in weight alone may be sufficient to lower the body's energy requirements and restore blood glucose to normal levels, if an alteration in diet fails, oral antidiabetic drugs are prescribed; Insulin may need to be given to people with Type 2 diabetes if the treatments fail, or in pregnancy, during severe illness, and before the patient undergoes any surgery requiring a general anesthetic.

4. Normal Value of Blood glucose for a fasting person is from 70 – 110 mg/dl, if the value came at border line (near the 110 ± 5) → preform another test to conform DM, either the 2-hour OGTT, or the Hb_{A1C}.

5. The American Diabetic Society considers the patient a Diabetic if:
1. Fasting blood glucose ≥ 126 mg/dl (regardless of symptoms)
2. Random Blood glucose ≥ 200 mg/dl (with presence of the classic DM symptoms)
3. $Hb_{A1C} \geq 6.5\%$

6. Patients with type 2 Diabetes should be treated to achieve an Hb_{A1C} between 7% and 8%, rather than the old recommendation 6.5% to 7%.

First: Oral Antidiabetics: (they are given for type II diabetes).

1- Classification and administration with respect to food:

	Groups	Example(s)	Administration
1	**Sulphonylureas**	Glibenclamide, Glimepiride	With food
2	**Biguanides**	Metformin	Take with or just after food
3	**Dipeptidyl peptidase-4 inhibitors (DPP-4)**	Sitagliptin, Saxagliptin, Vildagliptin	Without regard to meal
4	**Thiozolidinediones**	Pioglitazone, Rosiglitazone	Without regard to meal
5	**Meglitinides**	Nateglinide, Repaglinide	Within 30 minutes before meals, if a meal is skipped, the medication should be skipped
6	**Alpha-Glucosidase inhibitor**	Acarbose, Miglitol	Tablets should be chewed with first mouthful of food or swallowed whole with a little liquid immediately before food.
7	**(SGLT2) Sodium glucose transporter 2 inhibitors**	Dapagliflozin, Canagliflozin	Taken in the morning once daily with or without food

2- Adverse effects:

a) **Sulfonylureas** and **Meglitinides:** hypoglycemia and weight gain (about 2 kg).

b) **Thiozolidinediones**: Weight gain (increase S.C. fat or cause fluid retention), osteopenia, increase risk of myocardial infarction and death from cardiovascular causes.

c) **Metformin:** GIT disturbances (anorexia, nausea, vomiting, diarrhea); and **weight loss**

- To minimize GI side effects, metformin should be initiated at 500 mg once or twice daily, to be taken with food, followed by weekly or biweekly increases in increments of 500 mg daily); **Hypoglycemia is rare with a Biguanides given alone**, although it may occur if other contributing factors or drugs are present.

d) **Dipeptidylpeptidase-4 inhibitors (DPP-4):** increased risk of infection, Pancreatitis, severe and disabling joint pain.

e) **Sodium glucose transporter 2 (SGLT2) inhibitors:** increase (generally mild) urinary tract infections and cause genital Mycotic (fungal) infections.

Scientific name	D. form	Trade name	concentration
Biguanides			
Metformin	Tab	Glucophage®, Siofor®, Riomet®	500 mg , 850 mg , 1000 mg
	Tab XR		500 mg , 750 mg , 1000 mg
	Efferv. Tab	Metfull®	500 mg
Phenformin	Tab	Both withdrawn from markets due toxicity, mainly due to the lactic acidosis.	
Buformin	Tab		
Sulfonylureas			
Glibenclamide, **Or** (Glyburide in USA)	Tab	Daonil® , Diabeta® , Glynase®	5 mg
Glimepiride	Tab	Amaryl®, Glemax®, Glucophen®	1 mg , 2 , 3 , 4 mg , 6 mg
Gliclazide	Tab	Diamicron®	30 mg , 60 mg
Glipizide	Tab	Minidiab®, Minodiab®	5 mg , 10 mg
Gliquidone	Tab	Glurenorm®	30 mg
Glibornuride	Tab	Glutril®	25 mg , 100 mg
Glyclopyramide	Tab	Deamelin-S®	250 mg
Meglitinides			
Repaglinide	Tab	Novonorm® , Prandin®	0.5 mg , 1 mg , 2 mg
Nateglinide	Tab	Starlix®	60 mg , 120 mg
Mitiglinide	Tab	Glufast®	10 mg

Thiozolidinediones			
Pioglitazone	Tab	Actos®, Glustin®	15 mg , 30 mg , 45 mg
Rosiglitazone	Tab	Avandia®	2 mg , 4 mg , 8 mg
Lobeglitazone	Tab	Duvie®	0.5 mg
Glitazars or (Dual PPAR agonists)			
Saroglitazar	Tab	Lipaglyn®	2 mg , 4 mg
Dipeptidyl peptidase-4 inhibitors (DPP-4)			
Sitagliptin	Tab	Januvia®	50 mg , 100 mg
Saxagliptin	Tab	Onglyza®	2.5 mg , 5 mg
Vildagliptin	Tab	Galvus®, Zomelis®	50 mg
Alogliptin	Tab	Nesina®	12.5 mg , 25 mg
Linagliptin	Tab	Tradjenta®	5 mg
Gemigliptin	Tab	Zemiglo®	50 mg
Anagliptin	Tab	Suiny®	100 mg
Teneligliptin	Tab	Tenelia®	20 mg
Trelagliptin	Tab	Zafatek®	50 mg , 100 mg
Omarigliptin	Tab	Marizev®	12.5 mg , 25 mg
Evogliptin	Tab	Suganon®	5 mg
Gosogliptin	Tab	SatRx®	20 mg , 30 mg
Alpha-glucosidase inhibitor			
Acarbose	Tab	Precose®, Glucobay®	25 mg , 50 mg , 100 mg
Miglitol	Tab	Glyset®	25 mg , 50 mg , 100 mg
Voglibose	Tab	Voglib®	0.2 mg , 0.3 mg
Sodium glucose transporter 2 (SGLT2) inhibitors			
Dapagliflozin	Tab	Farxiga®, Forxiga®, Divinus®	5 mg , 10 mg
Canagliflozin	Tab	Invokana®	100 mg , 300 mg
Empagliflozin	Tab	Jardiance®	10 mg , 25 mg
Ertugliflozin	Tab	Steglatro®	5 mg , 15 mg
Ipragliflozin	Tab	Suglat®	25 mg , 50 mg
Tofogliflozin	Tab	Apleway®	20 mg
Sotagliflozin	Pending FDA approval		

Notes:

1. **About Metformin:**
   - **a.** **Metformin** is the first line of therapy for type 2 DM; it exerts its effect mainly by decreasing gluconeogenesis and by increasing peripheral utilization of glucose.
   - **b.** It causes a 1%–2% Hb_{A1C} reduction; recommended to **start metformin at diagnosis of DM.**
   - **c.** The sustained-release preparation of metformin will last 24 hours if given with the evening meal; Sustained-release preparations have fewer GI side effects; **Metformin** may be used for the glycemic management of Type 1 DM, (it reduces the needed doses of insulin).
   - **d.** Not associated with weight gain, thus **it is preferred in obese patients**.
   - **e.** **Metformin** is used for the symptomatic management of **polycystic ovary syndrome** [**PCOS**] → Metformin helps to normalize menstrual cycle (increasing the rate of spontaneous ovulation) Due Its ability to lower insulin resistance in these women with **PCOS** can result in ovulation and, therefore, possibly pregnancy.
   - **f.** **It is sometimes used to reduce weight, this is not FDA approved,** and in fact FDA rejected this indication in 2009 due to the risk of insulin resistance in normal patients, and thus increases the risk of DM in those patients.
   - **g.** A new study found that **Metformin targets Oncogene to prevent Prostate Cancer**.

h. May improve hirsutism [1]. (Rarely used to treat hirsutism).
i. **Metformin is contraindicated in diabetic patients with renal disease** (serum creatinine levels over 150 mmol/L or 1.7 mg/dL), and in those with **diabetic ketoacidosis;** Accumulation can contribute to toxicity (lactic acidosis) in patients with renal dysfunction.
j. It should be **discontinued** in cases of **acute myocardial infarction**, **exacerbation of congestive heart failure, and severe infection**.
k. Metformin should be used with caution in patients older than age 80 years and in those with a history of congestive heart failure or alcohol abuse.
l. **Long-term use may interfere with vitamin B_{12} absorption, (cause Neuropathies)**
m. **Metformin interacts with the I.V. Contrast** used in the Catheterization, and may lead to acute renal failure, the patient **should stop using Metformin before 2 days** from the operation and 2 days after.

2. **Sulfonylureas** act mainly by **augmenting insulin secretion** (Bind to receptors on pancreatic β-cells causing stimulation of insulin secretion); thus, thy are effective only when some residual pancreatic beta-cell activity is present.
   a. They also reduce hepatic glucose production and increase peripheral insulin sensitivity.
   b. **First-generation sulfonylureas (withdrawn from the markets)** have been associated with thrombocytopenia, agranulocytosis, hemolytic anemia, hyponatremia, SIADH, and disulfiram-like reactions; The three agents in this class include: **Tolbutamide** (Orinase®), **Tolazamide** (Tolinase®), and **Chlorpropamide** (Diabinese®).
   c. Second generation include: **Glimepiride**, **Gliclazide**, **Glipizide** and **Glibenclamide**;
   d. all should be avoided in patient with sulfa or sulfur allergy.
   e. **All 2nd Gen. Sulfonylureas are equally effective** in lowering blood glucose when administered in equipotent doses; On average, the A1C will fall by 1.5% to 2% with FPG reductions of 60 to 70 mg/dL.

3. **Meglitinides** (**Nateglinide**, **Repaglinide** = FDA approved; **Mitiglinide** = Japan) lower glucose by stimulating pancreatic insulin secretion, but insulin release is glucose dependent and diminishes at low blood glucose concentrations.
   a. They **should not be combined with Sulfonylureas**, because they have the same mechanism of action and also because of the increased risk of hypoglycemia.
   b. **Cause severe hypoglycemia** in patients who are also taking the lipid-lowering drug **(Gemfibrozil)**, and concurrent use is contraindicated.
   c. The average reduction in A1C is ~0.8% to 1.5%.
   d. They are most effective on postprandial glucose excursions

4. **Thiozolidinediones** or **TZDs (Pioglitazone, Rosiglitazone** = FDA approved; **Lobeglitazone** = Korea & Japan); they act by increasing expression of genes responsible for glucose metabolism, resulting in improved insulin sensitivity.
   a. TZDs act by activating PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptors, specific for PPARγ (PPAR-gamma); these receptors modulate the expression genes involved in lipid and glucose metabolism, insulin signal transduction and adipocyte tissue differentiation. (thus, **they have an effect on plasma lipid profiles**).
   b. may cause a small decrease in hemoglobin and hematocrit; used cautiously in anemia.
   c. May **cause fluid retention**, which can **exacerbate or lead to heart failure,** thus C.I. in patients with Class III/IV heart failure, and existing fluid retention.
   d. Associated with an **increased fracture rate in the upper and lower limbs**; women appear to have a higher risk than men, use caution in patients with osteopenia or osteoporosis.
   e. **Pioglitazone** is under an ongoing safety review for the **potential increased risk of bladder cancer,** its dosage and duration of use dependent; but the Data available are contradictory (several studies shows no risk, and several other trails shows proved risk).
   f. **Troglitazone** (Rezulin®) was removed from the market in 1999 due to many several cases of **liver toxicity**, (Pioglitazone and Rosiglitazone also reported some cases); although both agents have been withdrawn from some countries in Europe.

g. When given for ~6 months, **Pioglitazone** and **Rosiglitazone** reduce A1C values by ~1.5% and FPG levels by ~60 to 70 mg/dL at maximal doses, Maximal glycemic-lowering effects may not be seen until 3 to 4 months of therapy.
- Both drugs **increase HDL**, but **Pioglitazone** also **reduce LDL and Triglyceride**.
- **Rosiglitazone** also **increase LDL cholesterol.**

5. Saroglitazar is a dual peroxisome proliferator-activated receptor (PPAR) agonist indicated for the treatment of hypertriglyceridemia in Type II diabetics; it contains two main classes of PPAR agonists, which include PPARα (alpha) and PPARγ (gamma); **It has both lipid and glucose-lowering effects in a single molecule.**
- It lowers the high blood triglycerides (increase HDL, lowers LDL and TG) as well as lowering blood sugar and improves insulin resistance; Approved in India; still has no FDA approval yet.

6. DPP-4 inhibitors act by inhibiting the breakdown of GLP-1 secreted during meals, which in turn increases pancreatic insulin secretion, limits glucagon secretion, slows gastric emptying, and promotes satiety; The average reduction in A1C is ~0.7% to 1% at maximum dose.

a. **Sitagliptin**, **Saxagliptin**, **Alogliptin** and **Linagliptin** are the only DPP-4 approved by the FDA.
b. **Vildagliptin** is approved in Europe only (not by the FDA).
c. **Anagliptin**, **Teneligliptin**, **Trelagliptin** and **Omarigliptin** are approved in Japan.
- **Omarigliptin** is a unique DPP-4 inhibitor; it's given once weekly.

d. **Evogliptin** and **Gemigliptin** are approved in South Korea.
e. **Gosogliptin** is approved in Russia.
f. Used cautiously in an individual with a past medical history of pancreatitis and must be discontinued if an individual develops pancreatitis, also may cause Hypersensitivity reactions (include angioedema, severe skin rash, or difficulty breathing). (5)
g. DPP-IV inhibitors **provide a glucose-dependent insulin secretion** and thus are not appropriate for individuals with Type1 DM.
h. Can cause severe joint pain, Upper respiratory and urinary tract infections.
i. **DPP-4 inhibitors do not increase the risk of hypoglycemia** when used as monotherapy or in combination with medications that have a low incidence of hypoglycemia.
j. Safety studies of **Saxagliptin** and **Alogliptin** (but not **Sitagliptin**) have shown an **increased risk of heart failure hospitalization** (studies still pending on **Linagliptin**).
k. **Sitagliptin** is the highest DPP-4 with risk of pancreatitis and hypersensitivity reactions.
l. **Vildagliptin** may **cause hepatitis**; thus, routine liver function tests should be performed.
m. **Linagliptin** is the only DPP-4 inhibitor (approved by the FDA) that **doesn't require dosage adjustment** in both hepatic or renal diseases.

7. Alpha-Glucosidase inhibitors (**Acarbose, Miglitol);** Slows the absorption of glucose from the intestine to the bloodstream by slowing the breakdown of large carbohydrates into smaller absorbable sugars, they are contraindicated in inflammatory bowel disease, colonic ulceration, or obstructive bowel disorders.

a. **Acarbose** is also contraindicated in patients with hepatic impairment.
b. Average reductions in A1C of 0.3% to 1%; Also shown **to decrease body weight**.
c. Might not be effective in patients using low-carbohydrate diets.

8. Sodium glucose transporter 2 (SGLT2) inhibitors: SGLT2 is a transporter in the kidneys that is responsible for approximately 90% of renal glucose reabsorption, the SGLT2 inhibitors are proposed to inhibit this transporter, thus **increasing the urinary excretion of glucose** and lowering blood glucose levels, these agents are unique in that they provide an insulin-independent mechanism of action with near absence of hypoglycemia; Agents currently in clinical trials include: (**Sergliflozin**, and **Remogliflozin**).

a. They have some effect on delaying GI glucose absorption.
b. Causes a 0.3%–1.0% reduction in A1C.
c. Effects both fasting and postprandial glucose concentrations; Associated with **Mild weight loss**.
d. The FDA issued a warning in 2015 that **SGLT2 inhibitors may lead to ketoacidosis**.

e. **Canagliflozin** is linked with possible **increased bone fracture risk**, decreased bone mineral density, and **causes increase of foot or leg amputations**.
f. **Empagliflozin** can **reduce cardiovascular morbidity** in patients with type 2 DM with established cardiovascular disease (FDA approved label).
g. **Dapagliflozin** has been approved by FDA for **reducing hospitalization for heart failure** (HF) in adults with type 2 diabetes and other cardiovascular (CV) risk factors; Dapagliflozin also demonstrate benefits in HF patients even if they do not have diabetes.

Combination Products of Oral Anti-Diabetic Drugs			
Scientific name	D. form	Trade name	concentration
Biguanides + Sulfonylureas			
Metformin + Glibenclamide	Tab	Glucovance®	(500 mg + 2.5 mg), (500 mg + 5 mg)
Metformin + Glipizide	Tab	Metaglip®	(500 mg + 2.5 mg), (500 mg + 5 mg)
Metformin + Glimepiride	Tab	Amaryl-M®	(500 mg + 2 mg)
Biguanides + Thiozolidinediones			
Metformin + Rosiglitazone	Tab	Avandamet®	(500 mg + 2 mg), (500 mg + 4 mg)
Metformin + Pioglitazone	Tab	Actoplus Met®	(500 mg + 15 mg), (850 mg + 15 mg)
Biguanides + Meglitinides			
Metformin + Repaglinide	Tab	PrandiMet®	(500 mg + 1 mg), (500 mg + 2 mg)
Biguanides + DPP-4 inhibitors			
Metformin + Sitagliptin	Tab	Janumet®	(500 mg + 50 mg), (1000 mg + 50 mg or 100 mg)
Metformin + Vildagliptin	Tab	Galvus Met®	850 mg + 50 mg
Metformin + Saxagliptin	Tab	Kombiglyze®	(500 mg + 5 mg), (1000 mg + 2.5 mg), (1000 mg + 5 mg)
Metformin + Alogliptin	Tab	Kazano®	(500 mg + 12.5 mg), (1000 mg + 12.5 mg)
Metformin + Linagliptin	Tab	Jentadueto®	(500 mg + 2.5 mg), (850 mg + 2.5 mg), (1000 mg + 2.5 mg)
Sulfonylureas + Thiozolidinediones			
Glimepiride + Rosiglitazone	Tab	Avandary®	(1 mg + 4 mg), (2 mg + 4 mg) (2 mg + 8 mg), (4 mg + 8 mg)
Glimepiride + Pioglitazone	Tab	Duetact®	(2 mg + 30 mg) , (4 mg + 30 mg)
Biguanides + (SGLT2) inhibitors			
Metformin + Canagliflozin	Tab , Tab XR	Invokamet®, Invokamet XR®	(500 mg + 50 mg), (1000 mg + 50 mg), (1000 mg + 150 mg)
Metformin + Dapagliflozin	Tab XR	Xigduo XR®	(500 mg + 5 mg), (1000 mg + 5 mg), (1000 mg + 10 mg)
Metformin + Empagliflozin	Tab , Tab XR	Synjardy®, Synjardy XR®	(500 mg + 5mg), (1000mg + 12.5mg) (1000 mg + 25 mg)
Metformin + Ertugliflozin	Tab	Segluromet®	(500 mg + 2.5mg), (500 mg + 7.5mg) (1000 mg + 7.5 mg)
DPP-4 inhibitors + (SGLT2) inhibitors			
Linagliptin + Empagliflozin	Tab	Glyxambi®	(5 mg + 10 mg) , (5 mg + 25 mg)
Saxagliptin + Dapagliflozin	Tab	Qturn®	5 mg + 10 mg
Sitagliptin + Ertugliflozin	Tab	Steglujan®	(100 mg + 5 mg), (100 mg + 15 mg)

DPP-4 inhibitors + Thiozolidinediones			
Alogliptin + Pioglitazone	Tab	Oseni®	(12.5 mg + 15 mg), (25 mg + 15 mg)

Triple Combination Products			
Metformin + Glimepiride + Pioglitazone	Tab SR	Debistal-GM®	500 mg + 2 mg + 15 mg
Glimepiride + Voglibose + Metformin	Tab SR	Glimkaire-VM2®	2 mg + 0.2 mg + 500 mg
Saxagliptin + Dapagliflozin + Metformin	Tab XR	Qternmet XR®	(2.5 mg + 5 mg + 1000 mg), (5 mg + 10 mg + 1000 mg)
Linagliptin + Empagliflozin + Metformin	Pending FDA approval		

Second: Insulin's: (they are given for type I, and in some cases of type II diabetes).

1. Therapy with insulin is essential for the long-term survival of **all patients with type 1 diabetes mellitus**; it is also needed **for type 2 diabetes when other methods have failed to achieve good control**, and temporarily in the presence of **current illness** or **pre-operatively**.
   - **Pregnant women with type 2 diabetes** may be treated with insulin.
2. The most frequent **complication of insulin therapy is hypoglycemia**; it is usually associated with an excessive dosage of insulin or the omission of a meal by the patient.
3. The various formulations of insulin are classified, according to their **duration of action** after subcutaneous injection, **as short, intermediate,** or **long-acting**.
   - Some analogues, such as insulin Lispro and Aspart, are also short-acting, with a faster onset and shorter duration of action than soluble insulin (Short acting) and are sometimes known **as rapid-acting insulins**.

Type of insulin:	Appearance	Route(S)
Rapid-acting insulin Insulin **Lispro**, Insulin **Aspart**, and insulin **Glulisine**	Clear (صافي)	S.C, I.V
Short-acting insulin (soluble, regular, neutral)	Clear	S.C, I.V, and I.M
Intermediate-acting insulin **Isophane** insulin also called **NPH** (neutral protamine hagedorn) **Lente**	 Cloudy (خابط)	S.C only
long-acting insulin **Ultra-Lente** (insulin zinc Susp. protamine zinc Susp.) Insulin **Glargine** Insulin **Detemir**	 Cloudy Clear Clear	S.C only

4. The primary **sites used for injecting insulin are the lateral thigh, abdomen and upper arm.** Many practitioners recommend using the abdominal area because absorption from this site is least affected by exercise and is the most predictable.
   - Insulin is **generally given by subcutaneous injection**; the injection **site should be rotated to prevent local side effects (the lipid dystrophy)**; **Short-acting insulin's can also be given by I.V route for urgent treatment**.
5. **Stability and Storage** (see the product's leaflet also)
   a. Insulin is a fragile molecule that can be damaged by temperature extremes, all commercially available insulins are **stable for at least 28 days (~1 month) at room temperature (20°–30°C); All un-opened** vials or pen devices should be stored in the **refrigerator (2°–8°C)**.
   b. Insulin should not be used if it has been frozen or exposed to temperatures >37◦C.
   c. **Insulin preparations should be protected from light**.
6. In practice, **most patients store vials currently in use at room temperature because injection of cold insulin is uncomfortable**, this is wrong because the insulin will become un-useful due to deterioration; they Should be stored in the refrigerator (2°–8°C).
   a. To overcome the painful cold insulin injection, **the patient should be advised to warm the insulin with the palm of the hand just before injecting the insulin.**

7. Administration of insulin S.C with a syringe (called **insulin syringe**) is still the most common method of insulin administration, **dose of insulin is expressed as units.**
8. **Insulin pen devices** are also available for injecting insulin; Pen devices are often preferred as they make insulin administration much easier, especially for patients who need to take their insulin doses away from home.

Initial dosage of insulin:

First: T1DM:

Without concomitant infection or physiologic stress condition. Insulin should be dosed based on weight and requires a calculation of the total daily dose (TDD). The total daily dose for an adult with T1DM is estimated as 0.6 units/kg/day, which can then be applied to determine an initial starting dose of insulin.

1. **50/50 rule:** 50% of the TDD is given as a basal (e.g., NPH, glargine, detemir) dose and the remaining 50% is given as the bolus (regular, lispro, aspart, glulisine) dose, divided between the meals. For example, if a person who weighs 54 Kg is to start insulin, the estimated TDD would be approximately 32 units. Half of the TDD (16 units) would be initiated as the basal insulin and the remaining 16 units would be divided into an approximate bolus dose as follows:
   a. **Glargine** or **Detemir** as a basal with short- or rapid-acting insulin as bolus: 16 units once daily of basal insulin; 5 units t.i.d. of bolus insulin with meals.
   b. **NPH** as a basal requires twice daily dosing in persons with T1DM. Also, when using **NPH**, the total bolus dose should be decreased by 20% and given twice daily to prevent hypoglycemia. Thus, the regimen for this example would be 8 units of **NPH** and 6 units of bolus, given b.i.d.
2. **Premixed insulin** should be initiated as two-third of the TDD in the morning and the remaining one-third of the TDD in the evening, prior to meals. This means for the same example used earlier with a TDD of 32 units, the insulin regimen would be 21 units in the morning prior to breakfast and 11 units in the evening prior to the evening meal. It should be noted that this type of dosing is not preferred for the individual with T1DM because it cannot be easily adjusted for changes in diet, exercise, or health (sick days), nor does it allow the titration of one insulin type to target the specific phase of insulin release that is primarily contributing to the impaired glycemic control.

Second: Type 2 DM:

1. **Basal insulin alone** may be initiated as 10 units once daily in the average-sized individual or 0.1 to 0.2 units/kg/day in the overweight or obese individual. If administered in the evenings, the dose of insulin should be titrated as necessary to achieve fasting blood glucose levels in the target range. Bolus insulin can be added as needed based on pre- and post-meal blood glucose monitoring.
2. **Premixed insulin** should be initiated based on TDD of 0.2 units/kg/day, with two-thirds of the TDD given in the morning prior to breakfast and one-third of the TDD given in the evening prior to the last meal.

Insulin adjustment algorithms

Insulin adjustment algorithms allow for the correction of an elevated blood glucose level ordosing for carbohydrate intake; Though useful for optimizing glycemic control, adjustment algorithms are not for everyone.

A. **Adjustment based on blood glucose level:** Several variations exist in the dosing of correction insulin for elevated blood glucose; The rule of 1500 is typically used for dosing short-acting (e.g., Regular) insulin, while the rule of 1800 is used for dosing rapid-acting insulin. However, there are a myriad of algorithms used between 1500 and 2200. The higher the "rule" used, the lower the risk of inducing hypoglycemia.
   1. **The rule of 1800** is used to determine the correction factor (i.e., how many mg/dL the blood glucose will decrease with the injection of 1 unit of insulin); The calculation is: 1800/TDD = correction factor (CF); For eg, for the individual with a TDD of 32, one unit of insulin should change the blood glucose level by approximately 56 mg/dL (1800/32 = 56).

2. **The correction factor** can then be used as a point-of-care calculation to determine how much insulin to inject. The calculation is: [Current blood glucose—target blood glucose]/CF. For the individual previously mentioned, if the blood glucose level is 230 mg/dL, to achieve a target of 120 mg/dL with the above calculated CF of 56 mg/dL, the individual would need to inject 2 units of rapid-acting insulin to bring the blood glucose back into the target range. The target blood glucose is typically set by practice site protocol; The CF should be rechecked at least once per year or when there is a significant change in weight, as this is a weight-based calculation.

B. Adjustment based on carbohydrate intake uses the "rule of 500"; The "rule of 500" is as follows: 500/TDD = (x) grams of carbohydrate; This equation estimates how many grams of carbohydrates will be covered by 1 unit of insulin. Use of this rule requires the ability of the individual with diabetes or the caretaker to count carbohydrates.

Insulin adjustments for repeated, time-sequenced events of hypoglycemia or hyperglycemia:

1. When individuals experience repeated hypoglycemia or hyperglycemia at particular periods, several factors should be taken into consideration (e.g., appropriateness of insulin dose(s), eating habits, changes in exercise routine).
2. Adjustments to insulin dosing should be made based on clinical evaluation of the blood glucose levels and on the knowledge of insulin onset, peak, and duration of action.
3. For example, if an individual who is taking 16 units of NPH insulin and 6 units of regular insulin twice daily (6 a.m. and 6 p.m.) has in-target pre-lunch blood glucose levels, but is having hypoglycemia pre-supper, a downward adjustment to the morning NPH dose would be most appropriate based on its longer duration of action.
4. Adjusting the morning dose of Regular insulin would be inappropriate because the main effect of Regular insulin in this instance would be on the pre-lunch blood glucose value.
5. Changes in insulin doses may also be necessary for the following causes of hyperglycemia:
   a. **Dawn phenomenon** produces fasting hyperglycemia due to the release of counterregulatory hormones, which typically occurs during the early morning hours (2:00 a.m. to 4:00 a.m.), Evening basal insulin doses should be increased or moved to bedtime dosing to correct for hyperglycemia attributed to dawn phenomenon.
   b. **Somogyi effect** is considered rebound hyperglycemia; This can occur at any time (day or night) and is when the blood glucose goes too low and counterregulatory hormones are released to increase the blood glucose. When the somogyi effect produces fasting hyperglycemia, the evening basal doses of insulin should be decreased to prevent hypoglycemia.

Rapid-acting insulin						
Scientific name	D. form	Trade name	concentration	Onset	Peak	Duration
Insulin Lispro	Inj. Solu.	Humalog®, Kwikpen®	100 units/ml	5-15 min.	30 – 90 min.	3 – 5 hr.
Insulin Aspart	Inj. Solu.	NovoLog®	100 units/ml	5-15 min.	30 – 90 min.	3 – 5 hr.
	Inj. Solu.	Fiasp®	100 units/ml	**2.5-5 min.**	30 – 90 min.	3 – 5 hr.
Insulin Glulisine	Inj. Solu.	Apidra®	100 units/ml	5-15 min.	30 – 90 min.	3 – 5 hr.
Short-acting insulin						
Regular Insulin	Inj. Solu.	Humulin R®, Novolin R®	100 units/ml, 500 units/ml	30-60 min.	2 – 4 hr.	5 – 8 hr.
Velosulin	Inj. Solu.	Velosulin®	100 units/ml	30-60 min.	2 – 3 hr.	2 – 3 hr.

Notes

1. **Insulin Aspart, Lispro, Glulisine** are also available as **prefilled 3 ml Pen** ready to use.
2. Regular insulin has a relatively slow onset of action when given subcutaneously; requiring injection 30 minutes prior to meals.

3. **Lispro**, **Aspart**, and **Glulisine** insulins are analogs that are more rapidly absorbed, peak faster, and have shorter durations of action than regular insulin, this permits more convenient dosing within 10 minutes of meals (rather than 30 minutes prior), produces better efficacy in lowering postprandial blood glucose than regular insulin, and minimizes delayed post meal hypoglycemia
4. **Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection,** this type of insulin is often used with longer-acting insulin.
5. **Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes.**
6. The profile of **Fiasp®** is similar to **NovoLog®** (insulin aspart) 100 U/mL; but the formulation has been adjusted to increase the speed of initial insulin absorption.
   - **Fiasp®** can be taken at the start of a meal, or within 20 minutes of starting.

Intermediate-acting insulin						
Scientific name	D. form	Trade name	concentration	Onset	Peak	Duration
Insulin NPH (N) **or** Insulin Isophane	Inj. Solu.	Humulin N®, Novolin N®	100 units/ml	1 - 4 hr.	6 - 8 hr.	12 - 16 hr.
Insulin Lente *	Inj. Solu.	Humulin L® , Novolin L®	100 units/ml	1.5 hr.	4 - 8 hr.	24 hr.
Long-acting insulin						
Ultra-Lente *	Inj. Solu.	Novolin UL®	100 units/ml	4 - 6 hr.	14 - 24 hr.	28 - 36 hr.
Insulin Glargine	Inj. Solu.	Lantus®, Basaglar®	100 units/ml	1 hr.	Peakless	20 - 26 hr.
Insulin Detemir	Inj. Solu.	Levemir®	100 units/ml	1 hr.	Peakless	20 - 26 hr.
Insulin Degludec	Inj. Solu.	Tresiba®	100 units/ml	1 hr.	Peakless	42 hr.

Notes:

1. **Lente and Ultra-Lente insulin** was discontinued in the USA in 2005; one of the reasons for discontinuation was declining in their use due to physicians favoring NPH insulin and other basal insulin drugs.
2. **Insulin Glargine, Detemir** are also available as **prefilled 3 ml Pen** ready to use.
3. Glargine and Detemir should never be mixed in the same syringe with another insulin.
4. Glargine, Degludec and Detemir are long-acting, Peakless, human insulin analogs that result in less nocturnal hypoglycemia than NPH insulin when given at bedtime.
5. **Intermediate-acting insulin covers insulin needs for about half the day or overnight**, while **Long-acting insulin covers insulin needs for about one full day**.
6. Insulin glargine and insulin Degludec are given once daily, insulin Detemir is given once or twice daily according to individual requirements.
7. These types of insulin are often combined, when needed, with rapid- or short-acting insulin.

Biphasic insulin are mixtures providing for both immediate and prolonged action.

- These combinations are usually used in a twice daily regimen.
- The most common combination found in our market is the 70% NPH insulin + 30% regular.

Scientific name	D. form	Trade name	concentration
70% NPH insulin + 30% regular insulin	Inj. Solu.	Humulin 70/30®, Novolin 70/30® Mixtard 70/30®	(70 unit + 30 unit)/ml
50% NPH insulin + 50% regular insulin	Inj. Solu.	Humulin 50/50®	(50 unit + 50 unit)/ml
75% Lispro protamine + 25% insulin Lispro	Inj. Solu.	Humalog Mix 75/25®	(75 unit + 25 unit)/ml
50% Lispro protamine + 50% insulin Lispro	Inj. Solu.	Humalog Mix 50/50®	(50 unit + 50 unit)/ml
70% Aspart protamine + 30% insulin Aspart	Inj. Solu.	NovoLog Mix 70/30®	(70 unit + 30 unit)/ml

50% Aspart protamine + 50% insulin Aspart	Inj. Solu.	NovoLog Mix 50/50®	(50 unit + 50 unit)/ml
70% insulin Degludec + 30% insulin Aspart	Inj. Solu.	Ryzodeg®	(70 unit + 30 unit)/ml

Note:

Inhalable insulin (Exubera®) was available at September 2006 as inhale powder as a new method of delivering insulin, but withdrawn on October 2007 in the USA, due to the additional costs is so much more than the S.C dosage form, which makes it unlikely to be cost-effective.

- Inhaled insulin may cause bronchospasm and is contraindicated in patients with asthma, chronic obstructive pulmonary disease, or lung cancer.
- Requires spirometry testing at baseline, at 6 months of therapy, and annually thereafter.

Scientific name	Dosage form	Trade name	concentration
Insulin Inhale	Inhale powder	Exubera®	1 mg , 3 mg
	Inhale Powder (single use cartridges)	Afrezza®	4 units , 8 units , 12 units (per cartridge)

* 1 mg of **Exubera®** is equivalent to 3 units of insulin, onset 10 – 20 min, duration 6 hr.

Third: Other anti-diabetic agents:

A) Pramlintide (synthetic amylin analog) for type 1 and 2 DM

Indicated as an adjunct to mealtime insulin therapy in patients with type 1 & 2 diabetes, it delays gastric emptying, decreases postprandial glucagon secretion.

a. Administered by S.C injection and should be injected immediately before meals.
b. It causes a 0.5%–1% reduction in Hb_{A1C}.
c. Effective at controlling postprandial glucose excursions
d. When Pramlintide is initiated, the dose of rapid or short-acting insulin should be decreased by 50% prior to meals to avoid a risk of severe hypoglycemia.
e. **Pramlintide** is not to be mixed in the same syringe with any insulin preparation.
f. It has a Black box warning for severe hypoglycemia, especially in patients with T1D.
g. Contraindicated in Substantial gastroparesis and in Hb_{A1C} greater than 9%.

B) Bromocriptine (for type 2 DM)

1. Agonist for dopamine receptor D_2 is thought to reset circadian rhythm, which can reduce caloric intake and storage; other effects may be through α1 antagonism, α2-agonistic properties, and modulation of serotonin and prolactin.
2. **Indicated as adjunctive therapy only** for the management of Type 2 DM.
3. Used with caution in persons with cardiovascular disease (myocardial infarction, arrhythmias), dementia, psychosis, or peptic ulcer disease.
   a. Cause a 0.1%–0.6% reduction in A1C; with Possible cardiovascular benefit.
   b. **Take 0.8 mg within 2 hrs. After waking in the morning**; dose will be increased weekly until the maximum tolerated dose is achieved (Maximal daily dosage 4.8 mg).
   c. May cause gastrointestinal discomfort, nausea, or vomiting; **Take with food to lessen gastrointestinal discomfort.**

C) Incretin Mimetics (or GLP-1 analogs) for type 2 DM

1. These include: **Exenatide, Liraglutide, Lixisenatide, Dulaglutide, Semaglutide, Albiglutide.**
2. Incretin hormones are responsible for 60 to 70 percent of postprandial insulin secretion, thus these agents improve glucose-dependent insulin secretion, also slow gastric emptying time, decrease food intake, decrease postprandial glucagon secretion, promote β-cell proliferation.
   a. **Exenatide**, **Liraglutide**, **Lixisenatide**, **Dulaglutide** and **Albiglutide** all must be administered subcutaneously (S.C.).
   b. **Exenatide** should be injected twice daily within 60 minutes prior to morning and evening meals, (also reformulated as Injection Susp. used as once weekly dosing).

c. **Lixisenatide** is administered once daily 1 hr. before the first meal.
d. **Liraglutide** is used in once-daily dosing without regard to meals.
- **Liraglutide** is also indicated for **weight loss** (see chapter 18, section 4).
- **Liraglutide** shown to reduce cardiovascular outcomes in high-risk patients, question whether it's a class effect or a drug specific, other cardiovascular trials are pending.

e. **Dulaglutide** and **Albiglutide** is administered once weekly.
f. **Semaglutide** is the **first oral glucagon-like peptide (GLP-1) receptor analog** protein treatment approved for use by the FDA for type 2 DM; that does not need to be injected.
- Although, there is an injectable dosage form of **Semaglutide**, that is administered once weekly.
- The oral form of Semaglutide is taken once a day.

g. **Exenatide** and **Liraglutide have been associated with pancreatitis.**

3. They cause a 0.5%–1.5% reduction in A1C, also Effects on postprandial hyperglycemia is better than on fasting glucose concentrations; also causes a modest weight loss.

D) Bile acid Sequestrants: **Colesevelam** is the only studied and approved drug in this class.

1. Bile acid Sequestrants used primarily for cholesterol management; Its mechanism to reduce serum glucose concentrations is not clearly understood; but it is thought to be an antagonist to the farnesoid X receptor, which subsequently reduces hepatic gluconeogenesis; Used only in conjunction with insulin or oral DM medications and cause an additional 0.3%–0.5% reduction in A1C.
- C.I. in patients with a history of bowel obstruction or serum TG conc. greater than 500 mg/dL.

Scientific name	Dosage form	Trade name	concentration
Amylin Analog			
Pramlintide	Inj. Solu.	Symlin®	0.6 mg/ml
	Pen injector	Symlin Pen®	15 mcg , 30 mcg , 60 mcg per dose
Incretin Mimetics (GLP-1 analogs)			
Exenatide	Inj. Solu.	Byetta®	250 mcg/ml
	Inj. Susp.	Bydureon®	2 mg/vial
Liraglutide	Prefilled pen	Victoza®	6 mg/ml , (18 mg/3 ml pen)
	Prefilled pen	Saxenda®	6 mg/ml , (18 mg/3 ml pen)
Dulaglutide	Prefilled pen	Trulicity®	0.75 mg/0.5 ml , 1.5 mg/0.5 ml
Lixisenatide	Prefilled pen	Lyxumia®, Adlyxin®	50 mcg/ml , 100 mcg/ml
Albiglutide	Pen injector	Tanzeum®	30 mg , 50 mg (per pen)
Semaglutide	Pen injector	Ozempic®	1.34 mg/ml
	Tab	Rybelsus®	3 mg , 7 mg , 14 mg
Other Drugs For DM			
Bromocriptine	Tab	Parlodel®, Cycloset®	2.5 mg
Colesevelam	Tab , Cap	WelChol®, Cholestagel®	625 mg

Note:

A new approach is suggested for patients with type 2 DM including **Insulin + GLP-1 analog**; in which has the advantage of once daily dosing.
- The dose is adjusted individually for each patient, and the patient's blood glucose should be regularly tested to find the lowest effective dose.

Scientific name	D. form	Trade name	concentration
Insulin Degludec + Liraglutide	Pen inj.	Xultophy®	(100 IU + 3.6 mg) per ml
Insulin Glargine + Lixisenatide	Pen inj.	Soliqua®	(100 IU + 33 mcg) per ml

Note:

There are a variety of antidiabetic medication; each one has its own advantages and disadvantages, making the choice between them very hard regarding initiating DM treatment. Metformin is the drug of choice, but sometimes alone it's not enough to control DM; thus, the table below will help to choose what add-on therapy should be considered with Metformin.

- Eventually; the best drug for DM management is insulin.

Agent or Class	Glycemic Effect	Benefits	Limitations and Precautions
Sulfonylurea	Fasting and prandial	Efficacy, Low Cost	Weight gain, Hypoglycemia risk, speeds Beta-cell dysfunction
Meglitinides	Prandial	Prandial focus, Used in kidney impairment	Hypoglycemia risk, Weight gain, Mealtime dosing
Pioglitazone	Fasting and prandial	Improved insulin sensitivity and pancreatic function, Low risk of hypoglycemia	Weight gain and edema, Risk of heart failure, Risk of osteoporosis, Possible bladder cancer risk?
α-Glucosidase inhibitor	Prandial	No systemic absorption, Prandial focus, Weight loss	Mealtime dosing, Modest A1C effect
DPP-4 inhibitor	Prandial	Well tolerated, Weight neutral	Possible pancreatitis risk? Modest A1C effect, Possible increased heart failure risk (Saxagliptin, Alogliptin), Possible hepatitis risk? (Vilda.)
GLP-1 agonist	Fasting and prandial (depending on withier given daily, or weekly)	Greater effect on prandial glucose, Weight loss, Improves pancreatic function? Cardiovascular benefit? (Liraglutide)	Nausea and vomiting, Injection-site effects, Questionable pancreatitis or thyroid cancer risk? High Cost
Colesevelam	Prandial	Lipid Benefits, No systemic absorption	Large pill size, burden GI side effects, Small decrease in A1C Avoid with high TG
Bromocriptine	Fasting and prandial	Low risk of hypoglycemia, Possible Cardiovascular benefit?	Small decrease in A1C, CNS adverse effects
SGLT-2 inhibitors	Fasting and prandial	Low risk of hypoglycemia, Efficacy, Weight loss, Possible heart failure benefit (Dapagliflozin, Empagliflozin)	Urinary tract, genital infections, Diuresis, Euglycemic DKA?
Amylin agonist	Prandial	Modest weight loss, Efficacy on post Prandial glucose	High risk of hypoglycemia, Must be taken with insulin, Frequent injections Injection-site effects and GI adverse effects
Insulin	Basal: Fasting Bolus: Prandial	Significant A1C reduction, Flexibility in dosing strategies and titration	Hypoglycemia, Weight gain, Injection-site effects

Clinical Tip

Vitamin D is used in the improvement of Gestational DM (uncommon use), as women with lower serum levels of Vit. D during the 1st trimester of pregnancy is at a great RISK for developing Gestational DM.

That's because the active metabolite of Vit. D acts as a transcription factor in Glucose metabolism.

Fourth: Hypoglycemia

1. It's represented by **plasma glucose levels below 70 mg/dL**. However, symptoms are the driving determinant rather than an absolute glycemic value since the threshold for the onset of symptoms varies among individuals.
2. **Symptoms of mild hypoglycemia** include sweating, shaking, vision changes, immediate hunger, confusion, and lack of coordination. **Severe hypoglycemia** occurs when an individual is unable to self-treat due to mental confusion, lethargy, or unconsciousness. Some individuals may have neuroglycopenia and present with symptoms of crying, argumentativeness, inappropriate giddiness, or euphoria.
3. **Causes** can include advanced age, poor nutrition, renal disease, excess of glucose-lowering agents (insulin or insulin secretagogues), or strenuous activity.
4. **Treatment of Hypoglycemia**
   a. **Mild hypoglycemia:** Individuals should check their blood glucose level prior to treating, if possible, If the blood glucose level is low, the person should eat or drink 10 to 15 gm of a fast-acting glucose source (4 oz. of fruit juice or regular soda, 3 pieces of peppermint candy) to raise the plasma glucose level 30 to 45 mg/dL. If plasma glucose levels are below 50mg/dL, treatment with 20 to 30 g of carbohydrate may be necessary; The blood glucose level should be rechecked 15 to 20 min. after treatment; if blood glucose levels are low, then hypoglycemia treatment can be repeated.
   b. **Severe hypoglycemia:** Individuals able to swallow may be treated with glucose gel, syrup, or jelly placed inside the individual's check. If this is not possible, **glucagon**, which stimulates hepatic glucose production, may be given by SQ or IM injection (Nausea and vomiting are primary adverse effects of a glucagon injection), so the treated person may not immediately feel like consuming further carbohydrates. However, the glycemic response to glucagon is transient (approximately 1.5 hrs.), so a small snack should be eaten when the individual is able to do so.
   c. **Chronic hypoglycemia:** is usually treated with **Diazoxide**, administered by mouth (used for **chronic hypoglycemia** from excess endogenous insulin secretion, either from an islet cell tumor or islet cell hyperplasia **It has no place in the management of acute hypoglycemia**).

Scientific name	Dosage form	Trade name	concentration
Diazoxide	Tab	Eudemine®	50 mg
	Oral Susp.	Proglycem®	50 mg/ml
Glucagon	Inj. Powder	GlucaGen®	1 mg/vial

Notes:

- **Diazoxide** (a Glucose elevating agent) is used to treat Hyper-insulinemic hypoglycemia.
  a. **Injectable form** that was used for hypertensive emergency is no longer available.
- **Glucagon** (a Glucose elevating agent) is indicated for severe hypoglycemic reactions in patients with diabetes treated with insulin, **also indicated off-label for overdose of beta blockers or calcium channel blockers.**

5. **Other types of hypoglycemia**
   a. **Pseudo-hypoglycemia** occurs when the individual perceives hypoglycemic symptoms, but the blood glucose level may be normal, or slightly above normal. Some literature states that there is no need to treat pseudo-hypoglycemia; however, providing 5 to 10 g of a rapid-acting glucose source can diminish the symptoms without causing significant elevations in blood glucose.
   b. **Hypoglycemia unawareness** occurs when hormonal counter regulation and autonomic symptoms disappear. However, individuals do typically have select symptoms, such as those associated with neuroglycopenia, but they may be recognized too late to allow for timely treatment.

Fifth: Hyperglycemic Emergencies

1. The two most common emergencies are **diabetic ketoacidosis (DKA)** and **hyperosmolar hyperglycemic state (HHS) or** called **Hyperosmolar Non-Ketotic Coma (HONKC)**, they differ in the presence of ketoacidosis and the degree of hyperglycemia (see the table below)
   a. **DKA,** which is caused by profound insulin deficiency, typically occurs in persons with T1DM, but can also occur in those with T2DM, it is characterized by hyperglycemia, ketosis, dehydration, and electrolyte imbalance.
   b. **HHS** predominantly affects elderly individuals and is an extreme manifestation of impaired glucose regulation. HHS is associated with a higher mortality than DKA, likely due to severe metabolic changes, delay in diagnosis, or other medical complications that affect elderly.
2. **Treatment** of **DKA** and **HHS** is focused on correction of dehydration, hyperglycemia, and electrolyte imbalance, treatment may include any of the following as necessary: IV fluids, insulin, potassium, and/or sodium bicarbonate.

Approach for the treatment of DKA:

- To restore circulating volume if systolic blood pressure is below 90 mmHg (adjusted for age, sex, and medication as appropriate), **give 500 mL sodium chloride 0.9%** by I.V. infusion over10-15 minutes; repeat if blood pressure remains below 90 mmHg.
- When blood pressure is over 90 mmHg, sodium chloride 0.9% should be given by intravenous infusion at a rate that replaces deficit and provides maintenance.
- Include **potassium chloride** in the fluids unless anuria is suspected; adjust according to plasma potassium concentration (measure at 60 minutes, 2 hours, and 2 hourly thereafter; measure hourly if outside the normal range).
- **Start an intravenous insulin infusion**: soluble insulin should be diluted (and mixed thoroughly) with sodium chloride 0.9% intravenous infusion to a concentration of 1 unit/mL; infuse at a fixed rate of 0.1 units/kg/hour.
- Established **subcutaneous therapy with long-acting insulin analogues** (insulin Detemir or insulin Glargine) should be continued during treatment of diabetic ketoacidosis.
- Monitor blood-ketone and blood-glucose concentrations hourly and adjust the insulin infusion rate accordingly. Blood-ketone concentration should fall by at least 0.5 mmol/L/hour and blood-glucose concentration should fall by at least 3 mmol/ L/hour.
- Once blood-glucose concentration falls below 14 mmol/L, **Glucose 10%** should be given by intravenous infusion (into a large vein through a large-gauge needle) at a rate of 125 mL/hour, in addition to the **sodium chloride 0.9% infusion.**
- Continue insulin infusion until blood-ketone concentration is below 0.3 mmol/L, blood pH is above 7.3 and the patient is able to eat and drink; ideally give subcutaneous fast-acting insulin and a meal, and stop the insulin infusion 1 hour later.
- **Bicarbonate** administration is not needed and may be harmful, especially in children.

	DKA	HHS
Onset	Sudden	Gradual
Affected individuals	T1DM (occasionally T2DM)	Elderly
Plasma glucose	Between 250 mg/dL and 600 mg/dL	> 600 mg/dL
Gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain)	Present	Negative
Serum or urine ketones (nitroprusside reaction)	Positive	Minimal to none
Kussmaul respirations	Positive	Negative
Arterial pH	< 7.3	> 7.3
Serum osmolality 2[(*sodium* + *glucose*)/18]	Variable	> 320 mOsm/kg
Sodium bicarbonate	< 15 mEq	> 15 mEq

6.2- Thyroid and anti-Thyroid drugs

Thyroid Function Test	Hypothyroidism	Hyperthyroidism
Serum resin triiodothyronine uptake (RT_3U)	↓ (< 35%)	↑ (> 45%)
Serum total thyroxine (TT_4)	↓ (< 5 μg/dL)	↑ (> 12 μg/dLl)
Serum total triiodothyronine (TT_3)	↓ (< 80 ng/dL)	↑ (> 180 ng/dLl)
Free thyroxine index (FTI)	↓ (< 5.5)	↑ (< 10.5)
Serum thyrotropin (TSH) assay[a]	↑ (> 4.5 μU/mL)	↓ (< 0.4 μU/mL)[b]

First: Thyroid hormones (for Hypothyroidism):

1. **Hypothyroidism** is the inability of the thyroid gland to supply sufficient thyroid hormone, there are varying degrees of hypothyroidism from mild, clinically insignificant forms to the life threatening extreme, myxedema coma.
   - Causes may be due to an Autoimmune-induced thyroid injury, Iodine deficiency, Pituitary insufficiency (failure to produce adequate TSH secretion) or drug induced.
   - The symptoms of adult hypothyroidism develop slowly and include: weight gain, mental slowness, dry skin, hair loss, increased sensitivity to cold, and heavy menstrual periods.
   - In babies, low levels of thyroxine cause permanent mental and physical retardation and, for this reason, babies are tested for hypothyroidism shortly after birth.
2. Lifelong oral treatment with synthetic thyroid hormones (**Levothyroxine T4**), or (**Liothyronine T3**) is the only option for patients with Hypothyroidism; Blood tests are performed regularly to monitor treatment and permit dosage adjustments.
   - Hypothyroidism due to panhypopituitarism requires replacement with glucocorticoids as well as with Thyroid hormone; using Levothyroxine alone in such case can cause acute adrenal insufficiency.
3. Thyroid hormone: Thyroxine **(Levothyroxine)** is used **in hypothyroidism**, (**which is readily treated by lifelong replacement therapy**).
   a. Absorption of **Levothyroxine** is optimal **on an empty stomach**, **at least 60 minutes before meals**; it's best taken on an empty stomach, usually **before breakfast**; or **30 minutes before eating breakfast.**
      - Taking Levothyroxine at bedtime results in higher serum T4 and lower TSH levels.
   b. **Optimal starting dose** range from **25 mcg – 50 mcg** per day, or 1.6 mcg/kg per day.
      - In those with existing cardiovascular disease, consider 12.5–25 mcg/day.
   c. **Can be given every other day (even every 2 or 3 days according to response).**
   d. **Levothyroxine is the drug of choice for pregnant women.**
   e. Guidelines recommend against changing from brand to generic and vice versa; It is recommended to stay with one product throughout therapy.
   f. **Ciprofloxacin has been reported to interact with Levothyroxine** when given together, resulting in elevated TSH and reduced Free T4 and Free T3 levels.
4. Other treatment options include**: Thyroglobulin, Liothyronine** and **Liotrix,** but these agents are not preferred as **levothyroxine.**
   - They are not recommended by leading professional organizations or clinical guidelines.
5. **Excessive doses of thyroid hormone** may lead to heart failure, angina pectoris, and myocardial infarction (MI), allergic or idiosyncratic reactions.
   - **Levothyroxine** is Linked to increased risk of fractures (usually at higher dosages or over-supplementation)**.**
6. **Some patients use Levothyroxine for weight reduction, this is very wrong and dangerous;** Levothyroxine is ineffective for weight reduction in euthyroid patients (normal patients), and may produce serious or even life-threatening manifestations of toxicity, particularly when given with sympathomimetic amines such as those used for their anorectic effects.

Scientific name	Dosage form	Trade name	concentration
Levothyroxine	Tab	Eltroxin®, Levoxyl®, Synthroid®	25 mcg , 50 , 100 , 150 mcg
	Cap	Tirosint®	75 mcg , 150 mcg
	Inj. Powder		200 mcg , 500 mcg
Thyroglobulin	Tab	Proloid®	200 mg
Liothyronine	Tab	Cytomel®, Triostat®	5 mcg , 25 mcg , 50 mcg
	Inj. Solu.		10 mcg/ml
Liotrix (T3:T4)	Tab	Thyrolar®	(6.25 mcg + 25 mcg), (12.5 mcg + 50 mcg), (25 mcg + 100 mcg)
Levothyroxine + Liothyronine	Tab	Cynoplus®	120 mcg + 30 mcg
Levothyroxine + Liothyronine	Tab	Armour Thyroid®	38 mcg + 9 mcg
Thyrotropin Alfa	Inj. Powder	Thyrogen®	1.1 mg/vial

Notes:

1. **Thyroglobulin** is a purified hog gland extract that is standardized biologically to give a T4:T3 ratio of 2.5:1; It has no clinical advantages and is not widely used.
2. **Liothyronine (synthetic T3)** has uniform potency but has a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring with conventional laboratory tests.
3. **Liotrix (synthetic T4:T3 in a 4:1 ratio)** is chemically stable, pure, and has a predictable potency but is expensive.

Second: Anti-Thyroid drugs (for Hyperthyroidism)

1. In this condition (also called thyrotoxicosis), the thyroid is overactive and produces too much thyroxine, women are more commonly affected than men.
   - Symptoms include anxiety, palpitations, weight loss, increased appetite, heat intolerance, diarrhea, and menstrual disturbances.
2. Can be classified according to the cause into:
   a. **Toxic diffuse goiter** or (**Graves disease**): the most common hyperthyroid disorder; an Autoimmune disorder.
   b. **Pituitary adenomas**: Produce excessive TSH secretion that does not respond to normal T3 negative feedback
   c. **Toxic adenoma:** Nodule in thyroid, autonomous of pituitary, and TSH.
   d. **Toxic multinodular goiter** or (**Plummer disease**): Several autonomous follicles that, if large enough, cause excessive thyroid hormone secretion
   e. **Painful subacute thyroiditis:** Self-limiting inflammation of the thyroid gland caused by viral invasion of the parenchyma, resulting in the release of stored hormone.
   f. **Drug induced** (excessive exogenous thyroid hormone dosages, amiodarone therapy).
3. **Anti-thyroid** drugs are used for **hyperthyroidism;** either **to prepare the patients for thyroidectomy or for long-term management**.
4. **Carbimazole,** the commonly used drug, Inhibits iodination and synthesis of thyroid hormones
   a. **Rashes** and **pruritus** are common side effects of **Carbimazole** but they can be treated with antihistamines without discontinuing therapy.
   b. **Carbimazole induce agranulocytosis**:
      - Rarely, agranulocytosis can develop, and is the most **serious adverse reaction associated with this class of drugs**.
      - Patients or their careers should be told how to recognize such toxicity and should be advised to seek immediate medical attention if **mouth ulcers or sore throat, fever, bruising, malaise, or nonspecific illness develop.**
      - Full blood counts should be performed, **and treatment should be stopped immediately if there is any clinical or laboratory evidence of neutropenia.**

5. Other **drugs options** include: **Methimazole, Propylthiouracil,** and **Potassium Iodide.**
   - **Methimazole** is the active metabolite of **Carbimazole**.
   - **Propylthiouracil** (in addition to inhibiting iodination and synthesis of thyroid hormones); it can block T4/T3 conversion in the periphery as well.
   - **Propylthiouracil** is drug of choice during the first trimester of pregnancy, during the second and third trimesters, Methimazole (hence Carbimazole) is the drug of choice.
   - On 2009, the FDA published an alert notifying healthcare professionals of **the risk of serious liver injury, including liver failure and death, with the use of Propylthiouracil,** as a result, Propylthiouracil is no longer recommended in non-pregnant adults and in children as the front line anti-thyroid medication.
6. **Iodine's** and **iodides** (**Lugol solution**, saturated solution of **potassium iodide**) acts by inhibiting the release of stored thyroid hormone, they have minimal effect on hormone synthesis.
   - Helps to decrease vascularity and size of gland before surgery.
7. Other **treatment options** include: **Radioactive iodine (RAI) and Subtotal thyroidectomy.**
   a. **Advantages of RAI:** High cure rate, Avoids surgical risks (such as adverse reaction to anesthetics, hypoparathyroidism, nerve palsy, bleeding, and hoarseness).
   b. **Disadvantages of RAI:** Risk of delayed hypothyroidism, risk of genetic damage, must be given in multiple doses, this may delay therapeutic efficacy for a long period (several months or even a year).
8. **Propranolol** and **Nadolol (β-blockers)** are useful for **rapid relief of Thyrotoxic symptoms**; as (tachycardia, anxiety, tremor, and heat intolerance) and they can be used in conjunction with other anti-thyroid drugs.
   a. **Propranolol** usually dosed 20 to 40 mg four times daily.
   b. In addition to providing symptomatic relief, **propranolol at high doses** (more than 160 mg/day**) inhibit the peripheral conversion of T4 to T3.**
   c. Blockers are primary adjunctive therapy to RAI.
   d. Centrally acting Sympatholytics **(Clonidine)** and calcium channel antagonists **(Diltiazem)** may be useful for symptom control when C.I. to the β-blockade exist.
   e. Antiadrenergic therapy with the short-acting agent **(Esmolol)** is preferred because it can be used in patients with pulmonary disease or at risk for cardiac failure and because its effects can be rapidly reversed.

Scientific name	Dosage form	Trade name	concentration
Carbimazole	Tab	Neomercazole®, Vidalta®	5 mg
Methimazole	Tab	Northyx®, Tapazole®	5 mg , 10 mg
Propylthiouracil	Tab	PTU®, Propycil®	50 mg
Potassium Iodide	Tab	SSKI®, Iosat®	65 mg , 130 mg
	Oral Solu.	Pima Syrup®	65 mg/ml , 325 mg/5 ml
	Oral Solu.	ThyroSheild®	1 gm/ml

Notes:

1. **Carbimazole** is a pro-drug as after absorption it is converted to the active form, **Methimazole.**
2. Both **Methimazole** and **Propylthiouracil (PTU) are class (D) in pregnancy** (there is positive evidence of human fetal risk).

How to prepare Lugol solution in your pharmacy

Ingredients needed:
1. Potassium iodide (KI) 10 gm
2. Iodine 5 gm
3. Distilled water D.W. 100 ml

Procedure:
- Dissolve 10 gm KI in about 20-30 ml of D.W.
- Then Add 5 gm Iodine and heat gently with constant mixing until iodine is dissolved.
- Dilute to 100 ml with distilled water.
- Store in amber glass-stoppered bottle in the dark.

6.3- Sex hormones

First: Female sex hormones:

1. There are two types of female sex hormones: **Estrogen** and **Progesterone**, in women, these hormones are secreted by the ovaries from puberty until the menopause, each month, the levels of estrogen and progesterone fluctuate, producing the menstrual cycle.
2. During pregnancy, estrogen and progesterone are produced by the placenta, the Production of estrogen and progesterone is regulated by the two gonadotrophin hormones (FSH and LH) produced by the pituitary gland.
   - **Estrogen** is responsible for the development of female sexual characteristics, including breast development and widening of the pelvis; they also increase fat store, stimulate endometrial growth, increase uterine growth, increase vaginal lubrication, Thicken the vaginal wall, Maintenance of vessel and skin, reduce bone resorption, increase bone formation
   - **Progesterone** prepares the lining of the uterus for implantation of a fertilized egg; it is also important for the maintenance of pregnancy; it decreases contractility of the uterine smooth muscle; it inhibits lactation during pregnancy and the fall in progesterone levels following delivery is one of the triggers for milk production.
3. Sex drive is dependent on androgen levels only in the presence of estrogen, but without estrogen, free testosterone level actually decreases sexual desire (instead of increasing sex drive), as demonstrated for those women who have hypoactive sexual desire disorder, and the sexual desire in these women can be restored by administration of estrogen.

A- Estrogens:

1. The **two major uses** of estrogens are for **Hormone replacement therapy (HRT)** and as components of combination **oral contraceptives** (see chapter 7).
2. **Hormone replacement therapy (HRT)** with small doses of an estrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as **vaginal atrophy or vasomotor instability**; (In women with an intact uterus, the addition of a progestogen reduces the additional risk of endometrial cancer).
   a. **Vasomotor symptoms include hot flashes, night sweats** (The hot flash is a sensation of heat that typically begins in the face and chest and quickly spreads).
   b. Menopausal **atrophic vaginitis may respond to a short course of a topical vaginal estrogen** (see chapter 7), which is used for a few weeks and repeated if necessary.
   c. **The effective dose of estrogen used for HRT is less than that in oral contraceptives**.
   d. An estrogen may be given orally or transdermally (avoids 1st-pass effect).
3. **Other uses:** Estrogen therapy mimicking the natural cyclic pattern and usually in combination with a progestogen, is instituted to **stimulate development of secondary sex characteristics** in young women (11 to 13 years of age) with primary hypogonadism; Continued treatment is required after growth is completed; Similarly, estrogen and progestogen replacement therapy is used for women who have **premature menopause or premature ovarian failure**. Replacement therapy is usually continued until about age 50, the average age of normal menopause
4. **Side effects of Estrogens include:** Postmenopausal **uterine bleeding**, **thromboembolic events (DVT, PE)**, **myocardial infarction**, and breast and endometrial cancer is increased with use of estrogen therapy alone (without progestin)
   - **If estrogen is contraindicated or is undesirable, other options may be considered** as **Medroxyprogesterone** (see progestin's below) may provide some relief of vasomotor symptoms for certain patients.
   - the α2 adrenergic agonist **clonidine** diminishes vasomotor symptoms in some women, but itself has also undesirable side effects.
5. **The National American Menopause Society** recommends that HRT to be prescribed at the **lowest effective dose for the shortest possible time** to relieve menopausal symptoms.

Scientific name	Dosage form	Trade name	concentration
Conjugated Estrogen	Tab	Premarin®, Equin®	0.3 mg , 0.625 mg , 0.9 mg , 1.5 mg , 2.5 mg
	Vag. Cream	Estrin®	0.625 mg
Estradiol	Tab	Estrofem®, Delestrogen®	0.45 mg , 0.9 mg , 2 mg
	Tab SR	Climaval® , Elleste-Solo®	1 mg , 2 mg
	Patch	Elleste-Solo MX®, Estradot® , Evorel®	40 mcg , 80 mcg (per 24 hr.), 25 mcg , 50 mcg
	Gel	Climara®, Oestrogel®	0.06%
	Vag. Tab	Vivelle®, Minivelle®	10 mcg , 25 mcg
	Vag. Cream	Vagifem®	0.01%
Estriol	Vag. Gel	Blissel®	50 mcg/1 gm
Estradiol + Estriol + Estrone	Tab	Hormonin®	0.6 mg + 0.27 mg + 1.4 mg
Estropipate	Tab	Ortho-Est®, Ogen ®	1.5 mg , 3 mg , 6 mg
Tibolone *	Tab	Livial®	2.5 mg

* **Tibolone** has estrogenic, progestogenic and weak androgenic activity.

B- Selective Estrogen Receptor Modulators (SERMs):

These include: **Raloxifene, Bazedoxifene, Ospemifene and Clomiphene:**

1. **Clomiphene is used for treatment of female infertility due to anovulation;** by increasing gonadotropin levels, primarily FSH, it enhances follicular recruitment.
   - **a.** In the new pharmacological classifications, it's **classified as an anti-Estrogen.**
   - **b.** **The usual oral dose** is 50 mg daily for 5 days starting within about 5 days of onset of menstruation (preferably on 2nd day). If ovulation does not occur, a course of 100 mg daily for 5 days is given, the same dosing **maybe used for lactation Suppression**.
   - **c.** In some cases, Clomiphene is **used in conjunction with human gonadotropins** to induce ovulation (usually given to reduce the no. of gonadotropin inj.).
   - **d.** Patients should be warned that there is a **risk of multiple pregnancies** (rarely more than twins), also may cause ovarian cysts, hot flashes, and blurred vision.
   - **e.** **Other side effects include:** ovarian hyper-stimulation, in addition, clomiphene induced cycles have a relatively high incidence of luteal phase dysfunction due to inadequate progesterone production.
   - **f.** **Prolonged use (≥12 cycles) may increase the risk of ovarian cancer.**
   - **g.** The drug should **NEVER be administered to pregnant** women, **category (X).**
   - **h.** Clomiphene **has been found very effective in the treatment of secondary male hypogonadism in many cases**; this has shown to be a much more attractive option than testosterone replacement therapy (TRT).
   - **i.** Clomiphene may be given for **men with Oligospermia** (it increases sperm production in men); dosed as 25-100 mg per day.
   - **j.** Clomiphene is commonly used by male users **(usually athletes and bodybuilders)** to bind the estrogen receptors in their bodies, thereby **blocking the effects of estrogen; and thus, enhancing anabolic effects and musicalizing**, it also restores the body's natural production of testosterone.
2. **Raloxifene** is used in the **treatment of Osteoporosis,** it reduces the rate of bone loss and may increase bone mass at certain sites; it does not reduce menopausal vasomotor symptoms.
   - **Raloxifene** does not appear to increase the risk of developing endometrial cancer.
   - **Adverse effects include:** hot flashes, deep vein thrombosis, and leg cramps.
3. **Ospemifene** is indicated for **treatment of dyspareunia** (pain during sexual intercourse) encountered by some women, more often in those who are post-menopausal.

4. **Bazedoxifene** is combined with conjugated estrogens for the treatment of menopausal **osteoporosis** and the **treatment of moderate to severe hot flushes.**

Scientific name	Dosage form	Trade name	concentration
Clomiphene	Tab	Clomid®, Serophene®, Ovamit®	50 mg
Raloxifene	Tab	Evista®	60 mg
Ospemifene	Tab	Osphena®	60 mg
Bazedoxifene + Conjugated Estrogen	Tab	Duavee®	20 mg + 0.45 mg

Note: Experimental SERM-Estrogen Combinations

- There is considerable interest in menopausal hormone therapy using combinations of a pure **estrogen agonist** (as estradiol) **with a SERM** that has predominantly antagonist activity in the breast and endometrium but does not distribute to the CNS.
- The strategy is to obtain the beneficial actions of the agonist (e.g., prevention of hot flashes and bone loss) while the SERM blocks unwanted agonist action at peripheral sites (e.g., proliferative effects in breast and endometrium) but does not enter the brain to cause hot flashes.

C- Estrogen receptor Antagonists:

These are related to the SERMs but mainly **used for the treatment of breast cancer**, they include: **Tamoxifen, Toremifene** and **Fulvestrant.**

1. **Tamoxifen** is highly effective in the **treatment of breast cancer**, and it's now indicated as the hormonal treatment of choice for both early and advanced breast cancer in women of all ages.
   a. **Tamoxifen** is used (off-label) to **stimulate ovulation** in women with **anovulatory infertility** with doses of 5 – 40 mg every 12 hrs. For 4 days only.
   b. **Tamoxifen** is used (off-label) to **prevent estrogen related Gynecomastia**, resulting from elevated estrogenic levels; **(thus used by some athletes and bodybuilders).**
   c. **Adverse effects of Tamoxifen include** hot flashes and nausea, Pulmonary Embolism, menstrual irregularities and vaginal bleeding.
2. **Toremifene** has therapeutic actions similar to Tamoxifen, **usually used in breast cancer**; it is also approved by the FDA in 2013 for the treatment of prostate cancer.
3. **Fulvestrant** may be efficacious in women who become **resistant to Tamoxifen**; it is administered as a **once-monthly injection.**

Scientific name	Dosage form	Trade name	concentration
Tamoxifen	Tab	Nolvadex® , Soltamox®	10 mg , 20 mg
Toremifene	Tab	Fareston®, Acapodene®	60 mg
Fulvestrant	Inj. Solu.	Faslodex®	50 mg/ml

D- Anti-Estrogens: (Estrogen-Synthesis Inhibitors)

1. Aromatase is an enzyme responsible for the extra-adrenal synthesis of Estrogen; it converts Androgen into Estrogen in a process called Aromatization; which take place in the liver, fat, muscle, skin and breast tissue, drugs inhibiting that enzyme is called **Aromatase inhibitors**, they thus selectively block production of estrogens, they include:
   a. Type 1: **Formestane** and **Exemestane.** (irreversibly inactivate aromatase)
   b. Type 2: **Anastrozole, Letrozole,** and **Vorozole.** (reversible inactivation)
2. These agents **(Anti-Estrogens)** may be used as **first-line treatment of breast** cancer or as second-line drugs after Tamoxifen. They are highly efficacious and actually superior to Tamoxifen in adjuvant use for postmenopausal women.
   - They have the **added advantage of not increasing the risk of uterine cancer or venous thromboembolism**, because they dramatically reduce circulating as well as local levels of estrogens, and they produce hot flashes.

- **They lack the beneficial effect of Tamoxifen to maintain bone density**, and thus are usually administered with bisphosphonates.
- **ONLY Exemestane, Letrozole, and Anastrozole** are currently approved by the FDA**.**

3. **Formestane** possesses a **weak anabolic activity,** thus it's abused by some athletes and bodybuilders, Also **Exemestane** has **androgenic properties**; which cause acne and weight gain.
4. **Letrozole** is used (off-label) for **ovulation induction**, it acts by suppressing estrogen levels in young women, and this causes the brain and pituitary gland to increase the output of FSH (follicle stimulating hormone), thus in women that have polycystic ovary syndrome (PCOS) or anovulation; the increase in FSH hormone can result in development of a mature follicle in the ovary and ovulation of an egg.
   - The most common dose is 2.5 mg daily for 5 days starting within about 5 days of onset of menstruation (preferably on 2nd day), sometimes it is given in higher doses of 5 mg–7.5 mg.

Scientific name	Dosage form	Trade name	concentration
Formestane	Tab	Lentaron®	250 mg
Exemestane	Tab	Aromasin®	25 mg
Anastrozole	Tab	Arimidex®	1 mg
Letrozole	Tab	Femara®	2.5 mg
Vorozole	Tab	Rivizor®	2.5 mg

E- Progestogens or Progestins:

1. The two most frequent uses of Progestins are for **contraception**, either alone or with an estrogen, and in combination with estrogen for **hormone therapy** of postmenopausal women, also may be used in **menstrual disorders** such as **dysmenorrhea** and **menorrhagia** associated with dysfunctional uterine bleeding.
2. Progestogens may also be used in the **management of endometriosis**.
   - **Medroxyprogesterone** is also given in **Paraphilia in males** (a psychiatric disorder in which a person undergoes a sexual arousal toward things and objects or events that is normally non-sexual to a normal person; ex: sexually attractive to animals or Anime).
   - **Medroxyprogesterone** was also given as a **treatment for homosexuality in men** back then when the medical Agencies considered homosexuality as a psychiatric disorder.
3. Some Progestogens as **(Dydrogesterone, Hydroxyprogesteron, Allyl-Estrenol)** have been used for the **prevention of spontaneous abortion** in women with a history of recurrent miscarriage (habitual abortion), They are locally called "pregnancy Fixer" in Arabic "مثبت حمل", this term is actually not related to their role in pregnancy, their use as fixers are not supported by any scientific references, but experience and evidence based medicine proved them useful in some cases.
   a. Note that these Progestins **are not useful in normal pregnancies as Fixers**.
   b. They should be prescribed only by professionals due **their doses must be precise.**
   c. Their role in pregnancy is **limited in the threatened abortion only** (when there is vaginal bleeding in pregnancy).
   d. Also, can be **used in IVF luteal phase as a support for the endometrium** when there is a deficiency in progesterone levels**.**
   e. For more info about (infertility) and the progesterone role; refer to chapter 7.
4. Progestins also are **used diagnostically for secondary amenorrhea**; an oral progestin is given to an amenorrheic woman for 5-7 days, if endogenous estrogens are present, withdrawal bleeding will occur.
5. **Side effects of Progestins include**: are headache, depression, **weight gain, and changes in libido**, also they **increase the risk of thromboembolic events (DVT, PE).**

6. Injectable **Medroxyprogesterone** has been associated with an **increased risk of osteoporosis**, which has led to recommendations for limiting the duration of use to 2 years unless other forms of contraception are unsatisfactory.

Scientific name	D. form	Trade name	concentration
Progesterone (micronized)	Cap	Progesterone®	100 mg , 200 mg
Progesterone	Amp	Progesterone®	50 mg/2 ml
	Vag. Insert	Cyclogest®, Endometrin®	100 mg , 400 mg
	Vag. Gel	Crinone®	4% , 8%
Megestrol	Tab	Megace®	20 mg , 40 mg
Etonogestrel	Implant	Implanon®	68 mg
Levonorgestrel	Tab	Plan B®	0.75 mg , 1.5 mg
Norethisterone acetate (or) **Norethindrone**	Tab	Camila®	0.35 mg
	Tab	Primolut-N®, Normolut-N®	5 mg
Lynestrenol	Tab	Orgametril®	5 mg
	Tab	Exluton®	0.5 mg
Medroxyprogesterone	Tab	Provera®	5 mg , 10 mg
	Inj.	Depo-Provera®	150 mg
	Prefilled Inj.	Depo-Provera Pen®	104 mg/0.65 ml
Dienogest	Tab	Visanne®	2 mg
Desogestrel	Tab	Cerazette®	1 mg
Nomegestrol	Tab	Lutenyl®	5 mg
Hydroxyprogesteron	Amp	Primolut-Depot®, Makena®	250 mg , 500 mg
Dydrogesterone	Tab	Duphaston®	10 mg
Allyl-Estrenol	Tab	Gestin® , Gestal®	5 mg

Progestogens and Estrogens Combinations for Contraception:

Note: EE = Ethinyl Estradiol (Estrogen)

Scientific name(s)	D. form	Trade name	concentration
Levonorgestrel + EE	Tab	Microgynon®, Nova®, Nora®	0.1 mg + 20 mcg
Drospirenone + EE	Tab	Yasmine® , Zahraa®	3 mg + 0.03 mg
	Tab	Yaz® , Gianvi®, Warda®	3 mg + 0.02 mg
Desogestrel + EE	Tab	Marvelon®	0.15 mg + 0.03 mg
Gestodene + EE	Tab	Gynera®,Femodene®, Katya®	0.075 mg + 0.03 mg
	Tab	Sunya®	0.075 mg + 0.02 mg
Norgestrel + EE	Tab	Cryselle®	(0.3 mg + 30 mcg), (0.5 mg + 50 mcg)
Etonogestrel + EE	V. Ring	NuvaRing®	0.12 mg + 0.015 mg
Norgestimate + EE	Tab	Mononessa®	0.25 mg + 35 mcg
Norethindrone + EE	Tab	Femhrt® , Jinteli®	(0.4 mg + 35 mcg)
Etynodiol + EE	Tab	Zovia®	0.05 mg + 1 mg
	Tab	Kelnor®	0.035 mg + 1 mg
Norethindrone + Mestranol	Tab	Necon®	1 mg + 50 mcg
Dienogest + Estradiol	Tab	Natazia®, Qlairis®, Qlairista®	**4 phase tab**
Norelgestromin + EE	Patch	Evra®	(150 mcg + 35 mcg) per day
Norethindrone + Estradiol	Amp	Mesocept®	50 mg + 5 mg
Progesterone + Estradiol	Amp	DE-Pro Lezum®	12.5 mg + 2.5 mg

Progestogens and Estrogens Combinations for HRT:

1. In **menopause,** there is a decline in the levels of estrogen and progesterone occurs naturally following the age of 45-50 years, when the menstrual cycle ceases, the sudden reduction in levels of estrogen often causes distressing symptoms, and many doctors suggest that hormone supplements be used around the time of the menopause (hormone replacement therapy or HRT).
- Such hormone replacement therapy may also be prescribed for women who have undergone early or premature menopause, for example, as a result of surgical removal of the ovaries or radiotherapy for ovarian cancer.
- Estrogen is used together with a progestogen unless the woman has had a hysterectomy, in which case estrogen alone is used. If dryness of the vagina is a particular problem, a cream containing an estrogen drug may be prescribed for short-term use.

2. HRT is primarily used to alleviate symptoms of the menopause, such as hot flushes and vaginal dryness, it may also be used to prevent or treat osteoporosis in some women; However, the benefits of HRT must be weighed against the various increased health risks associated with its use, such as breast cancer, stroke, and thromboembolism.
- **Breasts:** There is a slightly increased risk of breast cancer with long-term use of HRT; The increase in risk is related to the length of time for which HRT is used, if HRT is stopped the risk reduces to its pre-treatment level within about five years.
- **Heart and circulation**: HRT increase the risk of thromboembolism.
- **Bones:** For women who go through premature menopause, HRT reduces the thinning of bone that occurs in osteoporosis and thus protects against fractures.
- **Brain:** HRT increases the risk of stroke.
- **Vagina:** Thinning of vaginal tissues leading to painful intercourse can be prevented by HRT.

Scientific name	D. form	Trade name	concentration
Norgestrel + Estradiol	Tab	Progyluton®	11 tab (2 mg Estradiol only) 10 tab (2 mg Estradiol **+** 0.5 mg Norgestrel)
Norgestimate + Estradiol	Tab	Cilest® , Prefest®	15 tab (1 mg Estradiol only) 15 tab (1 mg Estradiol **+** 0.09 mg Norgestimate)
Norethindrone + Estradiol	Tab	Climagest®	16 tab (1 mg Estradiol only) 12 tab (1 mg Estradiol **+** 1 mg Norethindrone)
	Patch	Activella®	(0.25 mg + 0.05 mg) per 24 hr.
Drospirenone + Estradiol	Tab	Angeliq®	(0.25 mg + 0.5 mg), (2 mg + 1 mg)
Norethindrone + Estradiol	Tab	Estalis®	0.1 mg + 0.5 mg
Norethindrone + Estradiol	Tab	Climesse®	0.7 mg + 2 mg
Norethindrone + EE	Tab	----------	1 mg + 5 mcg
Medroxyprogesterone + Conjugated Estrogens	Tab	Premphase® , Prempro®	(2.5 mg + 0.625 mg), (5 mg + 0.625 mg)
Medroxyprogesterone + Conjugated Estrogens	Tab	Premique®	(1.5 mg + 0.3 mg), (5 mg + 0.625 mg)
Levonorgestrel + Estradiol	Patch	Climara Pro®	1.39 mg + 4.4 mg
Progesterone + Estradiol	Cap	Bijuva®	100 mg + 1 mg

F- Anti-Progestins and Prostaglandins:

Anti-Progestins include: **Mifepristone**, **Onapristone, Asoprisnil** and **Ulipristal**.
Prostaglandins include: **Misoprostol, Dinoprostone, Carboprost, Sulprostone** and **Gemeprost.** (For more info see Chapter 7, section 2).

1. **Mifepristone** is used clinically to **induce abortions and for pregnancy termination**, usually combined with **Misoprostol (or other Prostaglandin)** for this purpose.
   - **Mifepristone** also acts as **Cortisol receptor blocker**, and prevents cortisol receptor binding, thus **reduces the excess cortisol effects** (as hyperglycemia) associated with Cushing syndrome.
   - **Other Uses** include: induce labor, and to treat uterine leiomyoma, endometriosis, meningioma, and breast cancer.
2. **Onapristone** is an oral anti-progestin hormone blocker that has been shown in clinical trials to **exhibit anti-tumor activity** in patients with breast cancer.
3. **Asoprisnil** shows **mixed progesterone agonist/antagonist activity and endometrial selectivity** in animal and humans. In non-human primates and humans, **Asoprisnil** induced amenorrhea and suppressed endometrial proliferation in the presence of normal estradiol (E2) concentrations.
   - Animal studies also shows its potential to control the production of prostaglandins in the endometrium that are thought to **play a role in endometriosis-related pain.**
4. **Ulipristal** is a partial agonist at the progesterone receptor, **used for emergency contraception**.
   - It remains effective up to 120 hours (5 days) after intercourse.
   - **Ulipristal** is also used for pre-operative treatment of moderate to severe symptoms of **uterine fibroids in adult women** of reproductive age in a daily dose of a 5 mg tablet.
5. **Misoprostol** was first introduced to **prevent and treat stomach ulcers**, but later on it has been **used to start labor, induce abortions** and to treat postpartum bleeding due to insufficient contraction of the uterus.
   - It is approved for use in the **prevention of NSAID-induced gastric ulcers.**

Scientific name	Dosage form	Trade name	concentration
Anti-Progestins			
Mifepristone	Tab	Mifeprex® , Korlym®	200 mg , 300 mg
Ulipristal	Tab	Ella®, EllaOne®	30 mg
	Tab	Esmya®	5 mg
Prostaglandins			
Misoprostol	Tab	Cytotec®	200 mcg
	Vag. Tab	Vagiprost®	200 mcg
Dinoprostone	Vag. insert	Cervidil®	10 mg , 20 mg
Carboprost	Inj. Solu.	Hemabate®	250 mcg\ml
Sulprostone	Inj. Solu.	Nalador®	500 mcg\vial
Gemeprost	Vag. Tab	Cervagem®	1 mg

Notes:

1. Both **Mifepristone** and **Misoprostol should be only given by Authorized prescription,** since they can be abused for inducing illegal abortions.
2. **Sulprostone** is used I.M. for the Induction of termination of pregnancy (maternal or fetal indication); induction of labor in the case of fetal death in utero. Treatment of postpartum atonic hemorrhage**.**
3. **Gemeprost** is used as a **treatment for obstetric bleeding (used in preparing the cervix before uterine surgery),** also it is used **with mifepristone to terminate pregnancy** up to 24 weeks gestation.

Second: Male sex hormones

1. Male sex hormones, or **Androgens**, are responsible for the development of male sexual characteristics, the main androgen is **Testosterone**, which in men is produced by the testes from puberty onwards; Women also produce testosterone in small amounts in the adrenal glands, but its exact function in the female body is not known (it may have a role in female libido).
   - **Testosterone** has two major effects: an androgenic effect and an anabolic effect, its androgenic effect is to stimulate the appearance of the **secondary sexual characteristics** at puberty, such as the growth of body hair, deepening of the voice, and an increase in genital size; and its anabolic effects are to increase muscle bulk and accelerate growth rate.
   - There are a number of synthetically produced derivatives of testosterone that produce varying degrees of the androgenic and anabolic effects, Derivatives with mainly anabolic effect are called **Anabolic Steroids.**

A- Androgens

1. The Androgens (as **testosterone** or its esters) are a group of steroids that have anabolic and/or masculinizing effects in both males and females.
   a. The primary indication for androgen is **as replacement therapy in male hypo-gonadal disorders** (given to men to promote the development of male sexual characteristics when hormone production is deficient); caused by either pituitary or testicular disorders.
   b. They may also help to stimulate development of **secondary male sexual characteristics** and to **increase sex drive (libido)** in adult men with inadequate testosterone levels.
   c. **Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is associated hypogonadism.**

2. **Adverse effects of Androgens:**
   a. **In females:** they can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development, menstrual irregularities.
   b. **In males:** Excess androgens can cause priapism, impotence, decreased spermatogenesis, and gynecomastia.

3. **Danazol** is a **mild androgen**, is used in the **treatment of endometriosis** (ectopic growth of the endometrium) **and fibrocystic breast disease.**
   a. **Danazol** also **possess anti-estrogenic activity**, it inhibits release of FSH and LH but has no effect on the aromatase.
   b. **Danazol** has been used—mostly off-label—for other indications, mainly **management of menorrhagia, fibrocystic breast disease**, immune thrombocytopenic purpura, premenstrual syndrome, breast pain (mastodynia).
   c. **Have many side effects**, which include: Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth.

4. **Mesterolone** is Dihydrotestosterone (DHT) derivative, in the late 70s and early 80s, it was used with some success in controlled studies of men suffering from various forms of depression, but it's no longer used for this purpose.
   - It's mainly prescribed for **infertility in men caused by hypogonadism** or to replace testosterone in men with hypogonadism.
   - Also used to treat various types of **sexual dysfunction**, which often result from a low endogenous testosterone level. It can usually reverse problems of sexual disinterest and impotency, and is sometimes used to **increase the sperm count.**
   - **Abused by some bodybuilders** for its anabolic effect and anti-estrogenic effect.

5. **Oxandrolone** improves both short-term and long-term outcomes in people recovering from severe burns and is well-established as a safe treatment for this indication.

Scientific name	Dosage form	Trade name	concentration
Testosterone	Inj. (I.M.)	Sustanon®, Nebido®	100 mg/ml , 250 mg/ml
	Inj. (I.M.)	Virormone®	50 mg/ml
	S.C Inj.	Depo-Testerone®	75 mg
	Tab	Striant®	30 mg
	Cap	Andriol Testocaps®	40 mg
	Skin Gel	Testim® , Testogel®	50 mg/ 5 gm tube
Methyl-Testosterone	Tab , Cap	Android® , Testred®	10 mg
Oxandrolone	Tab	Oxandrin®	2.5 mg , 10 mg
Mesterolone	Tab	Proviron®	25 mg
Danazol	Cap	Danol®, Danazol®	100 mg , 200 mg

***** All above androgens have a mild to moderate anabolic effect.

****** Some uses **Testosterone Gel for Erectile Dysfunction** by applying it topically on the penis, **this is wrong and not applicable, and no benefit is achieved.**

B- Anabolic steroids (Androgens with high anabolic effect)

1. Anabolic steroids are synthetically produced variants that mimic the anabolic effects of the natural hormone **Testosterone**, they increase muscle bulk and body growth.
   - Doctors occasionally prescribe anabolic steroids and a high-protein diet to promote recovery after serious illness or major surgery; the steroids may also help to increase the production of blood cells in some forms of anemia and to reduce itching in chronic obstructive jaundice.
   - Anabolic steroids have been widely abused by athletes because these drugs **speed up the recovery of muscles** after a session of intense exercise, this enables the athlete to go through a more demanding daily exercise program, which results in a significant **improvement in muscle power** and **mass (size),** they also **decrease body fat**, and **enhance athletic performance** and **body appearance**.
   - Their side effects range from acne and baldness to psychological changes (anger, depression, etc.), fluid retention, reduced fertility in men and women, hardening of the arteries, a long-term risk of liver disease, and certain forms of cancer.

2. **Anabolic steroids** can be used to treat **senile osteoporosis** and **chronic wasting** associated with human immunodeficiency virus (HIV) or cancer; they may also be used as adjunct therapy in severe burns and to speed recovery from surgery or chronic debilitating diseases.
   - **a.** Anabolic steroids are used to **increase lean body mass, muscle strength,** and **endurance** in athletes and body builders.
   - **b.** Anabolic steroids have been given for **osteoporosis in women;** but they are no longer advocated for this purpose.
   - **c.** Androgens act directly on the A.R in fat cells to affect fat burning; the stronger the androgen binds to the A.R, the higher the lipolytic (fat burning) effect on adipose tissue; Since some steroids even increase the numbers of A.R in muscle and fat, this fat loss effect would be amplified with the concurrent use of other compounds, such as Testosterone.
   - **d.** Extra or Excess steroids in the human body will be transformed by aromatize enzyme into Estrogen (natural process); thus, taking anabolic steroids without actually exercising will result in feminization or Gynecomastia!!

3. **Nandrolone** is an anabolic steroid with high androgenic effect, it is usually given in the form of oily intramuscular injections as an anabolic after debilitating illness.
   - It has the advantage of providing joint pain relief.

4. **Tetrahydrogestrinone** (THG), a potent androgen that appears to have been designed and synthesized in order to avoid detection by antidoping laboratories on the basis of its novel structure and rapid catabolism.

5. **Methandrostenolone** (Dianabol®); the most anabolic steroid abused worldwide, it's the most potent mass builder in terms anabolic activity; it can cause a notable increase in insulin levels, it also suppresses the natural production of testosterone leading to testicular atrophy; thus an exogenous testosterone supplement needs to be taken to combat these effects when taking it.
   - It is a relatively strong estrogenic anabolic steroid; it is converted to methyl-estradiol rather than estradiol; (which is far more powerful than estradiol); this can make side effects like gynecomastia and water retention and elevated Blood Pressure very possible.
   - To combat the estrogenic side effects, anti-estrogens are commonly recommended when supplementing with this steroid such as (Tamoxifen, Letrozole).
   - It can have a pronounced negative effect on cholesterol; This includes HDL cholesterol suppression and increases in LDL cholesterol; thus, increasing the risk of CHD.

6. **Trenbolone** is very potent and can be 3-5 times stronger than testosterone; it doesn't cause water retention in the body as other anabolic steroids does (it reduce water content under the skin), it can cause a major increase in aggression; it's also affects the natural testosterone levels and must be co administered with an exogenous testosterone supplement.
   - Considered as a fat loss agent.
   - Trenbolone chemical structure makes it resistant to the aromatize enzyme (conversion to estrogen) thus absolutely no percentage of Trenbolone will convert to estrogen.
   - It can easily cause adverse androgenic side effects in people who are prone to hair loss, prostate enlargement, oily skin and acne.
   - Trenbolone is also a strong progestin; thus, an anti-progestin is co administered (as Letrozole); it also increases prolactin; thus (Bromocriptine or Cabergoline) are often recommended to lower prolactin levels.

7. **Stanozolol** is a Dihydrotestosterone (DHT) derived anabolic androgenic steroid, (a structurally altered form of DHT); it carries an anabolic rating of 320 and an androgenic rating of 20.
   - Many studies have shown it can have a positive impact on strengthening tendons.
   - This steroid is great for promoting weight loss (fat burner).
   - It has no estrogenic activity; (does not aromatize at all), thus this steroid cannot cause gynecomastia or excess water retention.
   - Stanozolol is well known for reducing HDL cholesterol and increasing LDL cholesterol.

8. **Clenbuterol**; is not an anabolic steroid, in fact it is a powerful bronchodilator (B_2 agonist) that is used to treat breathing disorders like asthma; it has never been approved by the U.S. FDA, it's commonly used as a thermogenic and a fat burning agent.
   - It does not actively burn fat by attacking fat cells, but rather stimulates the metabolism by increasing the body's temperature; this occurs due to the beta-2 agonist activity stimulating the mitochondria of the cells to produce and release more heat; this heats up the body's temperature (slightly), enhances the metabolism and causes a burn body fat at a greater rate.

Scientific name	D. form	Trade name	concentration
Nandrolone	Inj.	Deca-Durabolin®	25 mg , 50 mg
Fluoxymesterone	Tab	Androxy®	2 mg , 5 mg , 10 mg
Oxymetholone	Tab	Anadrol®	50 mg
Metenolon	Tab	Primobolan® , Nibal®	50 mg
Dehydroepiandrosterone	Tab	DHEA®	25 mg , 50 mg
Methandrostenolone	Tab	Dianabol®	10 mg , 20 mg
Trenbolone	Tab	Tren® , Parabolan®	10 mg , 25 mg , 75 mg
	Amp		100 mg/ml , 200 mg/ml
Stanozolol	Tab	Winstrol®	10 mg , 20 mg , 50 mg
	Amp		50 mg/ml , 100 mg/ml
Clenbuterol	Tab	ThermoClen®	20 mcg

B- Anti-Androgens

1. Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors.
    a. **Ketoconazole** inhibits several of the CYP450 enzymes involved in steroid synthesis.
    b. **Finasteride** and **Dutasteride** are used for the treatment of benign prostatic hypertrophy; **inhibit 5α-reductase** resulting in the decrease in formation of Dihydrotestosterone in the prostate leading to a reduction in prostate size.
    c. **Flutamide, Bicalutamide and Nilutamide** act as competitive inhibitors of androgens.

1. **Cyproterone** acetate is an anti-androgen; it was used in the 1990s for the **control of excessive libido in severe hyper-sexuality or sexual deviation in men**.
    a. **Cyproterone** acetate may be used with **Ethinyl-estradiol (EE)** in women **for the control of acne and hirsutism; i**t is given after food.
    b. **Has weak progestogen activity** (acts like progesterone); Thus, it can be used to treat hot flashes, and is also a component of some combined oral contraceptive pills.
    c. **Fatigue and lassitude may be produced by the drug which may impair performance of skilled tasks** (e.g. driving).
2. **Spironolactone** (K sparing diuretic) is an inhibitor of aldosterone that also is a weak inhibitor of the androgen receptor and a weak inhibitor of testosterone synthesis.
    a. Spironolactone can be **used in women to treat hirsutism**; it is moderately effective, but may cause irregular menses.

Scientific name	Dosage form	Trade name	concentration
Ketoconazole	Tab	Nizoral®, Ketonaz®	200 mg
Finasteride **	Tab	Proscar®, Prostacare®	1 mg , 5 mg
Dutasteride	Cap	Avodart®	0.5 mg
Flutamide	Cap	Drogenil® , Cytomid®	125 mg
Bicalutamide	Tab	Casodex®	50 mg
Nilutamide	Tab	Nilandron®	150 mg
Cyproterone	Tab	Androcur®	50 mg
Spironolactone	Tab	Aldacton®	25 mg , 50 mg , 100 mg

** **Finasteride also is approved for use in the treatment of male pattern baldness.**

Other Anti-Androgens: (mainly used for prostate cancer)

Scientific name	Dosage form	Trade name	concentration
Abiraterone	Tab	Zytiga®	250 mg
Degarelix	Inj. Powder	Firmagon®	80 mg , 120 mg (per Vail)
Enzalutamide	Cap	Xtandi®	40 mg

Some Combination products:

Scientific name(s)	D. form	Trade name	concentration
Anti-Androgen + Estrogen			
Cyproterone + Ethinyl Estradiol	Tab	Diane® , Clairette®	2 mg + 0.035 mg
Androgen + Estrogen			
Methyl-Testosterone + Esterified Estrogens	Tab	Covaryx®, Estratest®	(1.25 mg + 0.625 mg) , (2.5 mg + 1.25 mg)

*** Diane® was withdrawn from the markets in 2012 in Canada and France** due the high risk (4 times more risk) of **venous thromboembolism** (blood clots in veins) than other alternatives.

- **Diane® should not be used in Contraception.**

Third: Gonadotropins and related drugs

A) Gonadotropins types include:

a. **Menotropins** (human menopausal gonadotropins or **hMG**) are obtained from the urine of postmenopausal women and **contain FSH** and **luteinizing hormone (LH).**
b. **Chorionic gonadotropin (hCG)** is a placental hormone **structurally related to LH** which is an **LH receptor agonist**, it is also excreted in the urine.
c. **Urofollitropin** is **FSH** obtained from postmenopausal women and is **devoid of LH.**
d. **Follitropin alpha** and **Follitropin beta** are human **FSH products** manufactured using recombinant DNA technology.
e. **Lutropin Alfa** is a **synthetic LH**, used usually concomitantly with FSH as separate injections.
f. **Recombinant hMG** contains both **Follitropin Alpha** and **Lutropin Alfa**
g. **Gonadorelin** is a **synthetic LH** releasing hormone (GnRH).

1. Follicle-stimulating hormone **(FSH)** and luteinizing hormone **(LH)** together, follicle-stimulating hormone alone, or chorionic gonadotropin, **are used in the treatment of infertility in women** with proven hypopituitarism or who haven't responded to clomiphene.
- **FSH** stimulates ripening of the egg follicle.
- **LH** triggers ovulation and ensures that progesterone is produced to prepare the uterus for the implantation of the egg.

2. All of these hormones are injected via the I.M. or subcutaneous route:
a. **In Females:** Injection of **hMG** or **FSH** over a period of 5 to 12 days causes ovarian follicular growth and maturation, then with an injection of **hCG** ovulation occurs.
   - **Method of ovulation induction:** (2nd line approach, see chapter 7, section 4)
     1. Usually an **Injection of hMG or FSH (75 IU every day)** is initiated over usually a period of 5 to 12 days to cause ovarian follicular growth and maturation; you may increase the dose as needed every 7 days by 37.5 IU.
     2. **Addition of Clomiphene 50 mg tab decrease the number of hMG or FSH injections** needed to complete the cycle of ovarian follicular maturation.
     3. Maximum daily dose of hMG or FSH is 300 IU daily.
     4. Maximum duration of this cycle is 35 days.
     5. **Then an injection of hCG (5000 IU) or (250 mcg of recombinant hCG) is given to cause ovulation.** (Injected after 1 day after the last hMG or FSH inj.)
     6. **Then Fertilization must occur within 36 hours after hCG administration**, either by intercourse (normal Sex) or intra-uterine insemination (IUI).

b. **In men** (who are deficient in gonadotropins) treatment with **hCG** causes **external sexual maturation,** and with the subsequent injection of **hMG** or **Follitropin**, **spermatogenesis occurs.**

3. In female, **adverse effects** include **ovarian enlargement** and possible hypovolemia, multiple births are common; **Men may develop Gynecomastia with overdose.**
- LH or hCG can cause tiredness, headaches, and mood changes.
- FSH can cause the ovaries to enlarge, producing abdominal discomfort.

Scientific name	Dosage form	Trade name	concentration
Menotropin (hMG) (FSH + LH)	Inj.	Merional® , Pergonal®	(75 IU + 75 IU), (150 IU + 150 IU)
Chorionic gonadotropin (hCG)	Inj.	Pregnyl® , Choragon®	5000 IU, 1500 IU, 10,000 IU
FSH (Urofollitropin)	Inj.	Diclair FSH®, Fastimon®	75 IU , 150 IU
Follitropin Alfa	Prefilled Inj.	Gonal-F®	75 IU (5.5 mcg)
	Prefilled Inj.	Gonal-F®	300 IU (22 mcg)

Lutropin Alfa	Inj. Powder	Luveris®	75 IU , 82.5 IU
Recombinant hMG (Follitropin Alfa + Lutropin Alfa)	Inj.	Pergoveris®	150 units (11 mcg) + 75 units (3 mcg)
Follitropin Beta	Inj.	Puregon®	50 IU
Choriogonadotropin Alfa	Prefilled Inj.	Ovitrelle®	250 mcg/0.5 ml (6500 I.U)
Corifollitropin Alfa	Prefilled Inj.	Elonva®	100 mcg/0.5 ml , 150 mcg/0.5 ml
Gonadorelin	Inj. Powder	Lutrepulse®	0.8 mg/vial

B) Gonadotropin-releasing hormone (GnRH) Analogs (agonists):

1. Also called Gonadorelin analogs, they include: **Nafarelin, Histrelin, Buserelin, Goserelin, Leuprolide,** and **Triptorelin**
2. Administration of Gonadorelin analogues produces an initial phase of stimulation of follicle stimulating hormone (FSH) and luteinizing hormone (LH); (thus they are useful in treatment of infertility; but the continued administration is followed by down-regulation of gonadotropin-releasing hormone receptors, thereby reducing the release of gonadotropins (FSH and LH); which in turn leads to inhibition of androgen (testosterone) and estrogen production; thus they are useful in prostate cancer (where testosterone is high), and in breast cancer (where estrogen is high) or endometriosis.
3. Gonadorelin analogues are used in the treatment of **Endometriosis**, Other uses include the treatment of **precocious puberty, infertility, anemia due to uterine fibroids** (together with iron)**, breast cancer,** and **before intra-uterine surgery,** Use of Leuprorelin and Triptorelin for 3 to 4 months before surgery reduces the uterine volume, fibroid size and associated bleeding [(1)].

Scientific name	Dosage form	Trade name	concentration
Nafarelin	Nasal Spray	Synarel®	2 mg/ml
Histrelin	Implant	Vantas®	50 mg
Buserelin	Nasal Spray	Suprefact®	150 mcg/dose
	Inj. (S.C)	Metrelef®	5.5 mg/5.5 ml
Goserelin	Implant (S.C)	Zoladex®, Zoladex LA®	3.6 mg (for 1 month), 10.8 mg (for 3 months)
Leuprolide	Inj.	Lupron®	5 mg/ml
Triptorelin	Inj. (S.C.)	Decapeptyl®	0.1 mg/ 1ml
	Inj. Powder	Trelstar®, Trelstar depot®	3.75 mg , 11.25 mg , 22.5 mg

Notes:

1. **Nafarelin** may be used in the treatment of endometriosis or uterine fibroids, to treat central precocious puberty, and to control ovarian stimulation in IVF.
2. **Goserelin** Acetate is used to treat hormone-sensitive **cancers of the breast** (in pre- and peri-menopausal women) and **prostate cancer**, and some benign gynecological disorders (**endometriosis, uterine fibroids and endometrial thinning**).
3. **Leuprolide** has been tested as a treatment for **reducing sexual urges**, High doses are sometimes used to chemically **castrate sexual offenders.**
   - **Also used for Endometriosis.**
4. **Triptorelin (0.1 mg)** is prescribed to women who are unable to conceive, it helps to assist pregnancy in certain women who suffer from fertility problems by stimulating the release of pituitary gonadotropins, **but higher Conc. (3.75 mg, 11.25 mg) is given for Prostate Cancer.**

C) Gonadotropin-releasing hormone (GnRH) Antagonists:

1. A GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of these drugs results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone.

2. These include: **Cetrorelix** and **Ganirelix**, they inhibit the release of gonadotrophins (LH, FSH).
   - They are used in the treatment of infertility by assisted reproductive techniques (IVF).
   - Also, may be used to treat hormone-sensitive cancers of the prostate and breast.

Scientific name	Dosage form	Trade name	concentration
Cetrorelix	Inj.	Cetrotide®	0.25 mg , 3 mg kit
Ganirelix	Prefilled Inj.	Antagon®, Orgalutran®	250 mcg/0.5 ml
Abarelix	Inj.	Plenaxis	100 mg
Elagolix	Tab	Orilissa®	150 mg , 200 mg
Relugolix	Tab	Relumina®	40 mg

Notes:

1. **Cetrorelix** is used to treat female infertility as either:
   a. **Single dose regimen**: 3 mg SC when serum estradiol levels show appropriate stimulation response (range days 5-9) usually day 7; if hCG not administered within 4 days, continue dose at 0.25 mg/day until hCG administered
   b. **Multiple dose regimen**: 0.25 mg SC morning or evening of stimulation day 5 or morning of stimulation day 6; continue until hCG administered

2. **Ganirelix** is used treat female infertility as 250 mcg SC qDay during mid-to-late follicular phase after initiating follicle-stimulating hormone on day 2 and 3 of the cycle, continue therapy until day of hCG administration.

3. **Elagolix** is specifically indicated for the management of moderate to severe pain associated with Endometriosis; Elagolix significantly decreases symptoms of dysmenorrhea (menstrual pelvic pain), non-menstrual pelvic pain, and dyspareunia (pain during sexual intercourse) in women with Endometriosis.
   - The duration of use of **Elagolix** in the treatment of endometriosis should be limited due to a progressive risk of bone loss, and the lowest effective dosage should be used.
   - **Elagolix** can be used for up to 24 months at the 150 mg once per day dosage and for up to 6 months at the 200 mg twice per day dosage.

4. **Relugolix** is approved in Japan (only) for the treatment of uterine fibroids (uterine leiomyoma) in women; It is used at a dosage of 40 mg once daily.
   - It is under development for the treatment of Endometriosis, Prostate Cancer in the USA.

6.4 -Posterior pituitary hormones

1. The pituitary gland, which lies at the base of the brain, produces a number of hormones that regulate physical growth, metabolism, sexual development, and reproductive function.
2. Many of these hormones act indirectly by stimulating other glands, such as the thyroid, adrenal glands, ovaries, and testes, to release their own hormones; (as discussed in the sections above).
   A. **Thyroid-stimulating hormone:** stimulates production and release of thyroid hormones.
   B. **Prolactin:** stimulates glands in the breast to produce milk in women.
   C. **Corticotrophin (ACTH):** controls production and release of adrenal corticosteroid hormones.
   D. **Gonadotrophins:** (FSH) and (LH) act on the sex glands to stimulate egg production and release in females, and sperm production in males; They also control the output of the sex hormones estrogen, progesterone, and testosterone.
   E. **Growth hormone:** promotes normal growth and development.
   F. **Melanocyte-stimulating hormone:** controls skin pigmentation.
   G. **Antidiuretic hormone:** (ADH or vasopressin) regulates the output of water in the urine.

3. In this section, we'll talk about the remaining hormones which are secreted from the posterior part; These include: **Vasopressin, (Desmopressin)** and **Oxytocin** (see chapter 7).
   - **Vasopressin** acts on the kidneys, controlling the amount of water retained in the body and returned to the blood, a lack of ADH is usually caused by damage to the pituitary; this in turn causes diabetes insipidus.

4. In **Diabetes Insipidus (DI)**, the kidneys cannot retain water and large quantities pass into the urine; The chief symptoms are constant thirst and production of large volumes of urine.
   - Classified into two types: **Central DI** (in which no vasopressin is secreted), and **Nephrogenic DI** (due the lack of antidiuretic hormone effect in the kidneys).

5. **Central Diabetes insipidus** is treated with ADH or a related synthetic drug, **Desmopressin**, they replace naturally produced ADH.
   - Adjunctive therapies include: **Chlorpropamide**, **Indomethacin**, **Carbamazepine.**
   - **Thiazide diuretics** may be prescribed for **Nephrogenic DI** (see Diuretics, chapter 3); The usual effect of such drugs is to increase urine production, but in diabetes insipidus they have the opposite effect, reducing water loss from the body.

Notes:

1. **Vasopressin** (antidiuretic hormone, **ADH**) is used in the treatment of pituitary (cranial) **diabetes insipidus** as is its analogue **Desmopressin**, also used for **nocturnal enuresis.**
   a. **Desmopressin** is more **potent and has a longer duration of action than Vasopressin**; unlike vasopressin it has no vasoconstrictor effect (It is given by mouth or by **intranasal** route for maintenance therapy).
   b. Patients being treated for primary nocturnal enuresis should be warned to limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards; and to stop taking Desmopressin during an episode of vomiting or diarrhea (until fluid balance normal).
   c. **Side effects include:** Headache, facial flushing, nausea, hyponatremia, seizures.
   d. **The nasal formulation of Desmopressin is no longer indicated for Nocturnal Enuresis by the FDA,** due to reports of seizures in children using the nasal spray.

2. Other rare uses:
   a. **Desmopressin** is also used to **boost factor VIII** concentration in mild to moderate hemophilia and in von Willebrand's disease, also given for the **treatment of Uremic bleeding in acute or chronic renal failure.**
   b. **Terlipressin,** a derivative of vasopressin**,** is used to control **Esophageal Variceal bleeding** in portal hypertension in patient with **liver cirrhosis**.

Scientific name	Dosage form	Trade name	concentration
Vasopressin	Inj. Solu.	Pitressin®	20 units/ml
Desmopressin	Nasal Spray	Minirin® , Stimate®	0.1 mg/ml (5 ml), 1.5 mg/ml (2.5 ml)
	Tab	Minirin®	0.1 mg , 0.2 mg
	Inj. Solu.	Stimate®	4 mcg/ml
Terlipressin	Inj. Powder	Teripress® , Glypressin®	1 mg

Notes:

1. **Desmopressin** 5 ml Nasal spray delivers 10 mcg per spray, while the 2.5 ml Nasal spray delivers 150 mcg per spray. **(the 2.5 ml container is 15 times more potent than the 5 ml container).** → (good luck trying to convene your patients about this fact)
2. **Terlipressin** is used as a **vasoactive drug** in the management of hypotension. It has been found to be effective when norepinephrine does not help; other Indications for use include **norepinephrine-resistant septic shock and hepato-renal syndrome.**
3. **Vasopressin related drugs:** Also called vasopressin V2-receptor antagonist, they can be used in the treatment of hyponatremia resulting from inappropriate secretion of antidiuretic hormone

Scientific name	Dosage form	Trade name	concentration
Conivaptan *	Inj. Solu.	Vaprisol®	5 mg/ml
Tolvaptan **	Tab	Samsca®	15 mg , 30 mg

*** Conivaptan** must be pre-mixed with D5W before administration. (As 20 mg/100 ml).
** **Tolvaptan** acts as vasopressin antagonist.

6.5– Other pituitary hormones (anterior):

A) Growth Hormone (GH) and its analogs

1. Also called **Somatotropin**, the synthetic form **(Somatropin)** is the only form used in medicine, since the GH derived from animal sources is ineffective in humans.
2. **GH** influences a wide variety of biochemical processes; for example, through stimulation of protein synthetic processes, cell proliferation and bone growth are promoted.
   a. Used in the treatment of GH deficiency or growth failure in children.
   b. Indicated for growth failure due to Prader-Willi syndrome, management of AIDS wasting syndrome, short bowel syndrome, and GH replacement in adults with GH deficiency.
   c. **Abused by some athletes seeking to enhance their performance**, GH is not approved for this purpose, and some who have taken it have developed diabetes (DM).
   d. It should not be used in pediatric patients with closed epiphyses, it should also be avoided in patients with increased intracranial pressure, diabetic retinopathy, and obese patients with Prader-Willi syndrome.
3. **Mecasermin** is a recombinant form of human insulin-like growth factor 1 (IGF-I) which is used in the long-term treatment of growth failure and short stature in children with severe primary IGF-I deficiency, for instance due to growth hormone deficiency or Laron syndrome (growth hormone insensitivity).

Scientific name	Dosage form	Trade name	concentration
Somatropin	Inj. Powder	Genotropin® , Saizen®	1.33 mg , 5 mg , 8.8 mg , 12 mg
	Inj. Solu.	Norditropin® , Nutropin®	5 mg/1.5 ml , 10 mg/2 ml , 20 mg/2 ml
Recombinant human growth hormone	Prefilled Inj.	Caretropin®	22 IU (7.5 mg)
Mecasermin	Inj. Solu.	Increlex®	10 mg/ml

B) GH inhibiting hormone and its analogs

1. Also called **Somatostatin,** it suppresses the GH and thyroid-stimulating hormone release, insulin, glucagon, and gastrin**, mainly used for the treatment of Acromegaly;** It has **3 approved analogs** including: **Octreotide, Lanreotide** and **Pasireotide.**
   - **Octreotide** is 40-45 times more potent than endogenous somatostatin.
   - **Octreotide** reduce both GH and **IGF-1;** while **Lanreotide** reduce GH and normalize IGF-1.
2. **Octreotide, Lanreotide** is used in the treatment of acromegaly caused by hormone-secreting tumors and in secretory diarrhea associated with tumors producing vasoactive intestinal peptide, Both **Octreotide, Lanreotide** have a risk of causing gallbladder problems.
3. About **Octreotide:**
   a. Used in **Esophageal Variceal Bleeding** to stop the bleeding.
   b. Used in the treatment of **Sulfonylurea Overdose.**
   c. Used in the treatment of **VIPOMAS** (a neuroendocrine tumors).
   d. Used also in **Several types of diarrhea** including: (AIDS-related, Ileostomy-related, Chemotherapy-related) and in Dumping syndrome.
   e. Depot formulation (LAR) can be administered once every 4 weeks.
4. **Pasireotide** is indicated for **treatment of adults with Cushing disease** in whom pituitary surgery is not an option or has not been curative.
5. **Adverse effects of Somatostatin analogs include**: diarrhea, abdominal pain, flatulence, nausea, and steatorrhea; Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment; also, they can cause Arrhythmias and Hypothyroidism.
6. **Pegvisomant**, is a GH receptor antagonist; it binds to liver GH receptors and inhibits IGF-1.
   - Indicated for the treatment of acromegaly.

Scientific name	Dosage form	Trade name	concentration
Somatostatin analogs (GH inhibitors)			
Octreotide	Inj. Solu.	Sandostatin®	0.1 mg/ml , 0.5 mg/ml , 1 mg/ml
	Depot Inj.	Sandostatin LAR®	10 mg , 20 mg , 30 mg
Lanreotide	Prefilled Inj.	Somatuline®	60 mg , 90 mg , 120 mg
Pasireotide	S.C. Inj.	Signifor®	0.2 mg/ml , 0.6 mg/ml , 0.9 mg/ml
GH receptor antagonist			
Pegvisomant	Inj. Powder	Somavert®	10 mg , 15 mg , 20 mg

C) Prolactin, Bromocriptine and Cabergoline

1. **Prolactin**, also called **lactogenic hormone**, is produced in both men and women; In women prolactin controls the secretion of breast milk following childbirth; The disorders associated with prolactin are all concerned with overproduction **(Hyperprolactinemia).**
   - Prolactin normal range (0 – 20 ng/ml).
   - High levels in women can cause **Galactorrhea** (lactation that is not associated with pregnancy and birth), **Amenorrhea** (lack of menstruation), and **infertility**.
   - If excessive prolactin is produced in men, the result may be **Galactorrhea**, **Erectile Dysfunction, Gynecomastia** and **infertility.**
   - In addition, it **decreases sexual drive** and **reproductive function** in both men and women.
2. Some drugs, such as Methyldopa, Estrogen, and the phenothiazine antipsychotics, can raise the prolactin level in the blood; the increased prolactin levels are usually treated with **Bromocriptine** or **Cabergoline**, (D2-receptor agonists); which inhibit prolactin production.

Notes:

1. **Bromocriptine** is a stimulant of dopamine receptors in the brain; it also inhibits release of prolactin by the pituitary, **Cabergoline** has actions and uses similar to those of Bromocriptine, **but its duration of action is longer.**
   a. **Bromocriptine** inhibits the secretion of prolactin from the anterior pituitary and is used in the treatment of **prolactinoma** (prolactin-secreting pituitary adenomas) and endocrinological disorders associated with hyperprolactinemia, including **amenorrhea**, **galactorrhea**, and **infertility** in both men and women.
   b. Bromocriptine is also FDA approved for the **treatment of Diabetics type 2 (DM);** (it's thought to act throw **resetting the circadian clock** as in a winter rhythm; thus, increasing the dopaminergic neuron activity in morning, which leads to increased glucose tolerance).
   c. Growth hormone secretion may be suppressed by **Bromocriptine** in some patients with **acromegaly**.
   d. Because of its dopaminergic activity **Bromocriptine** is also used **in the management of Parkinson's disease**.
   e. With Bromocriptine **In patients with peripheral vascular disease**, **a worsening of the vasospasm occurs, and in patients with peptic ulcer, there is a worsening of the ulcer.** also, it has the potential to cause pulmonary and retroperitoneal fibrosis.

2. About **Cabergoline**:
   - **More Potent** than Bromocriptine, due to Higher affinity for D2 receptors
   - Used in **infertility** due to hyperprolactinemia, dose usually is 0.5 – 1 mg twice a week.
   - Used as a **lactation suppressant** (dose: half tablet every 12 hr. for 2 days only), **this is not (FDA) approved;** also used after Abortion to stop milk production, (dose: 2 tabs once only).
   - **Cabergoline** has been found to raise a man's chances of sustaining multiple orgasms during sex **(Enhance erection and libido in men)**, don't try this at home, **it's not (FDA) approved**.
   - **Co-administration with Clarithromycin is C.I.;** it causes severe Vasospasm.

3. **Adverse Effects** [3]**:**
   a. **Nausea is the most common adverse effect** at the beginning of treatment with Bromocriptine, but vomiting, dizziness, and orthostatic hypotension may also occur, Syncope has followed initial doses.
   b. Adverse effects are generally dose-related and may therefore be more frequent with the higher doses; Nausea may be reduced by **gradual increase of the dose,** taking Bromocriptine **with food**; **Domperidone** may also be given **at least 1 hour before Bromocriptine**, for the first few days of therapy.

4. **Quinagolide** a non-ergot with high D2 affinity; approved only in Europe for hyperprolactinemia.

5. **Excessive daytime sleepiness** and **sudden onset of sleep** can occur with dopamine-receptor agonists, patients starting treatment with these drugs should be warned of the risk and of the need to exercise caution when driving or operating machinery; Those who have experienced excessive sedation or sudden onset of sleep should refrain from driving or operating machines until these effects have stopped occurring.

6. **The BNF stated that Cabergoline should be dispense in original container** (contains desiccant) [1]. (A desiccant is a hygroscopic substance that induces or sustains a state of dryness (desiccation) in its vicinity); This mediation is usually expensive which forces the patient sometime to buy it as one tab or two, this makes the pharmacist to open the original container and sells the tab in another bag, which may lead to desiccation and maybe tab deformity.

Scientific name	Dosage form	Trade name	concentration
Bromocriptine	Tab	Parlodel® , Cycloset®	2.5 mg , 5 mg , 10 mg
Cabergoline	Tab	Dostinex® , Cabaser®	0.5 mg
Quinagolide	Tab	Norprolac	25 mcg , 50 mcg , 75 mcg

6.6 - Drugs for Adrenal Gland Disorders

Hyper-function of the adrenal glands involves excess production of the adrenal hormones cortisol (resulting in Cushing syndrome) or aldosterone (resulting in hyperaldosteronism); Adrenal gland hypo-function is associated with primary (Addison disease) or secondary adrenal insufficiency.

1. Hypersecretory cortisol diseases (Cushing syndrome)

Cushing syndrome results from effects of supraphysiologic glucocorticoid levels originating from either **exogenous administration (as corticosteroid abuse)** or **endogenous overproduction** by the adrenal gland (adrenocorticotropic hormone [ACTH] dependent) or by abnormal adrenocortical tissues (ACTH independent).

- The most common findings in Cushing syndrome are central obesity and facial rounding (90% of patients). Peripheral obesity and fat accumulation occur in 50% of patients. Fat accumulation in the dorsocervical area (buffalo hump) is nonspecific, but increased supraclavicular fat pads are more specific for Cushing syndrome. Patients are often described as having moon faces and a buffalo hump.

Treatments available include: **Metyrapone**, **Ketoconazole**, **Etomidate**, **Mitotane**, **Cyproheptadine**, **Pasireotide** and **Mifepristone.**

1. **Metyrapone** inhibits 11 β-hydroxylase, thereby **inhibiting cortisol synthesis**; Initially, patients can demonstrate increased plasma ACTH concentrations because of a sudden drop in cortisol, this can increase androgenic and mineralocorticoid hormones, resulting in hypertension, acne, and hirsutism. Nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash have been reported after oral administration.
2. **Ketoconazole** inhibits cytochrome P-450 enzymes, including 11 β-hydroxylase and 17 α-hydroxylase; It is effective in lowering serum cortisol levels after several weeks of therapy; It also **has antiandrogenic activity**, which may be beneficial in women but can cause gynecomastia and hypogonadism in men.
   - Because of the **risk of severe hepatotoxicity**, monitoring should include liver function tests at baseline followed by weekly monitoring of serum ALT throughout therapy.
   - Ketoconazole may be used concomitantly with Metyrapone to achieve synergistic reduction in cortisol levels; in addition, ketoconazole's antiandrogenic actions may offset the androgenic potential of Metyrapone.
3. **Etomidate** is an imidazole derivative similar to ketoconazole that inhibits 11 β-hydroxylase.
4. **Mitotane** is a cytotoxic drug that inhibits the 11-hydroxylation of 11-deoxycortisol and 11-desoxycorticosterone in the adrenal cortex**, reducing synthesis of cortisol and corticosterone**. Similar to ketoconazole, Mitotane takes weeks to months to exert beneficial effects.
   - Mitotane can cause significant neurologic and GI side effects, Lethargy, somnolence, and other CNS effects are also common.
5. **Cyproheptadine**, a nonselective serotonin receptor antagonist and anticholinergic drug, can decrease ACTH secretion in some patients with Cushing disease. However, side effects such as sedation and weight gain significantly limit its use.
6. **Pasireotide** is a somatostatin analogue that binds and activates somatostatin receptors, thereby inhibiting ACTH secretion, leading to decreased cortisol secretion. It is approved for treatment of adults with Cushing disease for whom pituitary surgery is not an option or has not been curative.
   - Has a LAR dosage form that is given once every 4 weeks.
7. **Mifepristone** is a progesterone and glucocorticoid-receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in normal subjects. Evidence suggests that mifepristone is highly effective in reversing the manifestations of hypercortisolism (hyperglycemia, hypertension, and weight gain); It is FDA approved for treatment of endogenous Cushing's syndrome in patients who have type 2 diabetes or glucose intolerance and who are not eligible for, or have had poor response to, surgery.

Scientific name	Dosage form	Trade name	concentration
Steroidogenesis Inhibitors			
Metyrapone	Cap	Metopirone®	250 mg
Ketoconazole	Tab	Nizoral®	200 mg
Etomidate	Inj. Solu.	Amidate®	2 mg/ml
Adrenolytic Agents			
Mitotane	Tab	Lysodren®	500 mg
Neuromodulators of ACTH Release *			
Cyproheptadine	Tab	----------	4 mg
Pasireotide	S.C inj.	Signifor®	0.3 mg/ml , 0.6 , 0.9 mg/ml
	Vial (I.M.)	Signifor LAR®	20 mg , 40 mg , 60 mg
Glucocorticoid-Receptor Blocking Agents			
Mifepristone	Tab	Korlym®	300 mg
	Tab	Mifeprex®	200 mg

- Other Neuromodulators of ACTH Release include: Bromocriptine, Cabergoline, Valproic acid, Octreotide, Lanreotide, Rosiglitazone, and Tretinoin.

2. Hyperaldosteronism

Hyperaldosteronism involves excess aldosterone secretion and is categorized as either primary (stimulus arising from within the adrenal gland) or secondary (stimulus from extra adrenal).

- Patients may complain of muscle weakness, fatigue, paresthesias, headache, polydipsia, and nocturnal polyuria; Signs may include hypertension and tetany/paralysis.
- Treated with aldosterone receptor antagonists (Spironolactone, Eplerenone, Amiloride):
  - **Spironolactone** is a nonselective aldosterone receptor antagonist that competes with aldosterone for binding at aldosterone receptors, thus preventing the negative effects of aldosterone receptor activation.
  - **Eplerenone** is a selective aldosterone receptor antagonist with high affinity for aldosterone receptors and low affinity for androgen and progesterone receptors; it elicits fewer sex-steroid–dependent effects than spironolactone.
  - **Amiloride** is a potassium-sparing diuretic, is less effective than spironolactone. (for more info, see chapter 3 diuretics).

3. Hyposecretory adrenal disorders

1. Primary adrenal insufficiency (Addison disease) usually involves destruction of all regions of the adrenal cortex. There are deficiencies of cortisol, aldosterone, and the various androgens, and levels of CRH and ACTH increase in a compensatory manner.
2. Secondary adrenal insufficiency most commonly results from exogenous corticosteroid use, leading to suppression of the hypothalamic-pituitary-adrenal axis and decreased ACTH release, resulting in impaired androgen and cortisol production.
3. Patients commonly complain of weakness, weight loss, GI symptoms, salt craving, headaches, memory impairment, depression, and postural dizziness; Signs of adrenal insufficiency include increased skin pigmentation, postural hypotension, fever, decreased body hair, vitiligo, amenorrhea, and cold intolerance.
4. **Hydrocortisone** and **prednisone** are the glucocorticoids of choice, administered twice daily at the lowest effective dose while mimicking the normal diurnal adrenal rhythm of cortisol production; while in primary adrenal insufficiency, **Fludrocortisone** 0.05 to 0.2 mg orally once daily can be used to replace mineralocorticoid loss. (for corticosteroids see chapter 11).

6.7- Bone disorders (Osteoporosis, Osteomalacia)

1. **Osteoporosis** is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength predisposing to fracture; occurs most commonly in postmenopausal women and in those taking long-term oral corticosteroids.
   - Bone loss occurs when resorption exceeds formation, usually from high bone turnover when the number or depth of bone resorption sites greatly exceeds the ability of osteoblasts to form new bone; (**osteoblast** is responsible for bone formation, and **osteoclast** for resorption).
2. World Health Organization (WHO) Definitions Based on T-scores (T-score indicates that for every standard deviation [SD] below the mean young adult bone mineral density [BMD], fracture risk increases 2-fold)
   - Normal = BMD within 1 SD of the young adult mean.
   - Low bone mass (osteopenia) = BMD 1–2.5 SD below the young adult mean (often seen as T-score between -1 and -2.5).
   - Osteoporosis = BMD at least 2.5 SD below the young adult mean (often seen as T-score of less than -2.5).
3. In **osteomalacia** (called **rickets** when it affects children), a lack of vitamin D leads to loss of calcium, resulting in softening of the bones. There is pain and tenderness and a risk of fracture and bone deformity; while in children, growth is retarded.

First: Bisphosphonates

1. They include (oral: **Alendronate, Ibandronate** and **Risedronate** or I.V: **Zoledronic acid**); they **inhibit bone resorption** by binding very tightly to bone matrix, preventing its removal.
2. **Uses of Bisphosphonates:**
   a. Bisphosphonates have an important role in the **prophylaxis and treatment of osteoporosis** (postmenopausal osteoporosis) and corticosteroid-induced osteoporosis.
   b. Because bone resorption increases plasma Calcium concentrations, the **bisphosphonates are used as adjuncts to the treatment of severe hypercalcemia, especially when associated with malignancy**.
   c. They are also used in other disorders associated with excessive bone resorption and turnover, such as **Paget's disease of bone**, as well as in the management of bone Metastases.
3. Some bisphosphonate preparation may be given **once daily** (10 mg alendronate tablet), **once weekly** (70 mg alendronate tablet, Risedronate 35 mg tablet), as well as **once monthly** (Ibandronic acid 150 mg tablet).
4. **Administration**:
   a. Because bioavailability is very poor for bisphosphonates and to minimize GI side effects**, each oral dose should be taken with at least 6 ounces of plain tap water** (not coffee, juice, mineral water, or milk) **at least 30 (60 for Ibandronate) minutes before consuming any food**, supplements (including calcium and vitamin D), or medications.
   b. **The patient should also remain upright** (either sitting or standing) for at least 30 minutes after alendronate and Risedronate and 1 hour after Ibandronate administration.
   c. A patient who misses a weekly dose can take it the next day. If more than 1 day has lapsed, that dose is skipped until the next scheduled ingestion. If a patient misses a monthly dose, it can be taken up to 7 days before the next administration.
5. **Esophageal reactions**: Severe esophageal reactions reported with all oral bisphosphonates; patients should be advised to **stop tablets and seek medical attention** for symptoms of esophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn.
6. **Oral Bisphosphonate can cause osteonecrosis of the jaw (BRONJ)**, you should inform any patient who has dental appointments or has dental problems.

Scientific name	Dosage form	Trade name	concentration
Alendronate	Tab	Fosamax®	10 mg , 35 mg , 70 mg
	Oral Solu.	Borgalendro®	70 mg/75 ml
Risedronate	Tab DR	Actonel®	35 mg
Ibandronate	Tab	Boniva®	150 mg
	Prefilled Inj.		1 mg/ml (3 ml)
Etidronate	Tab	Didronel®	200 mg , 400 mg
Tiludronate	Tab	Skelid®	200 mg
Pamidronate	I.V. Solu.	Aredia®	30 mg , 60 mg , 90 mg
Zoledronic acid	I.V. Solu.	Reclast®, Zometa®, Aclasta®	4 mg/5 ml , 5 mg/100 ml

Combination Products

Scientific name	D. form	Trade name	concentration
Risedronate + Ca + Vit D_3	Tab	Actonel Combi®	35 mg + 1000 mg + 880 IU
Alendronate + Ca + Vit D_3	Tab	Fosamax Plus D®	70 mg + 140 mg + 5600 IU
Alendronic acid + Cholecalciferol	Tab	Fosavance®	70 mg + 5600 I.U

Note1: [8]

Several Bisphosphonates are available; are they all the same? Below some clinical facts:

1. **Alendronate:** 10 mg/day or 70 mg/week; decreases vertebral fractures by 47% and hip fractures by 51%.
2. **Risedronate:** 35 mg/week or 150 mg once monthly; decreases non-vertebral fracture risk by 33%–39% and vertebral fracture by 41%–49%.
3. **Ibandronate**: 150 mg once monthly, Increases BMD at spine and hip; but studies show only a decreased risk of vertebral fractures.
4. **Zoledronic acid:** 5 mg intravenously reduces non-vertebral fracture risk by 25%, hip fracture by 40%, and vertebral fracture risk by 70%.

Note2:

- Bisphosphonates have a different **relative resorptive potencies**; (their ability to get attached to the osteoclast cells in the bone matrix), as follows in the table:

Relative Resorptive Potency of Bisphosphonates

Drug	Generation	Relative Potency
Etidronate	First	1
Clodronate		10
Tiludronate	Second	10
Alendronate		100
Pamidronate		100-1,000
Risedronate	Third	1,000-10,000
Ibandronate		1,000-10,000
Zoledronate		10,000+

Note3:

- In a recent study; Endoscopic Comparison of Esophageal and Gastroduodenal Effects of Risedronate and Alendronate in Postmenopausal Women; showed that at doses used for the treatment of osteoporosis, Risedronate was associated with a significantly lower incidence of gastric ulcers than Alendronate; These findings confirm that bisphosphonates differ in their potential to damage the gastroesophageal mucosa. [7]

Note4:

- In another study; comparing Alendronate and Risedronate, head to head; Alendronate 70 mg Once Weekly yielded significantly greater BMD gains and larger decreases in bone turnover marker levels than Risedronate 35 mg Once Weekly over 24 months, with no difference in upper GI tolerability. [9]

Second: Calcium Metabolism Modifiers:

These include: Calcitonin, Denosumab, Romosozumab, Teriparatide, and Abaloparatide.

1. **Calcitonin** reduces bone resorption, but it is less effective than the bisphosphonates, a unique property of calcitonin is the **relief of pain associated with osteoporotic fracture**.
   - It acts by **inhibiting osteoclast activity** in the bone.
   - Nasal Calcitonin reduces the incidence of new vertebral fractures by 36%.
   - Dosage: 200 international units/day in one nostril, alternating nostrils daily.
2. **Denosumab** is a monoclonal antibody that targets receptor activator of nuclear factor kappa -B ligand (RANKL); (a cytokine essential for formation, function, survival of Osteoclasts), thus blocks osteoclast activation; it is approved for treatment of postmenopausal osteoporosis in women at high risk of fracture, it's also used for bone destruction caused by Rheumatoid Arthritis.
   a. It is administered 60 mg via S.C. injection every 6 months.
   b. Increased hip (6%) and spine (9%) BMD.
   c. Reduced spinal fracture risk by 68%, hip fracture risk by 40%.
   d. Considered alternative first-line therapy by AACE and ACP guidelines.
   e. Denosumab has been associated with an increased risk of infections, secondary malignancies, hypocalcemia, and dermatological reactions.
   f. It should be reserved for women intolerant or unresponsive to other therapies.
3. **Romosozumab** is a bone-forming monoclonal antibody that works by inhibiting the activity of sclerostin, resulting in increased bone formation and to a lesser extent decreased bone resorption; its FDA approved to treat osteoporosis in postmenopausal women at high risk for fracture; it's administered as once-monthly injections for a 12-month course to therapy.
   - Treatment with Romosozumab should be followed by an antiresorptive agent to maintain and enhance its therapeutic effect.
   - It may increase the risk of heart attacks, strokes, and deaths from cardiovascular disease.
4. **Teriparatide** is a recombinant segment of **human parathyroid hormone** that is administered subcutaneously for the treatment of osteoporosis.
   a. Parathyroid hormone given continuously leads to dissolution of bone' However, when it is given by intermittent dose S.C. once daily, bone formation is the predominant effect by preferentially stimulating osteoblastic activity over osteoclastic activity.
   b. It is the first approved treatment for osteoporosis that **stimulates bone formation**; other drugs approved for this indication inhibit bone resorption.
   c. Decreases vertebral fractures by 65% and non-vertebral fractures by 53%; but not shown to decrease hip fractures.
   d. Effective in the treatment of glucocorticoid-induced osteoporosis.
   e. Contraindications: Hypercalcemia, bone metastases, disorders that predispose women to bone tumors such as Paget's disease
5. **Abaloparatide** (related to Teriparatide); a modified Recombinant human parathyroid hormone; it is indicated for the treatment of post-menopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or intolerant to other available osteoporosis therapy.
   - Decreases vertebral fractures by 86% and non-vertebral fractures 43%; but not shown to decrease hip fractures.
   - It Has the **advantage over Teriparatide** that it has no contraindications.

Scientific name	Dosage form	Trade name	concentration
Calcitonin salmon	Inj. Solu.	Miacalcin® , Fortical®	200 I.U/ml
	Nasal Spray		3.7 ml (200 I.U)
Teriparatide	Prefilled Inj.	Forteo®	250 mcg/ml (2.4 ml)
Abaloparatide	Prefilled Inj.	Tymlos®	80 mcg/40 mcl
Romosozumab	Prefilled Inj.	Evenity®	105 mg/1.17 ml

Denosumab	Prefilled Inj.	Prolia®	60 mg/ml (1 ml)
	Prefilled Inj.	Xgeva®	70 mg/ml (1.7 ml)
Strontium Ranelate	Sachet	Protelos®	2 gm (granules for oral use)
Menaquinone-7	Cap	MenaQ7®	45 mcg , 180 mcg

Extra Notes:

1. **Strontium** increases bone formation in bone tissue culture as well as osteoblast precursor replication and collagen synthesis in bone cell culture.
   - Strontium stimulates the calcium-sensing receptors and leads to the differentiation of pre-osteoblast to osteoblast which increases the bone formation; it also stimulates osteoblasts to secrete osteoprotegerin in inhibiting osteoclasts formed from pre-osteoclasts in relation to the RANKL system, which leads to the decrease of bone resorption.
   - It showed significant reduction in vertebral fractures with 41% and hip fractures with 36% compared with patients treated with placebo.
   - Strontium increased the risk of venous thromboembolism, pulmonary embolism and serious cardiovascular disorders, including myocardial infarction.
2. **Menaquinone-7** (also called **Vitamin K2**) as a supplementation it helps to decrease bone loss.

Third: Vitamin D Analogs:

1. Usually is given as a prophylactic treatment for vitamin D deficiency or as a supplement with calcium for bone disorders, or for babies with **rickets.**
   - Alfacalcidol, Ergocalciferol, Calciferol, Cholecalciferol and 1,25-dihydroxycholecalciferol are all the same drug (Vitamin D3).
   - **Calcitriol, Calcifediol, Doxercalciferol, Paricalcitol** are also Vit. D analogues but they are indicated for **secondary hyperparathyroidism** associated with **Vit D insufficiency** in patients with **stage 3 or 4 chronic kidney disease** (CKD).
   - There are also **Topical Vit. D analogues** used mainly for **psoriasis** (see chapter 14, sec 12)

Scientific name	Dosage form	Trade name	concentration
Alfacalcidol	Cap	One-Alpha®	0.25 mcg , 0.5 mcg , 1 mcg
	Oral Drops		2 mcg/ml
	Inj. Solu. (I.V.)		2 mcg/ml
Ergocalciferol	Oral Solu. (only)	Sterogyl 15 "A" ®	600,000 IU/1.5 ml
	Oral Solu. (and) I.M. Inj. Solu.	Sterogyl 15 "H" ®	600,000 IU/1.5 ml
	Oral Drop	Sterogyl D®	2 Million IU/100 ml (20 ml)
Cholecalciferol	Oral Drops	Dibase®	10,000 IU/ml
	Oral Solu.		25,000 IU , 50,000 IU /2.5 ml
	Inj. Solu.		100,000 IU , 300,000 /ml
Vit D analogues for 2ndry hyperparathyroidism			
Calcitriol	Cap	Rocaltrol® , Calcijex®	0.25 mcg , 0.5 mcg
	Oral Solu.		1 mcg/ml
	Inj. Solu.		1 mcg/ml
Calcifediol	Cap	Rayaldee®	30 mcg
Doxercalciferol	Cap	Hectorol®	0.5 mcg , 2.5 mcg
	Inj. Solu.		2 mcg/ml
Paricalcitol	Cap	Zemplar®	1 mcg , 2 mcg , 4 mcg
	Inj. Solu.		2 mcg/ml

Note: How to calculate the required Vit D3 dose for patients

- Use the following equation; (75 – lab test ng/ml) × (Age in yrs.) × (wt. in kg) = dose per month IU
- Divide by 30 = dose per day, divide by 4 = dose per week, given for at least 2 months.

6.8– Calcimimetics

1. A **Calcimimetic** is a drug that **mimics the action of calcium on tissues**, by allosteric activation of the calcium-sensing receptor that is expressed in various human organ tissues. Calcimimetics are used to treat secondary hyperparathyroidism (SHPT).
   - In the treatment of SHPT patients on dialysis, they do not appear to affect the risk of early death in those patients.
   - they do decrease the need for a parathyroidectomy but caused more issues with low blood calcium levels and vomiting.
2. Currently there are two Calcimimetics available**: Cinacalcet** and **Etelcalcetide** (formerly **Velcalcetide**), they mimic calcium at the parathyroid hormone receptor. This binding will increase the sensitivity of calcium-sensing receptors (CaSR) on the parathyroid gland. As a result of the receptor "thinking" there is sufficient calcium, parathyroid hormone (PTH) secretion will be reduced; Lower calcium levels will be seen as well; they can be **used concomitantly with vitamin D therapy.**
   - Common side effects include: nausea and vomiting, **hypocalcemia**, and **adynamic bone disease** if intact parathyroid hormone (iPTH) levels drop below 100pg/ml.

Scientific name	Dosage form	Trade name	concentration
Cinacalcet	Tab	Sensipar®	30 mg , 60 mg , 90 mg
Etelcalcetide	Vial (Solu.)	Parsabiv®	5 mg/ml , 10 mg/2 ml

** **Etelcalcetide = Velcalcetide**, they are the same drug.

6.9 - Other Endocrine drugs: (5-6)

Scientific name	Dosage form	Trade name	concentration
Cysteamine	Cap , Cap DR	Cystagon® , Procysbi®	150 mg , 75 mg (DR Cap)
Trientine	Cap	Syprine®	250 mg
Sevelamer	Tab	Renvela® , Renagel®	400 mg , 800 mg
Fenoldopam	I.V infusion	Corlopam®	----------
Miglustat	Cap	Zavesca®	100 mg
Imiglucerase	Vial	Cerezyme®	200 units , 400 units
Riluzole	Tab	Rilutek®	50 mg

Notes:

1. **Cysteamine** is used in the treatment of disorders of Cysteine excretion; and for Nephropathic cystinosis.
2. **Trientine** is a chelating agent, and is used to bind up and remove copper in the body to treat Wilson's disease, and to treat Mg+ toxicity.
3. **Sevelamer** is a PO4 scavenger, used for the treatment of hyperphosphatemia.
4. **Fenoldopam** is a D1-dopamine receptor agonist: rapid-acting vasodilator; decreases peripheral resistance and increases renal blood flow; has minimal adrenergic effects
   a. It is also diuretic, natriuretic and used to treat a hypertensive crisis, beneficial in hypertensive patients with concomitant renal insufficiency.
   b. Used with Caution in patients with glaucoma or raised intraocular pressure as Fenoldopam raises intraocular pressure.
   c. Concomitant use of Fenoldopam with a beta-blocker should be avoided if possible, as unexpected hypotension can result from beta-blocker inhibition of sympathetic-mediated reflex tachycardia in response to Fenoldopam.
5. **Miglustat** is Used to treat type 1 Gaucher's disease and Neimann-Pick disease.
6. **Riluzole** is an NMDA receptor antagonist, it's the only drug approved **for the spasmolytic treatment of ALS** (Amyotrophic Lateral Sclerosis).

6.10- Rare Drugs used in Rare Metabolic Disorders

Disease Name	Explanation	Drug Name (Sci.)	Brand Name
Porphyria	A disease due to a mutation in one of the genes that make Heme	Heme arginate, Hematin	NormoSang®, Panhematin®
Fabry's disease	known as lysosomal storage diseases; the genetic mutation that causes Fabry disease interferes with the function of an enzyme which processes biomolecules known as sphingolipids, leading to these substances building up in the walls of blood vessels and other organs.	Agalsidase Alfa	Fabrazyme®
Carnitine deficiency	primary (inborn errors of metabolism) or 2ndry (in hemodialysis patients)	Levocarnitine	Carnitor®
Gaucher's disease	a rare genetic disorder characterized by the deposition of glucocerebroside in cells of the macrophage-monocyte system. The disorder results from the deficiency of the enzyme glucocerebrosidase.	Imiglucerase, Velaglucerase Alfa, Miglustat	Cerezyme®, Vpriv®, Zavesca®
Homocystinuria	an inherited disorder of the metabolism of the amino acid methionine due to a deficiency of cystathionine beta synthase. eading to accumulation of homocysteine and its metabolites (homocystine, homocysteine-cysteine complex, and others) in blood and urine.	Betaine Or (Trimethylglycine)	Anhidra®
Mucopolysaccharidosis	caused by the absence or malfunctioning of lysosomal enzymes needed to break down glycosaminoglycans (GAGs). These long chains of sugar carbohydrates occur within the cells that help build bone, cartilage, tendons, corneas, skin and connective tissue. GAGs are also found in the fluids that lubricate joints.	Elosulfase Alfa, Idursulfase, Laronidase	Vimizim®, Elaprase®, Aldurazyme®
Nephropathic cystinosis	a lysosomal storage disease characterized by the abnormal accumulation of the amino acid cystine.	Mercaptamine (Cysteamine)	Cystagon®
Niemann-Pick Type C disease	rare progressive genetic disorder characterized by an inability of the body to transport cholesterol and other fatty substances (lipids) inside of cells. This leads to the abnormal accumulation of these substances within various tissues of the body, including brain tissue.	Miglustat	Zavesca®

Pompe disease	Glycogen storage disease type II, also called Pompe disease, is an autosomal recessive metabolic disorder; which damages muscle and nerve cells throughout the body. It is caused by an accumulation of glycogen in the lysosome due to deficiency of the lysosomal acid alpha-glucosidase enzyme.	Alglucosidase Alfa	Myozyme®
Tyrosinaemia type I	a genetic disorder characterized by elevated blood levels of the amino acid tyrosine, a building block of most proteins. This condition is caused by a shortage of the enzyme fumarylacetoacetate hydrolase, one of the enzymes required for the multi-step process that breaks down tyrosine	Nitisinone	Orfadin®
Urea cycle disorders	Hyperammonaemia due to N-acetylglutamate synthase deficiency	Carglumic acid	Carbaglu®
	Long-term treatment of urea cycle disorders	Sodium phenylbutyrate	Buphenyl®
Wilson's disease	genetic disorder in which copper builds up in the body; Symptoms are typically related to the brain and liver.	Penicillamine	Cuprimine®
Acute hepatic porphyrias (AHPs)	group of four inherited diseases of heme biosynthesis that present with episodic, acute neurovisceral symptoms.	Givosiran	Givlaari®

References

1- BNF 82.
2- Mary Anne, koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th Ed.
3- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition
4- Current Challenges in Management of Hypothyroidism. Supplement to U.S. Pharmacist
5- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition.
6- Lexi-comp: Drug information handbook, 2022 Ed.
7- Gastroenterology Magazine 2000; 119:631–638
8- ACCP Updates in Therapeutics® 2018: Pharmacotherapy
9- https://www.ncbi.nlm.nih.gov/pubmed/18324951
10- Richards KA, Liou JI, Cryns VL, et al. J Urol. 2018.

OBSTETRICS AND GYNECOLOGY

Chapter Seven: Obstetrics and Gynecology

7.1- Drugs used in Obstetrics

- **A.** Tocolytics
- **B.** Induction and augmentation of labor
- **C.** Prevention and treatment of Postpartum hemorrhage
- **D.** Anti-D Immunoglobulin injection
- **E.** Obstetric Gels that Facilitate Delivery
- **F.** Thromboembolic Events in Pregnancy

7.2- Galactagogues (Breastmilk boosting drugs)

7.3- Preparations for vaginal and vulvar conditions

- **A.** Topical and Systemic Hormonal replacement therapy (HRT) for vaginal atrophy
- **B.** Vaginal infections
  - ➢ Fungal infections (Thrush)
  - ➢ Bacterial infections
  - ➢ Trichomoniasis infections
  - ➢ Chlamydia infections
  - ➢ Combination Products for Vaginal Infections
  - ➢ Other Vaginal products

7.4- Contraception methods

1. Combination oral contraceptives
2. Progestin-only pills
3. Transdermal patches
4. Injectable progestins
5. Spermicidal contraceptives
6. Vaginal ring
7. Progestin intrauterine device
8. Progestin implants
9. Barrier Female Contraceptives
10. Post-coital contraception: (Emergency Contraception)

7.5 – Polycystic ovary syndrome (PCOS)

7.6 - Vaginal Gels to aid natural fertility

7.7– Infertility in Women

- **A.** Ovulation induction
- **B.** Controlled Ovarian Stimulation
- **C.** Assisted Reproductive Technology
- **D.** IVF Protocols

7.8 – Sexual Dysfunction in Women

- **A.** Low Sexual Desire in Women
- **B.** Female Sexual Arousal Disorder

7.9 – Vaginal Douches (Female Hygiene products)

Chapter Seven: Obstetrics and Gynecology

7.1- Drugs used in Obstetrics

1. Normal labor has three stages; In the first stage, the uterus begins to contract, initially irregularly and then gradually more regularly and powerfully, while the cervix dilates until it is fully stretched. During the second stage, powerful contractions of the uterus push the baby down the mother's birth canal and out of her body; The third stage involves the delivery of the placenta.
   - Term labor: Weeks 37–40.
   - Preterm labor: Uterine contractions with cervical changes before week 37.
2. Drugs may be required during one or more stages of labor for any of the following reasons: to induce or augment labor; to delay premature labor and to relieve pain, or to terminate pregnancy.

A) Tocolytics:

1. When contractions of the uterus start before the 34th week of pregnancy, doctors usually advise bed rest and may also administer a drug that relaxes the muscles of the uterus (**Tocolytics**), and thus halts labor; the drug is given in hospital by injection, but it may be continued orally at home.
2. Also called **Myometrium relaxants**, they **inhibit uterine contractions**, especially if cervix dilated less than 4 cm and membranes intact; the purposes of **Tocolytic** therapy are threefold:
   a. Postpone delivery long enough to allow for the maximum effect of antenatal steroid administration.
   b. Allow for transportation of the mother to a facility equipped to deal with high-risk deliveries.
   c. Prolongation of pregnancy when there are underlying, self-limited conditions that can cause labor, such as pyelonephritis or abdominal surgery that are unlikely to cause recurrent preterm labor.
3. Prophylaxis for patients with a history of preterm labor 16–36 weeks: Hydroxyprogesteron acetate (Primolut-Depot®) 250 mcg I.M. every week from 16 to 36 weeks' gestation.
4. **Tocolytics inhibit uterine contractions and are used in premature labor to delay early delivery**; Examples of Tocolytics include: **β2-agonists** (like salbutamol, Terbutaline) and **calcium-channel blockers** (Nifedipine), **magnesium sulfate** and **NSAIDs** as (Sulindac and indomethacin), All have been used for their Tocolytic actions.
   - **β2-agonists: salbutamol** and **terbutaline** are licensed for inhibiting uncomplicated premature labor by I.V. route between 22 and 37 weeks of gestation to permit a delay in delivery of up to 48 hours; Oral therapy is no longer recommended.
     - They have FDA warning for I.V. use beyond 48 hours because of severe adverse effects in the mother such as elevated heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia.
   - **Nifedipine** (unlicensed indication) can be given initially in a dose of 20 mg followed by 10–20 mg 3–4 times daily adjusted according to uterine activity.
   - **Magnesium sulfate** inhibits uterine activity by antagonism of calcium, it's the drug of choice in patients with diabetes.
   - **NSAIDs** have the risks of Premature closure of ductus arteriosus, necrotizing enterocolitis, intracranial hemorrhage, and **their use is strictly limited to 72 hours only**.
5. **Atosiban** (oxytocin receptor antagonist) is licensed in Europe (not approved in USA) for the inhibition of uncomplicated premature labor between 24 and 33 weeks of gestation, it's may be preferable to a beta agonist because it has fewer side effects.

Scientific name	Dosage form	Trade name	concentration
Atosiban	Inj.	Tractocile®	7.5 mg/ml

B) Induction and augmentation of labor:

1. Induction of labor may be advised when a doctor considers it risky for the health of the mother or baby for the pregnancy to continue, if natural labor does not occur within two weeks of the due date or when a woman has pre-eclampsia; Other common reasons for inducing labor include premature rupture of the membrane surrounding the baby (breaking of the waters), slow growth of the baby due to poor nourishment by the placenta, or death of the fetus in the uterus.
   - When labor needs to be induced, oxytocin may be administered I.V.
   - Alternatively, a prostaglandin pessary (Supp.) may be given to soften and dilate the cervix.
   - If these methods are ineffective or cannot be used because of potential adverse effects; a caesarean delivery may have to be performed.

2. **Oxytocin** (the natural hormone); is responsible for signaling contractions of the womb during labor; The hormone stimulates the uterine muscles to contract, so labor begins; it also increases the production of prostaglandins, which move labor along and increases contractions even more.
   - Once the baby is born, Oxytocin promotes lactation by moving the milk into the breast.
   - Studies of Oxytocin also have found that it is an important chemical messenger that controls some human behaviors and social interaction.
   - It is oxytocin that triggers the bond between a mother and an infant, and it may also play a role in recognition, sexual arousal, trust and love.
   - It is sometimes referred to as the "**love hormone**" because levels of oxytocin increase during hugging and sex orgasm; Females usually have higher levels than males.

Notes:

1. **Oxytocin** is administered by slow I.V. infusion (or by Pump) to induce or augment labor [(2)].
   - **Oxytocin** may also be used to strengthen the force of contractions in labor that has started spontaneously but has not continued normally.
   - A combination of **Oxytocin** and another uterine stimulant (**Ergometrine**) is given to most women as the baby is being born or immediately following birth to prevent excessive bleeding after the delivery of the placenta; This combination encourages the uterus to contract after delivery, which restricts the flow of blood.
   - Adverse effects: Uterine rupture, uteroplacental hypoperfusion, fetal distress from hypoxia.

2. **Carbetocin** and **Demoxytocin** are Oxytocin analogs with longer half-life (not FDA approved yet).
3. **Castor Oil** is also given to induce or augment labor by oral route.
4. **Misoprostol** was first introduced to prevent and treat stomach ulcers, but later on it has been used to start labor, induce abortions and to treat postpartum bleeding due to insufficient contraction of the uterus.
   - It is approved for use in the prevention of NSAID-induced gastric ulcers.
   - Adverse effects: Headache, nausea, vomiting, diarrhea, abdominal pain, and uterine hyper stimulation
5. **Misoprostol** and **Dinoprostone** is given orally or vaginally for the **induction of labor** (and the **termination** of pregnancies).
   a. The most commonly encountered side effects are uterine hyper stimulation and meconium-stained amniotic fluid.
   b. Use of misoprostol is contraindicated in women with a previous uterine scar because of its association with uterine rupture, a catastrophic medical event.
6. **Sulprostone** is used I.M. for the **Induction of termination of pregnancy** (maternal or fetal indication); induction of labor in the case of fetal death in utero; Treatment of postpartum atonic hemorrhage.
7. **Gemeprost** is used as a treatment for obstetric bleeding (used in preparing the cervix before uterine surgery), also it is used with **mifepristone** to terminate pregnancy up to 24 weeks gestation.

Scientific name	Dosage form	Trade name	concentration
Castor Oil	Oral Solu.	Castor Oil® , Emulsoil®	30 ml
Oxytocin	Inj.	Pitocin®, Syntocinon®	10 units\ml
Carbetocin	Inj.	Pabal®	100 mcg\ml
Demoxytocin	Buccal Tab	Sandopart	100 mcg
Prostaglandins			
Misoprostol	Tab	Cytotec®	200 mcg
	Vag. Insert	Vagiprost®	200 mcg
Dinoprostone	Vag. Insert	Cervidil® , Propess®	10 mg
	Vag. Supp.	Prepidil®	20 mg
	Vag. Gel	Prostin E2®	400 mcg\ml , 800 mcg\ml
	Inj. Solu. I.V.	Prostin E2®	1 mg\ml , 10 mg\ml
Carboprost	Inj. Solu.	Hemabate®	250 mcg\ml
Sulprostone	Inj. Solu.	Nalador®	500 mcg\vial
Gemeprost	Vag. Tab	Cervagem®	1 mg

** All these medications above may be abused to induce illegal abortions, **NEVER give them without an Authorized prescription.**

C) Prevention and treatment of Postpartum hemorrhage:

1. If the uterus fails to contract adequately after delivery (**uterine atony**), or if retained placental remnants prevent retraction of the placental bed, postpartum hemorrhage may occur; these two causes account for about 80% of cases of postpartum hemorrhage.
2. Postpartum hemorrhage **may be fatal** to the mother unless promptly dealt with, and management generally involves:
    - **a.** Removal of the placenta if it has not been expelled.
    - **b.** The use of **Oxytocic's to contract the uterus**.
    - **c.** Blood Transfusion, if blood loss is severe**.**
3. Parenteral oxytocin, or an ergot alkaloid (**Ergometrine** or **Methylergometrine**), is the oxytocic generally used to control bleeding due to uterine atony.
4. **Methylergonovine, Carboprost, misoprostol and Dinoprostone** (see above) have all been used to stop postpartum hemorrhage; but less evidence of efficacy is available for misoprostol and Dinoprostone.
5. **Anti-Fibrinolytics** as **(Tranexamic acid** and **Aminocaproic acid)** can be effective in reducing blood loss **only in injections with high doses**, this is a controversy option due to safety concerns with high doses; (see chapter 3, section 17 for more info on anti-Fibrinolytics).

Scientific name	Dosage form	Trade name	concentration
Ergometrine	Tab , Inj.	Ergotrate® , Ergonovine®	0.2 mg (tab) 0.2 mg/ml (Inj. 1 ml)
Ergometrine + Oxytocin	Inj.	Syntometrine®	(500 mcg + 5 units)/ml
Methylergometrine	Tab , Inj.	Methergine®	0.125 mg , 0.2 mg (tab) 0.2 mg/ml (Inj.)

**** NEVER give them without an Authorized prescription.**

Scientific name	Dosage form	Trade name	concentration
Tranexamic acid	Amp	Exacyl® , Cyklokapron®	100 mg , 50 mg
	Tab	Cyklokapron® , Lysteda®	500 mg , 650 mg
Aminocaproic acid	Tab	Amicar® , Cyclo-C®	500 mg
Aprotinin	Inj. Solu.	Trasylol®	10 million IU/ml

D) Anti-D Immunoglobulin injection:

1. Given as **I.M. injection** that is used to prevent the immunological condition known as **Rhesus disease** (or hemolytic disease of newborn); The medicine is a solution of IgG Anti-D (anti-RhD) antibodies that suppresses the mother's immune system from attacking Rh-positive blood cells which have entered the maternal blood stream from fetal circulation.
2. It is for the pregnant women carrying factor Rhesus negative (Rh-) with a positive husband (Rh+), and the blood group was positive (Rh+), usually given in the 2nd pregnancy due to the 1st one is often passes safely; **Time of Administration**: given between the 24 and 38 weeks of pregnancy to the mother, or immediately after birth within 72 hours of birth.

Scientific name	D. form	Trade name	concentration
Anti-D Immunoglobulin	Inj.	Rhoclone® , RhoGAM®	150 mcg , 300 mcg
	Inj.	WinRho SDF®	120 mcg , 300 mcg

E) Obstetric Gels for labor facilitation

1. These are **sterile obstetric gels** that is to be applied by doctor below the cervix via a soft vaginal Catheter, then the gel immediately begins to form a lubricating film on the surface of the birth canal, they help both the mother and the baby by **reducing friction in the second stage of labor** and significantly **shortening time taken to deliver the baby**.
2. Usually these product's **effects are physical and it contains no active pharmaceutical or hormonal ingredients**, the perineum should also be massaged during labor.

Trade name	D. form	Scientific names	concentration
Natalis 1®, ***DiaNatal***®	Obs. Gel	Hydroxyethyl cellulose, glycerol, xanthan gum, sodium chloride, propylene glycol, water	15 ml , 11 ml

F) Thromboembolic Events in Pregnancy

1. Pregnancy increases the risk of **venous thromboembolism** (VTE) 4 to 5 fold over that in the non-pregnant state; The two manifestations of VTE are **deep venous thrombosis** (DVT) and **pulmonary embolus** (PE); this risk is also doubled to 8-10 folds with co-current use of Progestins (Dydrogesterone, Hydroxyprogesteron, Allyl-Estrenol); which are used in pregnancy for Prophylaxis of preterm labor and habitual abortion.
   - Obesity, low movement or Immobilization, prolonged bed rest and smoking; all increase risks of VTE; Cesarean delivery has twice the risk of VTE as vaginal delivery.
   - Pregnancy after the age of 35 years augments the risk of VTE, as does multigravidas of more than four pregnancies.
2. Although most reports suggest that VTE can occur at any trimester in pregnancy, studies suggest that **VTE is more common during the first half of pregnancy**.
   - Thus; prophylaxis treatment in high risk group is preferred to start in the 4th or 5th month of pregnancy.
3. Sequelae of DVT and PE include complications such as pulmonary hypertension, post-thrombotic syndrome, and venous insufficiency.
4. One study found that 80% of pregnant women with DVT experience pain and swelling of the lower extremity (**usually pain in the leg or gulf, unilateral on one side**), DVT will evolve to PE if not treated; Patients with massive PE may end with Syncope, Hypotension and **sudden death**.
   - **VTE (DVT, PE) is the second most common cause of death during pregnancy.**
5. **Heparin** UFH (unfractionated) and **Low Molecular Weight Heparins (LMWHs)** are the preferred drugs for managing VTE in pregnancy, But **LMWHs is preferred over heparin.**
   - Prophylaxis: **Enoxaparin** 4000 IU S.C. daily.
   - Treatment: **Enoxaparin** 100 IU/kg S.C. every 12 hours.

6. Prophylaxis with LMWHs or UFH should be discontinued 12–24 hours before cesarean section or vaginal delivery; while Therapeutic doses should be discontinued 24–36 hours before cesarean section or vaginal delivery; then Continue anticoagulation for 6 weeks postpartum.
7. **Heparin dose in prophylaxis**: 5000–7500 units S.C every 12 hours for first trimester, 7500–10,000 units S.C. every 12 hours for second trimester, and 10,000 units S.C. every 12 hours for third trimester; while **Heparin dose in treatment** is 10,000 units S.C. every 12 hours.

Injectable Anticoagulants			
Unfractionated Heparin	Inj. Solu.	Heparin®	1000 IU/ml , 2500 IU/ml , 5000 IU/ml
LMW Heparins			
Enoxaparin	Prefilled Syringe	Lovenox®, Clexan®	2000 IU , 4000 IU , 6000 IU
	Multidose Vial		100 mg/ml (3 ml vial)
Dalteparin	Prefilled Syringe	Fragmin®	2500 IU , 5000 IU , 7500 IU
	Inj. Solu.		10,000 IU/ml , 25,000 IU/ml
Tinzaparin	Multidose Vial	Innohep®	20,000 IU/2ml , 40,000 IU/2ml
	Prefilled Syringe		3500 IU , 7000 IU , 10,000 IU

7.2- Galactagogues (Breastmilk boosting drugs)

1. **Galactagogues** are substances that aid the initiation and maintenance of milk supply at a level which meets the needs of the baby; The production of milk is controlled by the hormone prolactin, Nipple stimulation controls the release of prolactin whilst oxytocin controls the release of the milk, experienced as the letdown.
2. Poor milk supply can result from:
   a. Less than perfect positioning and attachment of the baby at the breast resulting in incomplete breast drainage.
   b. Infrequent, restricted, limited feeds.
3. Reduction in milk supply is frequently noted after premature delivery with milk supply maintained only by expression over a period of weeks, also, Smoking is associated with decreased milk production and smokers are more likely to wean earlier because of low milk supply or to notice inhibition of letdown.
4. Most medications that act as galactagogues work by **increasing prolactin levels**; Examples of Galactagogues:
   a. **Domperidone** is a prescription drug used for decades for gastrointestinal disorders. The most recent systematic review of five randomized control trials of women expressing for premature babies demonstrated a moderate increase in daily breastmilk volume of 88.3mL/day with the use of domperidone compared with placebo; These studies suggest that domperidone has few side effects. However, there have been recommendations that domperidone not be used in women with a history of cardiac arrhythmias.
      - The normal dose is 10 mg three times a day.
   b. **Metoclopramide** is another prescription drug used to treat gastrointestinal disorders. Metoclopramide has been used for nearly three decades to increase breastmilk production. However, it crosses the blood-brain barrier, unlike domperidone. This means that metoclopramide has the potential to cause central nervous system side effects such as restlessness, drowsiness, fatigue and depression.;
      - Clinical studies have shown that it increases prolactin levels and consequentially milk supply at a dose of 10 mg three times daily.

c. Fenugreek is an herbal spice, which is a member of the pea family; Its mechanism of action has been theorized as stimulation of sweat production (the breast is a specialized sweat gland). The recommended dose is 2-3 capsules three times a day; Milk production is to increase within 24-72 hours.
- Fenugreek can also interact with insulin and warfarin
- It also stimulates the uterus and should not be used in pregnancy.
- Hypoglycemic effects have also been reported with chronic use.

5. Other natural remedies said to increase milk supply include anise, basil, blessed thistle, caraway, chasteberry and fennel but evidence is anecdotal rather than scientific.

6. One 2011 study **compared Domperidone and Metoclopramide as galactagogues**; This study showed that there were no statistically significant differences between these two drugs in terms of increased milk production or side effects; This study found that both domperidone and metoclopramide were very effective at increasing breastmilk production and had minimal (and all non-life-threatening) side effects.

Scientific name	D. form	Trade name	concentration
Metoclopramide	Tab	Placil®, Meclodin®	5 mg , 10 mg
Domperidone	Tab	Motilium® , Motinorm®	10 mg
Herbal Combination			
Fenugreek seed powder + Vit. D + Vit. E + Niacin + Folic acid + Calcium	Tab	Stimulact® (DaVinci)	500 mg + 100 IU + 7 IU + 7 mg + 200 mcg + 250 mg
Fenugreek + Marshmallow + Fennel + Red Raspberry + Blessed Thistle	Cap	Lactation Support®	1,115 mg herbal blend
Fenugreek seed powder + Fennel seed + Anise + Chamomile flower + Multivitamin Combo	Cap	Nursing Blend®	1,360 mg herbal blend + Multivitamins

7.3- Preparations for vaginal and vulvar conditions

A) Topical and Systemic (HRT) for vaginal atrophy:

1. **Atrophic vaginitis** is inflammation of the vagina as a result of tissue thinning due to not enough estrogen; Symptoms may include pain with sex, vaginal itchiness or dryness, and an urge to urinate or burning with urination.
2. Estrogen plays a vital role in keeping vaginal tissues lubricated and healthy, when levels of estrogen are low, vaginal tissue becomes atrophic, thin, dry and shrunken; also, the vagina may become more prone to inflammation in an atrophic state.
3. **Low Estrogen levels** are related to menopause, breastfeeding or due to some medications as oral contraceptives pills.
4. A cream containing an **Estrogen** may be applied on a short-term basis to improve the vaginal epithelium in menopausal atrophic vaginitis, also oral estrogen may be given but the topical estrogen comes with less side effects profile.
5. It is important that topical estrogens should be used in the **smallest effective amount** to minimize systemic effects.
   - Topical estrogens are also used in postmenopausal women before vaginal surgery for prolapse when there is epithelial atrophy.
   - The risk of endometrial hyperplasia and carcinoma is increased when systemic estrogens **are administered alone for prolonged periods.**

Topical Estrogens			
Scientific name	Dosage form	Trade name	concentration
Estradiol	Vag. Cream	Vagifem®	0.01%
	Vag. Tab	Vivelle®, Minivelle®	10 mcg , 25 mcg
	Gel	Climara®	0.06%
Estriol	Vag. Gel	Blissel®	50 mcg/1 gm
	Vag. Cream	Gynest® , Ovestin®	0.01% , 0.1%
	Vag. insert	Ortho-Gynest®	500 mcg
Conjugated Estrogen	Vag. Cream	Estrin®	0.625 mg

Systemic Estrogens			
Conjugated Estrogen	Tab	Premarin®, Equin®, Estrin®	0.625 mg , 0.9 mg , 2.5 mg
Estradiol	Tab	Estrofem®, Delestrogen®	0.45 mg , 0.9 mg , 2 mg
	Vag. Ring	Estring®	7.5 mcg/24 hr.
Estropipate	Tab	Ortho-Est®, Ogen ®	1.5 mg , 3 mg , 6 mg

B) Vaginal infections:

First: Fungal infections (Thrush):

1. The discharge associated with thrush is **curd-like** or **cottage cheese-like with little or no odor,** it can occur in any age group, the onset of symptoms is sudden.
2. **Vaginal candidiasis** is treated primarily with antifungal pessaries or cream inserted high into the vagina (including during menstruation – can be taken during the period)
3. **Single-dose preparations** offer an advantage **when compliance is a problem**.
4. **Imidazole drugs** (Clotrimazole, Econazole, and Miconazole) are effective against candida in short courses of 1 to 14 days according to the preparation used; treatment can be repeated if initial course fails to control symptoms or if symptoms recur.
5. All **internal preparations** should be administered **at night** (this give the drug time to be absorbed, and eliminate the possibility of accidental loss).
6. **Oral treatment** of vaginal infection (**Fluconazole** or **Itraconazole**) is also effective.

Scientific name	Dosage form	Trade name	concentration
Clotrimazole	Vag. Cream	Canestene®, Gyne-Mycelex®	1% , 2%
	Vag. Tab	Canestene®	100 mg , 200 mg
Butoconazole	Vag. Cream	Femstat®	2%
Miconazole *	Vag. Cream	Gyno-Daktarin®, Mycoheal® Monistat®	2% , 4%
	Vag. Supp.	Gyno-Mikazole®	200 mg , 400 mg
Nystatin *	Vag. Tab	Monicure®	100,000 Units
Terconazole	Vag. Cream	Terazole®	0.4% , 0.8%
	Vag. Supp.		80 mg
Tioconazole	Vag. Oint.	Vagistat®, Topazole V®	6.5%
Fenticonazole	Vag. Cream	Gynoxin®	2%
	Vag. Cap		200 mg , 600 mg
Econazole	Vag. Supp.	Ecorex®	150 mg
	Vag. Cream	Gyno-Pevaryl®	1%

*** Miconazole** and **Nystatin** comes in many combination products of vaginal creams and supp.

* **For other types of antifungal → see chapter 5, Section 2.**

7. **Therapeutic regimens:** 1- and 3-day regimens may take up to 7 days for full effect, (see table below); **Recurrent vulvovaginal candidiasis** (four or more episodes a year): Needs prescription drug treatment = Initial topical treatment for 7–14 days + fluconazole 100 , 150 , or 200 mg dose every third day for three doses.

Drug	Dose	Length of Therapy
Butoconazole	2% cream: 5 g intravaginally	1 dose
Clotrimazole	1% cream: 5 g intravaginally at bedtime (OTC)	7–14 days
	2% cream: 5 g intravaginally at bedtime (OTC)	3 days
Miconazole	2% cream: 5 g intravaginally at bedtime (OTC)	7 days
	4% cream: 5 g intravaginally at bedtime (OTC)	3 days
	100-mg vaginal suppository at bedtime (OTC)	7 days
	200-mg vaginal suppository at bedtime (OTC)	3 days
	1200-mg vaginal suppository × 1 (OTC)	1 dose
Terconazole	0.4% cream: 5 g intravaginally at bedtime	7 days
	0.8% cream: 5 g intravaginally at bedtime	3 days
	80-mg vaginal suppository at bedtime	3 days
Tioconazole	6.5% ointment: 5 g intravaginally (OTC)	1 dose
Fluconazole	150-mg oral tablet	1 dose

Second: Bacterial infections:

1. **Bacterial vaginosis** is associated with a **white discharge** that has a **strong fishy odor.**
2. **Odor is worse after sexual intercourse** and may worsen during menses; Itching and soreness are not usually present.
3. **Metronidazole** or **Clindamycin** either orally or vaginally are effective treatment (for 7 days).
   - Metronidazole 500 mg orally twice daily for 7 days or clindamycin 2% cream, 1 full applicator intravaginally at bedtime for 7 days, or metronidazole 0.75% gel, 1 full applicator intravaginally once daily for 5 days.
   - **Alternatives:** Clindamycin ovules 100 mg intravaginally at bedtime for 3 days, clindamycin 300 mg orally twice daily for 7 days, tinidazole 2 gm orally once daily for 2 days, tinidazole 1 gm orally once daily for 5 days, Secnidazole 2 gm packet of granules once.
   - **Pregnant women:** Oral or vaginal therapy regimens of metronidazole (as above); try not to use Clindamycin cream during pregnancy, because it increases the risk of preterm delivery.
   - Treatment of sexual partners is not necessary.

Scientific name	Dosage form	Trade name	concentration
Metronidazole	Tab	Flagyl® , Flazole®	250 mg , 500 mg
	Infusion		500 mg/100 ml
	Vag. Gel	Zidoval® , Vandazole®	0.75% (37.5 mg)
	Vag. Supp.		500 mg , 1 gm
Tinidazole	Tab	Fasigyn®, Tindamax®	500 mg
Tinidazole + Norfloxacin	Cap	Tinidol plus®	600 mg + 400 mg
Clindamycin	Cap	Cleocin® , Clindamycin®	75 mg , 150 mg
	Vag. Cream Vag. Supp.	Clindamax®	2% (Cream), 100 mg (Supp.)
Secnidazole	Tab	Flagentyl®, Sindose®	500 mg
Ornidazole	Tab	Avrazor® , Borneral®	500 mg
	Vag. Supp.	Ornidaz®	500 mg

Third: Trichomoniasis infections (4)

1. Trichomoniasis, a protozoan infection is primarily transmitted through sexual intercourse; it is uncommon compared to bacterial vaginosis and thrush, up to 50% of patients are asymptomatic.
2. If symptoms are experienced a **profuse, frothy, greenish-yellow** and **malodorous discharge** accompanied by **vulvar itching is typical;** other symptoms can include vaginal spotting, dysuria and urgency.
3. **Metronidazole, Tinidazole** (and their relatives) or **clindamycin** either orally or vaginally are effective treatment. (See above).
   - Metronidazole 2 gm orally in a single dose or tinidazole 2 gm orally in a single dose.
   - **Alternative:** Metronidazole 500 mg orally twice daily for 7 days.
   - All sexual partners should be treated.

Forth: Chlamydia infections (4)

1. Chlamydia is known as the "Silent Epidemic" because in women, it may not cause any symptoms in 70–80% of cases and can linger for months or years before being discovered.
2. Symptoms that may occur include **unusual vaginal bleeding** or **discharge, pain in the abdomen, painful sexual intercourse (dyspareunia),** fever, painful urination or the urge to urinate more frequently than usual (urinary urgency).
3. **Can transfer from the pregnant women to the baby causing Blindness.**
4. Also occur in men.
5. Current treatment guidelines recommend **Azithromycin, Doxycycline, Erythromycin,** or **Ofloxacin**; agents recommended for pregnant women include Erythromycin or Amoxicillin.
   - Azithromycin 1 g in a single dose or doxycycline 100 mg twice daily for 7 days.
   - **Alternatives:** Erythromycin 500 mg orally four times daily for 7 days, ofloxacin 300 mg orally twice daily for 7 days, levofloxacin 500 mg/day orally for 7 days,
   - Abstain from sexual intercourse for at least 7 days and until sexual partners are treated.

Combination Products for Vaginal Infections

Trade name	Dosage form	Scientific name(s)	concentration
Monicure Plus®	Vag. Supp.	Miconazole + Nystatin	100 mg + 100,000 I.U
Monicure NH®	Vag. Supp.	Miconazole + Nystatin + Neomycin + Hydrocortisone	100 mg + 100,000 I.U 50 mg + 5 mg
Mixovul®	Vag. Ovule	Metronidazole + Miconazole + Lidocaine	750 mg + 200 mg + 100 mg
PolyGynax®	Vag. Cap	Neomycin + Nystatin + Polymyxin B Sulphate + Dimethylpolysiloxane *	35,000 I.U + 100,000 I.U + 35,000 I.U + 2.2 gm
Ginal Cent®	Vag. Cap	Metronidazole + Miconazole + Neomycin + Centella Asiatica + Polymyxin B Sulphate	400 mg + 100 mg + 45 mg + 15 mg + 5 mg
Gynocaps®	Vag. Cap	Miconazole + Metronidazole	100 mg + 500 mg
Gyno-D®	Vag. Supp.	Miconazole + Metronidazole	150 mg + 500 mg
Gyno-D Zole®	Pessaries	Miconazole + Metronidazole	150 mg + 500 mg
Ovumix®	Vag. Ovules	Miconazole + Metronidazole	200 mg + 750 mg
Gynomix®	Vag. Supp.	Tioconazole + Tinidazole	6% + 4%
Dektacort V®	Vag. Cream	Miconazole + Hydrocortisone	(20 mg + 10 mg) per 1 gm
Furazole plus®	Vag. Supp.	Furazolidone + Nifuroxime	7.5% + 12 mg

*** Dimethylpolysiloxane = Dimethicone**, they are the same drug.

Other Vaginal Infections products			
Resulen®	Vag. Supp.	Policresulen	----------
V-Gel®	Vag. Cream	Herbal preparation	----------
Fluomizin®	Vag. Tab	Dequalinium Chloride	10 mg
Premeno® duo	Vag. Ovule	Hyaluronic acid Na^+	5 mg
Xaluron®	Vag. Supp.	Hyaluronic acid Na^+	5 mg
Relactagel®	Vag. Gel	lactic acid + Glycogen	4.5% + 0.1%

*** Policresulen** is a topical hemostatic and antiseptic, it's also can be used for common anal disorders, such as hemorrhoids.

**** Dequalinium Chloride** is an **antiseptic and disinfectant**, it is a topical bacteriostatic, used in wound dressings and mouth infections and may also have antifungal action, it also may cause skin ulceration with high concentrations

** **Hyaluronic acid** is given for vaginal Dryness.

7.4- Contraception methods

1. Drugs are available that decrease fertility by a number of different mechanisms, such as **preventing ovulation, impairing gametogenesis or gamete maturation, and interfering with gestation**; (For hormonal replacement therapy HRT see chapter 6, section 3)
2. All hormonal contraceptive methods (oral pills, Injections, patches) have side effects on the women, which maybe disturbing; **So why don't men just use condoms?**
   - But to be scientifically fair; oral contraception has benefits (aside from pregnancy prevention) that include treatment of acne, hirsutism, premenstrual syndrome (PMS), and menstrual cycle regulation.

Major classes of contraceptives (9 methods):

A. Combination oral contraceptives (COCs):

1. Products containing a combination of an estrogen and a progestin are the most common type of oral contraceptives, combination of **Estrogen (prevent the development of the dominant follicle) and Progestin (prevent ovulation)**, have these types:
   a. **Monophasic pills** contain a constant dose of estrogen and progestin given over 21 days.
   b. **Triphasic oral contraceptive** products attempt to mimic the natural female cycle and most contain a constant dose of estrogen with increasing doses of progestin given over three successive 7-day periods.
   c. **Extended-cycle contraception** (84 active pills followed by 7 days of placebo).
   d. **Continuous oral contraceptive** product (active pills taken 365 days of the year).
2. **Adverse effects** (and their relevance) of COCs include: Bleeding irregularities (32%), Nausea (19%), Weight gain (14%), Mood swings (Rage, Sadness, Depression) (14%), Breast tenderness (11%), Headache (11%) and Acne (8%).
   - If the Nausea is very troublesome; Suggest the patient take the pill at night before bed.
   - Acne is related to the androgenic properties of Progestin.
3. When using COCs watch out for these **serious adverse effects (ACHES):**
   - **A = Abdominal pain**; could signal liver problems or gallbladder.
   - **C = Chest pain**, shortness of breath; could signal myocardial infarction or blood clot in lung.
   - **H = Headaches** (severe); could signal stroke, blood clot.
   - **E = Eye problems** (blurred vision, flashing lights); could signal optic neuritis, stroke, clots.
   - **S = Severe leg pain** with or without swelling; could signal DVT.

Scientific name(s)	D. form	Trade name	concentration
Levonorgestrel + EE	Tab	Microgynon®, Nova®, Nora®	0.15 mg + 0.03 mg
Drospirenone + EE **	Tab	Yasmine® , Zahraa®	3 mg + 0.03 mg
	Tab	Yaz® , Gianvi®, Warda®	3 mg + 0.02 mg
Desogestrel + EE	Tab	Marvelon®	0.15 mg + 0.03 mg
Gestodene + EE	Tab	Gynera®, Femodene®	0.075 mg + 0.03 mg
	Tab	Sunya®	0.075 mg + 0.02 mg
Norgestrel + EE	Tab	Cryselle®, Eugynon®	(0.3 mg + 30 mcg), (0.5 mg + 50 mcg)
Norgestimate + EE	Tab	Mononessa®, Cilest®	0.25 mg + 35 mcg
Norethindrone + EE	Tab	Femhrt® , Jinteli®	0.4 mg + 35 mcg
Etynodiol + EE	Tab	Zovia®	0.05 mg + 1 mg
Norethindrone + Mestranol	Tab	Necon®	1 mg + 50 mcg
Dienogest + Estradiol	Tab	Qlairis® , Qlairista®	**4 phase tab**
Dienogest + Estradiol	Tab	Natazia®	**4 phase tab**

* EE = Ethinyl Estradiol * **Bold marked are the items that's found in our market.**

**** Drospirenone** is an Analog of spironolactone, similar to spironolactone 25 mg but with no diuretic effect.

Note: Products containing Drospirenone

a. **Drospirenone** is an **Analog of spironolactone**, similar to spironolactone 25 mg.
b. When using Drospirenone; Exercise caution with drugs that increase potassium such as high doses of NSAIDs, heparin, ACEIs, and potassium-sparing diuretics; it has **No diuretic effect**, has **anti-mineralocorticoid effects**; thus, it decreases bloating effect of Ethinyl estradiol.
c. It has **Antiandrogenic effects**: Best for acne, hirsutism, or male pattern balding in women.
d. It has a Possible increased risk of DVT and PE.

B. Progestin-only pills (POPs):

1. Products containing a progestin only, these preparations are less effective than the combination pill, **the progestin-only pill may be used for patients who are breastfeeding** (unlike estrogen, **Progestins do not have an effect on milk production**), who are intolerant to estrogen, smokers, or have other contraindications to estrogen-containing products.
- There are no hormone-free days with the POPs, may start on any day or on first day of period.

2. **Indications of Progestin-only Pills:** those who cannot use or tolerate combined hormonal contraceptives (see list below) or those seeking long-term contraception:
a. History or current MI, stroke, DVT, CVD.
b. Atrial fibrillation or with Blood pressure ≥ 160/100 mm Hg.
c. Active, symptomatic liver disease or History of cholestasis.
d. Migraine headache with neurologic impairment or aura.
e. Retinopathy or neuropathy because of diabetes.
f. Surgery within the past 4 weeks.

3. **Adverse effects caused by Progestins:** Headaches Increased appetite, Increased weight gain, Depression, fatigue, Changes in libido, Androgenic effects (Hair loss, hirsutism, Acne, oily skin).

Scientific name(s)	D. form	Trade name	concentration
Medroxyprogesterone	Tab	Provera®	5 mg , 10 mg
	Inj.	Depo-Provera®	150 mg
Lynestrenol	Tab	Exluton®	0.5 mg
Levonorgestrel	Tab	Norgeston®	30 mcg
Desogestrel	Tab	Cerazette®	1 mg
Norethindrone	Tab	Camila®, Lyza® , Errin®	0.35 mg

Advantages of progestin only pills	Disadvantages of progestin only pills
1. Oral progestogen-only preparations may offer a suitable alternative when the estrogens are contra-indicated (including those patients with venous thrombosis or a past history of venous thrombosis) [2]. **2.** **Confusion with pill taking is minimized because there is no placebo week** and all 28 pills in each pack are the same [5].	**1.** They must be taken **more regularly than COCs**, they are taken as One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (**if delayed by longer than 3 hours' contraceptive protection may be lost)** [3] **2.** They may have a **higher failure rate than combined preparations** [1] (from 0.3% to 8%) [5].

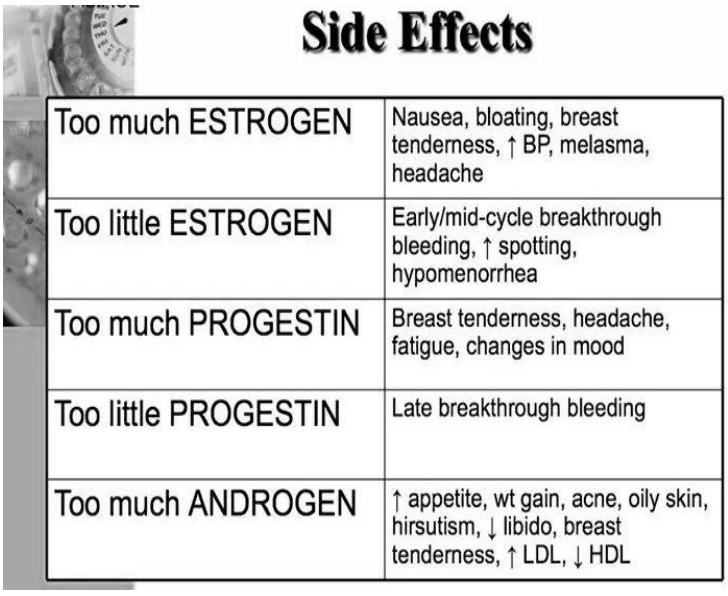
The use of oral contraceptives during breast-feeding:

1. The American College of Gynecology (ACOG) recommends **waiting at least 6weeks before starting any estrogen-containing contraceptive** regardless of breast-feeding status (By this time, the increased risk of thrombosis that occurs during pregnancy should be reduced to baseline), However, COCs have been reported to decrease milk quantity and quality. Therefore, many providers suggest avoiding COCs in women who are exclusively breastfeeding.
2. **For non–breast-feeding women, a progestin-only contraceptive** may be used immediately postpartum and 6 weeks postpartum if solely breast-feeding and in some cases 3 weeks postpartum if partially breast-feeding.

The Selection of appropriate contraceptive pills:

This depends on the side effects developed by the women taking COC pills:

- (Nausea, Dizziness, bloating, breast enlargement, tension, and migraines headaches) **are all due the higher Estrogenic content, so switch to a COC progestin dominant** as: Microgynon®, Eugynon®.
- (Acne, weight gain, vaginal dryness, depression/lethargy, scanty menses) **are all due higher progestin content, switch to a COC estrogen dominant** as: Marvelon®, Gynera®.
- This table will help you to decide which contraceptive pills is suitable for the patient.



C. Transdermal patches:

An alternative to combination oral contraceptive pills is a transdermal contraceptive patch containing (**Ethinyl estradiol** and the progestin **Norelgestromin**)

- **a.** One contraceptive patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock; week 4 is patch free, and withdrawal bleeding occurs.
- **b.** It has been shown to be less effective in women weighing greater than 90 kg.

Scientific name(s)	D. form	Trade name	concentration
Norelgestromin + EE	Patch	Evra®	(0.15 mg + 0.02 mg) per day
		Xulane®	(0.15 mg + 0.035 mg) per day

D. Injectable Progestins:

1. **Medroxyprogesterone** is an injectable contraceptive (commonly used) that is administered **every 3 months (11–13 weeks),** Weight gain is a common adverse effect.
   - **a.** Preferred start: First 5 days of menses; or at Any time in cycle if not pregnant.
   - **b.** Wait a few hours before massaging area where shot was given.
   - **c.** Return to **normal fertility may be delayed** for several months after discontinuing use.
   - **d.** **May contribute to bone loss** and predispose patients to **osteoporosis** and/or fractures, Therefore, the drug **should not be continued for more than 2 years** unless the patient is unable to tolerate other contraceptive options.
     - ➢ All patients using injectable Progestins should be taking sufficient calcium (1000–1200 mg/day) and exercising regularly.

Scientific name(s)	D. form	Trade name	concentration
Medroxyprogesterone	Inj. Solu. (I.M)	Depo-Provera®	150 mg
	Inj. Susp (S.C.)	Sayana-Press®	104 mg/0.65 ml
Norethisterone	Inj.	Noristerat®	200 mg/ml

E. Spermicidal contraceptives (Nonoxinol):

1. Vaginal spermicides (a chemical that kills sperm such as **Nonoxinol 9**) may be used as foam, creams, gels or pessaries - dissolvable tablets, inserted into the vagina after sex.
2. The vaginal pessaries/dissolvable tablets **required about 15 minutes to produce its effect** (onset of action) and has a duration of action of about 1 hour**.**
   - ➢ They preferably used adjunctively with other forms of contraceptives to provide additional protection against unwanted pregnancy; because they are generally considered relatively ineffective when used as the sole method of contraception.

Scientific name	D. form	Trade name	concentration
Nonoxinol 9	Vag. Supp.	Nonoxinol®	100 mg
	Vag. Gel	Gygel®	2%
Nonoxinol 9 + Benzethonium CL	Vag. Supp.	Today-Plus®	100 mg + 4.6 mg
Menfegol	Vag. Foam tab	Menfegol®	60 mg
Monalazone	Vag. tab	Monalazone®	9.5 mg

F. Vaginal ring:

1. An additional contraceptive option is a vaginal ring containing **Ethinyl Estradiol** and **Etonogestrel,** the ring is inserted into the vagina and is left in place for 3 weeks; week 4 is ring free, and withdrawal bleeding occurs.
   - **a.** The contraceptive vaginal ring has efficacy, contraindications, and adverse effects similar to those of oral contraceptives.
   - **b.** Should not be removed during intercourse; Even if the partner feels it.
   - **c.** Disadvantage with the vaginal ring is that it may slip or be expelled accidentally; also, it may Decreased libido (maybe a psychological effect); and cause Vaginal discomfort and secretions.

Scientific name	D. form	Trade name	concentration
Etonogestrel + EE *	Vag. Ring	NuvaRing®	0.12 mg + 0.015 mg

*** Etonogestrel** is the active form of **Desogestrel.**

G. Intrauterine Device (IUD):

1. **Levonorgestrel** releasing **intra-uterine system (L-IUD)** offers a highly effective method of **long-term contraception**; This intrauterine device provides contraception for up to **5 years**.
   - It is a suitable method of contraception for women who already have at least one child and do not have a history of pelvic inflammatory disease or ectopic pregnancy.
   - Increased risk of infection for 20 days after insertion.
2. Another type of intra-uterine system includes **Copper IUD** (which acts mainly as **Spermicide**); Copper ions inhibit sperm motility and acrosomal enzyme activation so that sperm seldom reaches fallopian tube and are unable to fertilize the ovum.
   - long term contraception; for about **10 years**.
   - Increased risk of infection for 20 days after insertion.
   - C.I. to Copper IUD include: Women with current or recent (within 3 months) sexually transmitted infection (STI), Uterus less than 6 cm or greater than 9 cm, Allergy to copper; Wilson's disease, and recent Endometrial infection (past 3 months).

Scientific name	D. form	Trade name	concentration
Copper IUD	IUD	Paragard®	380 mm2
Levonorgestrel	IUD	Mirena®	20 mcg/24 hr.
		Kyleena®	17.5 mcg/24 hr.

H. Progestin implants:

1. **A sub-dermal implant containing Etonogestrel** offers long-term contraception; one 4-cm capsule is placed sub-dermally in the upper arm and provides contraception for approximately **3 years**, the implant is nearly as reliable as sterilization, and the effect is totally reversible when surgically removed and return to fertility within 1–3 months
   - **a.** Once the progestin-containing capsule is implanted, this method of contraception does not rely on patient compliance.
   - **b.** Principal side effects of the implants are irregular menstrual bleeding and headaches.
   - **c.** The **Etonogestrel** implant has not been studied in women who weigh more than 130% of ideal body weight and **may be less effective in overweight women.**

Scientific name	D. form	Trade name	concentration
Etonogestrel	Implant (subdermal)	Implanon® , Nexplanon®	68 mg

I. Barrier Female Contraceptives

1. As males have condoms as a barrier contraceptive; Females also does have such methods, these include (**Female condoms**, **Cervical Caps**, **Diaphragms** and **Contraceptive Sponge**); in all which act similarly as physical barriers to sperms.
2. **Female condoms** are made from soft, thin synthetic latex or latex; They're worn inside the vagina to prevent semen getting to the womb; If used correctly, they are 95% effective.
   - It may cause UTIs if left in the vagina for a prolonged period.
3. **Cervical cap** is a little cup made from soft silicone and shaped like a sailor's hat; its inserted deep inside the vagina to cover the cervix, stopping sperm from joining an egg, in order for a cervical cap to work best, it must be used with spermicide (a cream or gel that kills sperm).
   - Inserted at least 15 min. before sexual intercourse, and can be left for 48 hours.
4. **Diaphragm** is a shallow, bendable cup that is inserted inside the vagina; It covers the cervix during sex to prevent pregnancy (a shallow cup shaped like a little saucer that's made of soft silicone; it bends into half and inserted inside the vagina to cover the cervix).
   - Inserted before the sexual intercourse and remains in the vagina for 6-8 hours.

5. The **contraceptive sponge** prevents sperm from entering the uterus; It is soft and disk-shaped, and made of polyurethane foam, it contains spermicide, which blocks or kills sperm, before having sex, its inserted deep inside the vagina so that it covers the cervix; the vaginal muscles hold it in place, it has a strap on one side for easier removal.
   - Can be left inside for 24 hours.

J. Post-coital contraception: (Emergency Contraception)

1. Emergency contraception uses **high doses of Progestin** (0.75 mg or 1.5 mg Levonorgestrel) or **high doses of Estrogen** (100 mcg Ethinyl Estradiol) **plus Progestin (0.5 mg Levonorgestrel) administered within 72 hours of unprotected sex** (the morning-after pill).
   - For these regimens, a second dose of emergency contraception should be taken 12 hours after the first dose, and for maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected sex and **preferably within 72 hours.**
   - Progestin-only Emergency Contraceptive pills are not effective for those with a BMI of 30 kg/m2 or greater **(not effective in women who weigh more than 80 kg).**
2. Recently there is **new drug approved** for emergency contraception **(Ulipristal)**, used orally as soon as possible (within 120 hr. or 5 days) after unprotected sex.
   - **Ulipristal** is a **selective progesterone receptor modulator (SPRM)**, which is also used for pre-operative treatment of moderate to severe symptoms of Uterine Fibroids in adult women of reproductive age in a daily dose of a 5 mg tablet.
   - Not approved for use during breastfeeding.
   - Not recommended for women with a BMI greater than 35 kg/m2.
   - Recommended to wait 5 days before initiating or resuming hormonal contraception after taking **Ulipristal**; Starting hormonal contraception before waiting 5 days might alter the effect of Ulipristal as well as the effect of hormonal contraception

Scientific name	D. form	Trade name	concentration
Levonorgestrel	Tab	Plan B®, I-pill®	1.5 mg
Ulipristal	Tab	Ella® , EllaOne®	30 mg
	Tab	Esmya®, Fibristal®	5 mg

7.5– Polycystic ovary syndrome (PCOS)

1. Polycystic ovary syndrome (PCOS) is a set of symptoms due to **elevated androgens** (male hormones) in females; Signs and symptoms of PCOS include irregular or no menstrual periods, heavy periods, excess body and facial hair, acne, pelvic pain, difficulty getting pregnant, and patches of thick, darker, velvety skin.
   - Can be a **cause of infertility** in up to 20% of infertile couples
   - Mainly considered to be **caused by androgen excess** or **hyperandrogenism**.
   - Underlying cause appears to be **insulin resistance** (in patients with and without obesity), with subsequent compensatory insulin hypersecretion or increased insulin action, this increased action stimulates androgen secretion by the ovaries or adrenal cells, leading to increased luteinizing hormone (LH) secretion but normal or low follicle-stimulating hormone (FSH) concentrations, with a subsequent decrease in follicular maturation and anovulation.
     - That's why **Metformin** and **Pioglitazone** are useful in PCOS (they're insulin sensitizers).
2. Risk factors include: obesity, a lack of physical exercise, a family history of someone with the condition; and Diagnosis is based on two of the following three findings: no ovulation, high androgen levels, and ovarian cysts (Cysts may be detectable by ultrasound).
   - DDx = Elevated free or total serum testosterone, and LH/FSH ratio greater than 2.

3. **PCOS has no cure**; Treatment may involve lifestyle changes such as weight loss and exercise, oral contraceptive pills may help with improving the regularity of periods, excess hair growth, and acne, Metformin and anti-androgens may also help, other typical acne treatments and hair removal techniques may be used, Efforts to improve fertility include weight loss, clomiphene, or metformin; In vitro fertilization (IVF) is used by some in whom other measures are not effective.
4. Pharmacotherapy for PCOS: **Fertility improvement:** using **Clomiphene**, **Gonadotropin**, and **Letrozole** (see Infertility section below).
   Symptomatic improvement:
   - **Hormonal contraceptives (Estrogen/Progestin combination):** Endocrine Society first-line therapy for menstrual abnormalities, hirsutism, or acne.
     - They increase sex hormone binding globulin production, which increases binding of free testosterone; This reduces the symptoms of hirsutism caused by high testosterone and regulates return to normal menstrual periods.
   - **Metformin:** Effective for metabolic and glycemic abnormalities, if present, but only modestly effective for hirsutism (Alternative to hormonal contraception for irregular menses when hormonal contraceptives are contraindicated); Few data to support use for increased fertility (may improve pregnancy rate but not shown to improve rates of live births).
     - Used to treat insulin resistance seen in PCOS; also supports ovarian function and return to normal ovulation.
   - **Spironolactone:** Often added to hormonal contraceptives, it can help with hirsutism, it is used for its antiandrogenic effects.
   - **Pioglitazone:** Questionable whether benefits outweigh risks in PCOS; Not recommended in Endocrine Society guidelines. [9]
     - Although several studies show benefit of Pioglitazone in PCOS.
5. **Inositol**: A 2017 review concluded that while both **myo-inositol** and **D-chiro-inositol** may regulate menstrual cycles and improve ovulation, but there is a lack of evidence regarding effects on the probability of pregnancy; a 2012 and 2017 review have found myo-inositol supplementation appears to be effective in improving several of the hormonal disturbances of PCOS; also, Myo-inositol reduces the number of gonadotropins injections and the length of controlled ovarian hyperstimulation in women undergoing in vitro fertilization.

Scientific name	D. form	Trade name	concentration
Metformin	Tab	Glucophage®, Siofor®, Riomet®	500 mg , 850 mg , 1000 mg
	Tab XR		500 mg , 750 mg , 1000 mg
Spironolactone	Tab	Aldacton®	25 mg , 50 mg , 100 mg

Herbal Combinations for PCOS			
Inositol + Choline	Tab	***Choline & Inositol®***	500 mg + 500 mg
Inositol + Choline + Folic Acid + Vit. K2 + Co-Q10 + ALA	Tab	***Forte Choline & Inositol®***	500 mg + 500 mg + 200 mcg
Inositol + Folic Acid	Sachet	***OvuSitol®***	2000 mg + 200 mcg
Myo-Inositol + Folate + White kidney Bean Extract	Sachet	***Myofol®***	2000 mg + 200 mcg + 100 mg
Myo-Inositol + D-chiro-inositol + Multivitamin Combo	Caplet	***PolySitol® (AMS)***	2000 mg + 50 mg

7.6- Vaginal Gels to aid natural fertility

1. These Vaginal gels creates an environment in which sperm has the best chances of reaching a woman's eggs; with a neutral pH of 7.2 they protect sperm from too acidic environment, thereby ensuring their survival; also, their osmotic properties provide optimum room for maneuver, and thus Sperm motility is boosted.
2. Some formulations contain Magnesium (Mg^{2+}) and Calcium (Ca^{2+}) Ions for Fertility Support.
3. They inserted into the vagina 5-10 minutes before sexual intercourse, they also act as a lubricant.

Trade name	D. form	Scientific name(s)	concentration
Prefert®	Vag. Gel	Sodium Chloride + Sodium Phosphate + Potassium Phosphate + Arabinogalactan + Hydroxyethyl cellulose + Polyhexanide	6 ml Gel
Conceive Plus®	Vag. Gel	Deionized Water + Hypromellose + Sodium Chloride + Glycerol + Sodium Phosphate + Methylparaben + Potassium Chloride + Magnesium Chloride + Calcium Chloride	4 gm Gel

7.7 – Infertility in Women

1. Infertility is defined as the inability to conceive **after one year** of unprotected intercourse, many factors affect infertility rates, but advancing maternal age appears to be a prominent influence, an important focus when evaluating causes of infertility is ovulatory function, which is associated with up to 40% of female factor infertility
   - Ovarian function is regulated through complex feedback mechanisms within the hypothalamic-pituitary-ovarian axis, this involves release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, and Estrogen and progesterone from the ovaries, **Anovulation results from the disruption of communication at any of these levels and is associated with a variety of causes.**
2. Conditions such as **Thyroid dysfunction, Hyperprolactinemia,** and **Polycystic Ovary Syndrome (PCOS)** can induce anovulation, and each is treated separately.
   - Fertility improves with BMI of 20–25 kg/m2 or within 15% of ideal body weight; fertility decreased in those less than 95% of ideal body weight or in those greater than 125%.
   - **Impaired cervical mucus production or quality** is an additional structural factor that can impact sperm motility and the fertilization process.
3. **Treatment Approaches:**

A. The treatment approach is empiric but typically incorporates medications to **stimulate ovulation**; This may or may not be combined with **intrauterine insemination** or other infertility procedures, there are two general treatment strategies that focus on ovulation: **"ovulation induction" (OI) and "controlled ovarian stimulation" (COS)**, the approach depends on a patient's underlying ovulatory function.
   - **Ovulation induction:** is pursued in patients who are not ovulating to promote an ovulatory cycle, this method may be accompanied by timed natural intercourse or the use of insemination procedures to achieve pregnancy.
   - **Controlled ovarian stimulation:** incorporates many of the same medications, but is appropriate for women who are already having ovulatory cycles but are still experiencing infertility, also it's appropriate for infertility procedures where the development of multiple ovarian follicles is desirable.

B. The physician may add (**Cabergoline** or **Bromocriptine**) for the treatment of **Infertility** caused by **hyperprolactinemia** to the main prescription, **Doses:**
   1. **Cabergoline =** 0.5 mg – 1 mg twice a week. (For more info see chapter 6, section 5-C).
   2. **Bromocriptine =** start with 1.25 mg – 2.5 mg every day, then increase gradually by 2.5 mg\week till achieving clinical response.

C. Also, the physician may add **Mucolytics** such as (**N-Acetyl-Cysteine, Guaifenesin, Bromhexine**) in high doses to **decrease Cervical Mucus thickness** and thus **enhancing sperm motility** and thus enhancing Fertility.

D. A new study found that **daily low dose Aspirin (81 mg) increase the chances of conception** by 17% for women who previously miscarried; this is though due to reducing the systemic inflammation which improves the environment in which an embryo grows.

First: Ovulation induction:

This process is designed to mimic the hormonal patterns of the normal menstrual cycle, the choice of medications for Ovulation induction is dictated by hypothalamic-pituitary- ovarian function.

➢ Ovulation Induction in Patient with adequate hypothalamic function:

1. An oral regimen of **Clomiphene** (which exhibits estrogenic agonist and antagonist activity) is often utilized first line. Clomiphene inhibits estrogenic binding in the hypothalamus to stimulate release of GnRH and pituitary gonadotropins and induce ovarian follicular development. **Ovulation is successful in 80% of patients using Clomiphene.**

- **Clomiphene Dose:** 50 mg daily for 5 days starting within about 5 days of onset of menstruation (preferably on 2nd day); if ovulation does not occur, a course of 100 mg daily for 5 days may be given. (for more info see chapter 6, section 3-B)

2. Oral aromatase inhibitors **(Letrozole)** are not approved by the US (FDA) for Ovulation Induction, but used off-label to increase release of GnRH and pituitary gonadotropins through an estrogenic antagonist effect.

- **Dose:** 2.5 mg daily for 5 days starting within about 5 days of onset of menstruation (preferably on 2nd day), sometimes it is given in higher doses of 5 mg or 7.5 mg per day. (i.e.; same dosing as Clomiphene).

Scientific name	D. form	Trade name	concentration
Clomiphene	Tab	Clomid®, Serophene®, Ovamit®	50 mg
Letrozole	Tab	Femara®	2.5 mg

For Hyperprolactinemia

Scientific name	D. form	Trade name	concentration
Bromocriptine	Tab	Parlodel® , Cycloset®	2.5 mg , 5 mg , 10 mg
Cabergoline	Tab	Dostinex® , Cabaser®	0.5 mg

➢ Ovulation Induction in Patient with Hypothalamic or pituitary dysfunction (or if oral regimens are not successful)

Injectable Gonadotropins are administered in the following manner:

1. Usually an **Injection of hMG or FSH (75 IU every day)** is initiated over usually a period of 5 to 12 days to cause ovarian follicular growth and maturation; you may increase the dose as needed every 7 days by 37.5 IU.
2. **Addition of Clomiphene 50 mg tab** (or **Letrozole**) decrease the number of hMG or FSH injections needed to complete the cycle of ovarian follicular maturation.
3. Maximum daily dose of hMG or FSH is 300 IU daily.
4. Maximum duration of this cycle is 35 days.
5. **Then an injection of hCG (5000 IU)** or **(250 mcg of recombinant hCG) is given to cause ovulation.** (Injected after 1 day after the last hMG or FSH inj.)
6. **Then Fertilization must occur within 36 hours after hCG administration**, either by intercourse (normal Sex) or intra-uterine insemination.

Scientific name	Dosage form	Trade name	concentration
Menotropin (hMG) (FSH + LH)	Inj.	Merional® , Pergonal®	(75 IU + 75 IU), (150 IU + 150 IU)
Chorionic gonadotropin (hCG)	Inj.	Pregnyl® , Choragon®	5000 IU , 1500 IU , 10,000 IU
FSH (Urofollitropin)	Inj.	Diclair FSH®, Fastimon®	75 IU , 150 IU
Follitropin Alfa	Prefilled Inj.	Gonal-F®	75 IU (5.5 mcg)
	Prefilled Inj.	Gonal-F®	300 IU (22 mcg)
Lutropin Alfa	Inj. Powder	Luveris®	75 IU , 82.5 IU
Recombinant hMG (Follitropin Alfa + Lutropin Alfa)	Inj.	Pergoveris®	150 units (11 mcg) + 75 units (3 mcg)
Follitropin Beta	Inj.	Puregon®	50 IU
Choriogonadotropin Alfa	Prefilled Inj.	Ovitrelle®	250 mcg/0.5 ml (6500 I.U)
Corifollitropin Alfa	Prefilled Inj.	Elonva®	100 mcg/0.5 ml , 150 mcg/0.5 ml
Gonadorelin	Inj. Powder	Lutrepulse®	0.8 mg/vial

Second: Controlled Ovarian Stimulation (COS)

1. The oral and injectable medications used for Ovulation Induction are also incorporated into regimens for COS; they are administered in doses and schedules intended to develop multiple ovarian follicles, rather than one dominant follicle.
2. This results in a greater number of oocytes available for fertilization, **this is mostly achieved by injections of gonadotropins directly (as method above),** and this treatment can be combined with intra uterine insemination (IUI).

Third: Assisted Reproductive Technology (ART)

1. Procedures using ART provide a valuable treatment option for many couples who are not candidates for OI/COS alone or with intra-uterine insemination (IUI).
   - The primary ART is **IVF (in vitro fertilization)**, which involves retrieval of oocytes after COS, fertilization in vitro, and transfer of the embryo directly to the uterus through the cervix, bypassing the fallopian tubes.
   - **Intra-cytoplasmic sperm injection (ICSI)**, or the injection of sperm directly into the oocyte during the fertilization process, accompanies IVF if severe sperm dysfunction is evident.
2. Alternate procedures for ART include **gamete intra-Fallopian transfer** and **zygote intra-Fallopian transfer,** which alter the timing of fertilization and location of transplantation.
   - In **gamete transfer**, the retrieved oocytes are transferred with the sperm to the fallopian tube to allow for natural fertilization.
   - In **zygote transfer**, the oocytes are fertilized in vitro, but are transferred at an earlier stage of development to the fallopian tubes, rather than the uterus.

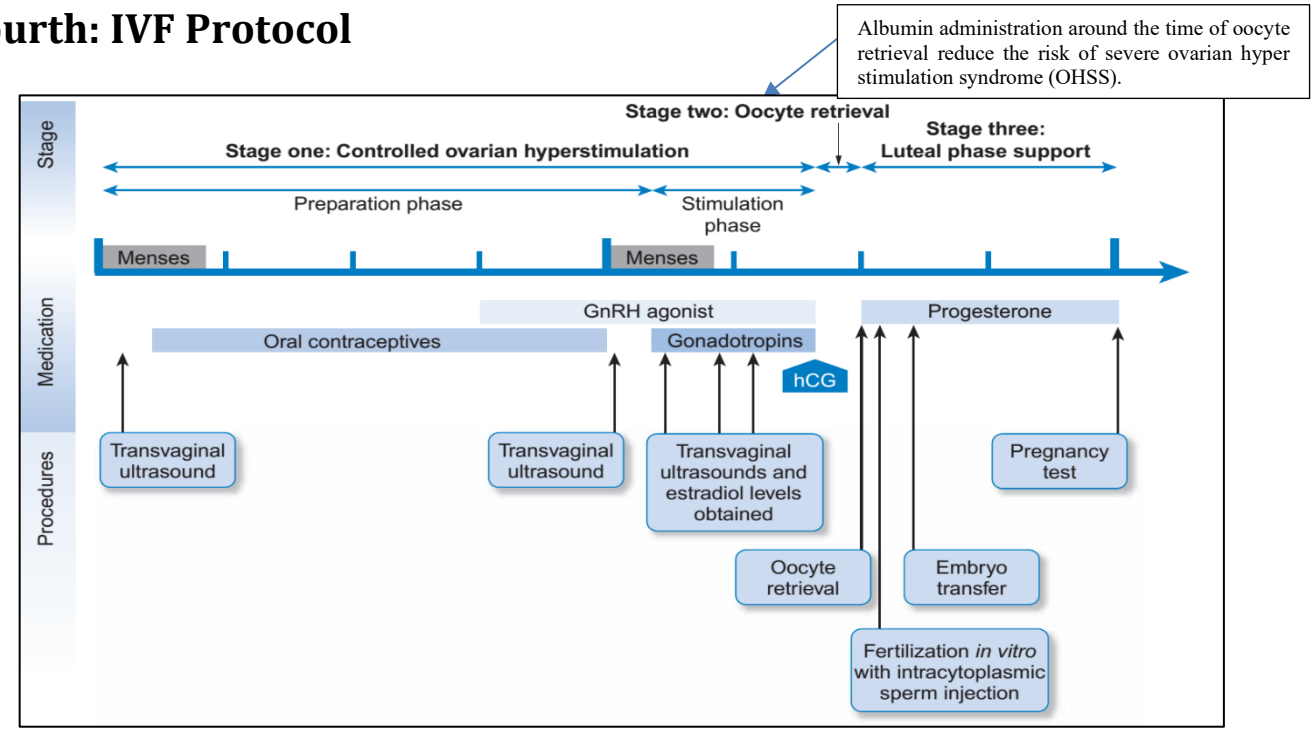
Classification	Procedure	Description
Insemination	Intrauterine, intracervical, intravaginal	Delivery of a prepared semen sample to the intended site (vagina, cervix, uterus) during ovulation
Assisted reproductive technology	Assisted hatching	Mechanical or chemical separation of the blastocyst from the zona pellucida (membrane surrounding the oocyte) during embryonic development in vitro
	Embryo cryopreservation	Freezing and storage of embryos for future ART cycles
	Gamete intrafallopian transfer	Laparoscopic transfer of the unfertilized oocytes and sperm to the fallopian tube for fertilization
	In vitro fertilization—embryo transfer	Transfer of one or more embryos resulting from in vitro fertilization into the uterus through the cervix
	Intracytoplasmic sperm injection	In vitro injection of the sperm into the oocyte
	Preimplantation genetic diagnosis/screening	Examination of oocytes, zygotes, or embryos for specific genetic conditions (diagnosis) or for general genetic alterations (screening)
	Zygote intrafallopian transfer	Laparoscopic transfer of the fertilized oocyte (zygote) into the fallopian tube

3. **The basic steps in an IVF protocol include:** COS, oocyte retrieval, fertilization, embryo culture and embryo transfer. Medications are primarily used during three main stages of IVF: COS, oocyte retrieval, and luteal phase support.

Role of Medications in an In Vitro Fertilization Cycle

IVF Stage	Medications[a]	Role
Stage One: Controlled ovarian stimulation	Oral contraceptives	Control the onset of menses and the start of controlled ovarian stimulation
	GnRH agonists or GnRH antagonists	Prevent a premature LH surge or disruption of controlled ovarian stimulation
	Gonadotropins (FSH or FSH plus LH)	Stimulate development of multiple ovarian follicles for oocyte retrieval
Stage Two: Oocyte retrieval	hCG	Induce final follicular maturation to prepare for oocyte retrieval
Stage Three: Luteal phase support	Progesterone	Maintain the endometrium for embryo transfer and implantation

Fourth: IVF Protocol



7.8– Sexual Dysfunction in Women

A. **Human Female Sexual response cycle** consist of 4 stages or phases; which all lead to normal sexual process; any dysfunction in any stage will lead to a **Sexual Dysfunction**:
   1. **Excitement (Desire, Libido) phase:** in which the heart rate increase, breathing rate increase, blood pressure increase and the body temperature increase; leading to flushing (sex flush); in this phase the women's Clitoris swells, and the muscles of the vagina undergo relaxation and produce lubricating liquid, and the nipples become hardened and erect.
   2. **Plateau (Arousal) phase:** the period between sexual excitement and orgasm, in which the Clitoris becomes extremely sensitive, and the vagina produces further lubricating liquid.
   3. **Orgasmic phase:** accompanied by quick cycles of muscle contractions in the lower pelvic muscles, which surround both the anus and the sexual organs; orgasms are accompanied with euphoric sensation; although orgasm intensity varies widely from women to another, the overall sensation is similar to that of male orgasm.
   4. **Resolution phase:** if orgasm is achieved; resolution may last 10-15 minutes with sensation of calmness and relaxation, and if the orgasm is not achieved; irritability and discomfort can result, in which it can last for several hours.

B. Factors Effecting Libido in women:

1. **Hormones and Neurotransmitters:**
   - Dopamine increase libido, while Prolactin decrease libido (Prolactin play an important role to control sexual desire in females); thus, libido is low in lactating women.
   - Estrogen, Progesterone and Norepinephrine all increase libido.
   - Testosterone (male hormone); in females: testosterone levels rise gradually and reach to highest levels in ovulation days, and during this period the female desire for sex increases.
   - Oxytocin is responsible for the orgasm and sexual pleasure.
   - Serotonin decrease libido.
2. **Psychological Factors:** Lack of privacy, lack of intimacy (no love feelings), stress, fatigue, distraction, depression; all decrease libido.
3. **Medications:** hormonal contraceptive decrease free testosterone levels; which ↓ libido.

First: Low Sexual Desire in Women

1. Also Called **Hypoactive sexual desire disorder (HSDD)**, and also referred as **inhibited sexual desire (ISD)** is considered a sexual dysfunction and is characterized as a lack or absence of sexual fantasies and desire for sexual activity, as judged by a clinician.

2. If a male had a sexual problem, he'll take **Sildenafil** or **Tadalafil** and the problem is solved, but what if the female had such problem?
   - Unfortunately; there are many products marketed for sexual arousal for females and they have no scientific background or any evidence of efficacy, (as gums, drops and sprays).
   - Many other combinations are found in the market, they may include multi-vitamins, Zinc, proteins, B-complex, vitamin E …. etc. (all may be beneficial as a secondary supplement).

3. Sometimes the **low sexual desire** in women are **due hormonal imbalance**; thus, correcting these imbalances may result in sexual activity improvement:
   - **Very Low testosterone levels**: treated with testosterone supplementation, for short term therapy only (as it may cause weight gain, acne and excess body hair).
   - **Low Estrogen levels**: systemic Estrogens or Topical Estrogens.
   - **High Prolactin levels**: treated with Cabergoline or Bromocriptine.

4. The **only drug approved by the FDA** for **Hypoactive sexual desire disorder (HSDD)** in women is **Flibanserin,** the medication increases the number of satisfying sexual events per month by about one half over placebo from a starting point of about two to three.
   - **Flibanserin** was originally developed as an antidepressant, before being repurposed for the treatment of HSDD, it's a **5-HT$_{1A}$ agonist** (increase Dopamine and Norepinephrine; which is both responsible for sexual excitement), and a **5-HT2A antagonist** (decrease Serotonin; which is responsible for sexual inhibition).
   - **Dose 100 mg** one daily at bedtime, **dosed at bedtime because** administration during waking hours increases risks of hypotension, syncope and CNS depression.
   - **Not indicated to enhance sexual performance (not useful for normal females).**
   - The most commonly reported adverse events included dizziness, nausea, feeling tired, sleepiness, and trouble sleeping.

5. **Yohimbine**, a selective α2 receptor blocker, may be useful for general sexual problems in women, it acts by **increasing blood flow** and nerve impulses to the vagina; but unfortunately, its without strong evidence of benefit.

6. **Dehydroepiandrosterone (DHEA)** is a precursor to Estrogen and Testosterone, it has been used off-label to increase libido in postmenopausal women.

7. Several other products are **used off-label** to enhance libido in females, which include: (**Amphetamine**, **Methylphenidate** and **Bupropion**), in which they all act by enhancing Dopamine release or by increasing its release.

8. **Ginkgo Biloba**, **Ginseng** and **Fish Roe** (Caviar) are herbal products that is thought to increase general sexual heath (including enhancing sexual desire), in both males and females; but this claim is not supported or confirmed by strong studies or trails.

Scientific name	Dosage form	Trade name	concentration
Flibanserin	Tab	Addyi®	100 mg
Yohimbine	Cap	Aphrodien®	2.5 mg , 6 mg , 10 mg
Dehydroepiandrosterone	Tab	DHEA®	25 mg , 50 mg
Lyophilized Fish Roe + Ginkgo Biloba	Cap	Aphrofem®	475 mg + 25 mg

Second: Female Sexual Arousal Disorder (FSAD):

1. It's the inability to complete sexual activity with adequate lubrication, it's similar to Erectile Dysfunction in males; Symptoms include: lack of vaginal lubrication or dilation, decreased genital swelling and decreased nipple or genital sensation.
2. Causes may psychological (no desire in the partner, no intimacy), or due hormonal imbalances (low Estrogen, Low Testosterone), or due menopause (atrophic vaginitis) or due infection (Vaginitis); Each cause is treated individually.
3. **Bremelanotide** is used to treat **Female Sexual Arousal disorder**
   - It is also used for **Low Sexual Desire** which occurs before menopause and is not due to medical problems, psychiatric problems, or problems within the relationship.
   - **Bremelanotide** is a **non-selective agonist of the melanocortin receptors**, MC1 to MC5 (with the exception of MC2)
   - It is given by an injection just under the skin of the thigh or abdomen; used at least 45 minutes before anticipated intercourse, only one dose per 24 hours or no more than eight doses per month is recommended.
   - **Not indicated to enhance sexual performance (not useful for normal females).**
   - It should be stopped after eight weeks if there is no improvement in sexual desire and associated distress.
   - It may also cause a temporary increase in blood pressure and decrease in heart rate after each dose, and darkening of the gums, face, and breasts.
4. **Tibolone** is a synthetic steroid molecular with estrogenic, progestogenic and androgenic action. In addition to improvements in vasomotor symptoms and vaginal atrophy when used as hormonal replacement therapy (HRT) in postmenopausal women, **Tibolone has been shown to improve sexual desire compared with placebo.**
   - **Tibolone** is also being investigated as a possible treatment for Female Sexual Arousal Disorder (FSAD) and for Hypoactive Sexual Desire Disorder (HSDD).

Scientific name	Dosage form	Trade name	concentration
Bremelanotide	Prefilled Inj.	Vyleesi®	1.75 mg/0.3 ml
Tibolone	Tab	Livial®	

7.9- Vaginal Douches (Female Hygiene products)

1. Douching is the act of washing or cleaning out the vagina with water and other ingredients, this practice is not recommended by most doctors; **(Douching is connected as a main cause for Infertility and Ectopic pregnancy).** [8]
   - Douching may interfere with both the vagina's normal self-cleaning and with the natural bacterial culture of the vagina**.**
2. Some women chose to use douches; typically, by using a pre-made mixture is bought in a plastic bottle with a nozzle that can be squirted into the vagina. [8]
   - Douching is used for personal hygiene or aesthetic reasons, for preventing or treating an infection, to cleanse after menstruation or sex (Douching after sexual intercourse is not an effective form of birth control).

Trade name	Dosage form	Scientific name(s)	concentration
Germ X®	Vag. Douche	Povidone-Iodine	10% (pH = 5.5)
Gyno Baking Soda®	Vag. Douche	Sodium Bicarbonate + Sodium Carbonate	2% + 0.025% (pH = 8.9)
FemmeCare Baking Soda®	Vag. Douche	Sodium Bicarbonate + Sodium Carbonate	2% + 0.025% (pH = 8.0 – 9.0)
FemmeCare Astri®, Femigiene Astri®	Vag. Douche	Benzalkonium Chloride + Aluminum Potassium Sulfate	0.04% + 0.90%
FemmeCare Vinegar®	Vag. Douche	Acetic Acid + Sorbic Acid	1.25% (pH =2.8 – 3.5)
FemmeCare Chamomile®	Vag. Douche	Chamomile Extract	0.063%
Gyno Foam®	Vag. Douche	Hexamidine + Chamomile Ex. + Na Benzoate + Allantoin + Others	(pH = 4.2)
Evita®	Vag. Douche	Various Ingredients	----------
Canesten Sensicare®	Vag. Douche	Various Ingredients	(pH = 5)
Femin-X® Intimate	Vag. Douche	Various Ingredients	(pH = 3.8) , (pH = 4.2)
Lactacyd®	Vag. Douche	Various Ingredients	----------

References

1- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition.
2- Lippincott's pharmacology 7 Ed.
3- Rosemary R Berardi. Handbook of Nonprescription Drugs, 18th Edition
4- Community Pharmacy: Symptoms, Diagnosis and Treatment, By Paul Rutter, 4th Ed.
5- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th Ed.
6- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition.
7- Lexi-comp: Drug information handbook, 2022 Ed.
8- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1380405/
9- ACCP Updates in Therapeutics® 2021: Pharmacotherapy Preparatory Review

GENITO-URINARY SYSTEM

Chapter Eight: Genito-Urinary System

8.1- Drugs for Benign Prostatic Hyperplasia (BPH)

a. α1-blokers
b. 5α-reductase inhibitors
c. Combination Products
d. Other drugs may be used for BPH

8.2- Urinary Incontinence (UI)

a. Bladder over-activity
b. Urethral under-activity

8.3- Overflow Incontinence

8.4- Nocturnal Enuresis

8.5- Drugs for Erectile Dysfunction

a. Phosphodiesterase type-5 inhibitors
b. Testosterone-Replacement Regimen
c. Alprostadil injection
d. Other agents for ED
e. Herbal combination Products for ED

8.6- Drugs for Men Ejaculation Problems

a. Drugs for Premature Ejaculation
b. Delayed Ejaculation
c. Retrograde Ejaculation

8.7- Infertility in Men

8.8- Sexually Transmitted Diseases (STDs)

8.9- Kidney Stones

8.10- Alkalization of Urine

8.11- Other Urologic drugs

Chapter Eight: Genito-Urinary System

8.1- Drugs for Benign Prostatic Hyperplasia (BPH):

1. **BPH** is also called prostate enlargement, is a noncancerous (benign) increase in size of the prostate gland; Symptoms may include frequent urination, trouble starting to urinate, weak stream, inability to urinate, or loss of bladder control.

2. **BPH** is the most common cause of **lower urinary tract symptoms (LUTS)**, which are divided into storage, voiding, and symptoms which occur after urination.
   - **Storage symptoms** (Irritative) include the need to urinate frequently, waking at night to urinate, urgency (compelling need to void that cannot be deferred), involuntary urination, including involuntary urination at night, or urge incontinence (urine leak following a strong sudden need to urinate).
   - **Voiding symptoms** (Obstructive) include urinary hesitancy (a delay between trying to urinate and the flow actually beginning), intermittency (not continuous), involuntary interruption of voiding, weak urinary stream, straining to void, a sensation of incomplete emptying, and uncontrollable leaking after the end of urination.
   - These symptoms may be accompanied by bladder pain or pain while urinating, called Dysuria.

3. **The α1-selective alpha blockers** (like: Alfuzosin, Doxazosin, Tamsulosin and terazosin) relax smooth muscle in BPH producing an increase in urinary flow-rate and an improvement in obstructive (voiding) symptoms.
   - **α1-blokers can cause orthostatic hypotension** which may be severe and produce syncope after the initial dose; this reaction can be avoided by starting treatment with a low dose, (preferably at night), Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely.
   - **Tamsulosin** and **Silodosin** are **selective for prostatic α1A receptors**; therefore, they are less likely to cause orthostatic hypotension.
   - Intraoperative floppy iris syndrome is a concern with α-blockers, especially **Tamsulosin**; Men with LUTS being offered α-blockers should avoid cataract surgery.

4. **The 5α-reductase inhibitors** (**Finasteride** and **Dutasteride**): decreases the conversion of testosterone to the more active form: Dihydrotestosterone (DHT), thus reduce prostate volume, thus relieving storage (irritative); but this takes a number of months (at least 6 months).
   - **Finasteride** competitively inhibits type II 5-α-reductase and lowers prostatic DHT by 80%.
   - **Dutasteride** is a nonselective inhibitor of both type I and II 5-α-reductase, has the advantage that is Prostatic DHT production is quickly suppressed with this agent.
   - Both can reduce Prostate size by about 25% during 6 months.
   - Both can cause a marked decrease in libido.
   - Long-term therapy with an α-reductase inhibitor can increase the risk of high-grade tumors of the prostate in healthy men without a history of prostate cancer.

5. **Alpha1-blokers** can produce rapid symptomatic relief only (not affect the prostate volume) while **5α-reductase inhibitors** reduce prostate volume but this effect is delayed; therefore, both drugs may be used together in combination for a better outcome.

6. **Phosphodiesterase type 5 inhibitors** (**Tadalafil** 5 mg once daily) is approved for use in BPH, mechanism is thought to be caused by phosphodiesterase-induced smooth muscle relaxation in the bladder, urethra, and prostate.
   - Recommended to be **Used as monotherapy**; the FDA does not recommend use in combination with α-blockers because the combination has not been adequately studied for BPH, and there is a risk of lowering the blood pressure.
   - In common practice, most physicians combine **Tadalafil 5 mg** with **Finasteride 5 mg** once daily for less than 26 weeks; as the benefit of Tadalafil is reduced gradually after the 4th week.

7. **Tamsulosin** may be used also for **expulsion of lower ureteral stones;** by reducing ureteral spasm, increasing pressure proximal to the stone, and relaxing the ureter in the region of and distal to the stone; (Used for both males and females).
   - Maybe **useful for small stones only** (less than 5 mm), as a Double-blind, placebo-controlled trial found Tamsulosin did not significantly increase stone passage rate compared with placebo for stones <9 mm. [9]
   - **Tamsulosin** is also used as an add-on treatment for acute urinary retention, patients may void more successfully after catheter removal if they are taking Tamsulosin; also, they are less likely to need re-catheterization.
8. Regarding **Finasteride:**
   - It could **produce feminization** of a male fetus if **used in pregnant women**; therefore, it's recommended that women who are or may become pregnant should not handle crushed or broken Finasteride tablets.
   - It has been **detected in semen**; therefore, use of a condom is recommended if the patient's sexual partner is, or may become, pregnant.
   - Used in **treatment alopecia (hair loss) in men,** Finasteride is given orally in a low dose (1mg daily); while the dose used for BPH is 5 mg daily. [6]
   - Some men may experience sexual dysfunction, depression, anxiety, or breast enlargement.
   - It has been found to be **effective in the treatment of Hirsutism** (excessive facial and/or body hair growth) in women, in a study of 89 women with hyperandrogenism due to persistent adrenarche syndrome, low dose (1 mg) Finasteride produced a 93% reduction in facial hirsutism and a 73% reduction bodily hirsutism after 2 years of treatment. [10]

α1-blockers			
Scientific name	D. form	Trade name	concentration
Doxazosin	Tab	Cardura® , Cardosyr®	1 mg , 2 mg , 4 mg
Prazosin	Tab	Minipress® , Prazo®	1 mg , 2 mg , 5 mg
Terazosin	Tab	Hytrin®	1 mg , 2 mg , 5 mg , 10 mg
Alfuzosin	Tab	Xatral®	2.5 mg , 5 mg , 10 mg
Tamsulosin	Cap	Flomax® , Omnic®	0.4 mg
	Tab	Omnic OCAS®	0.4 mg
Silodosin	Cap	Rapaflo®, Urorec® , Flopadex®	4 mg , 8 mg
Indoramin	Tab	Doralese®	20 mg
5α-reductase inhibitors			
Finasteride	Tab	Proscar®, Prostacare®	1 mg , 5 mg
Dutasteride	Cap	Avodart®, Doxaten®	0.5 mg
Phosphodiesterase type 5 inhibitors			
Tadalafil	Tab	Cialis®	5 mg , 20 mg
Combination Products			
Dutasteride + Tamsulosin	Cap	Jalyn®, ComboDart®, Urimax-D® Tamdus D®, OmiDurt®, Bioprost®	0.5 mg + 0.4 mg
Dutasteride + Alfuzosin	Tab ER	Alfamax-D®	0.5 mg + 10 mg
Silodosin + Tamsulosin	Tab	Vesomni®	6 mg + 0.4 mg
Other drugs may be used for BPH			
Flutamide	Cap	Drogenil® , Cytomid®	125 mg
Bicalutamide	Tab	Casodex®	50 mg , 150 mg
Goserelin	Implant (S.C)	Zoladex®, Zoladex LA®	3.6 mg (for 1 month), 10.8 mg (for 3 months)
Leuprolide	Inj.	Lupron®	5 mg/ml
Megestrol acetate	Tab	Megace®	20 mg , 40 mg

8.2- Urinary incontinence (UI)

1. Normal bladder emptying occurs with a decrease in urethral resistance and contraction of the bladder muscle; Aging causes a decrease in bladder elasticity and capacity, thus resulting in more frequent voiding, decline in bladder outlet and increase in urethral resistance.
   - Also, urethral resistance occurs in women with loss of estrogen, and decrease in flow rate occurs in men with prostatic enlargement.
2. Urinary incontinence (UI) occurs as a result of over-functioning or under-functioning of the urethra, bladder, or both; **Urethral under-activit**y is known as **stress UI**, while **Bladder over-activity** is known as **Urge UI** (bladder muscle is overactive and contracts inappropriately).

The choice of pharmacologic therapy depends on the type of UI

1. **Bladder over-activity or Urge Urinary incontinence (U-UI)** is associated with increased urinary frequency and urgency, with or without urge incontinence, the detrusor muscle is overactive and contracts inappropriately during the filling phase.
   - **a.** The pharmacotherapy of first choice for **Urge UI** is anticholinergic/antispasmodic drugs, which antagonize muscarinic cholinergic receptors.
   - **b.** The anti-muscarinic (**Oxybutynin**) has direct smooth muscle relaxant properties and has been most widely used for **Urge UI**, (used twice or 3 times daily).
     - **Side effects include:** dry mouth, constipation, vision impairment, confusion, tachycardia, orthostatic hypotension, sedation and weight gain.
   - **c.** **Tricyclic antidepressants** have also been used in urge incontinence because of their anti-muscarinic activity; These include only**: (Imipramine, doxepin, Nortriptyline, or Desipramine)** given at bed time.
     - Their use today is limited; due their potential to cause cardiac side-effects.
   - **d.** **Purified bovine collagen implant** (Contigen®) is indicated for urinary incontinence caused by intrinsic sphincter deficiency (poor or non-functioning bladder outlet mechanism), the implant should be inserted only by surgeons or physicians trained in the technique for injection of the implant.
   - **e.** **Flavoxate** is used to treat urinary bladder spasms, indicated for symptomatic relief of interstitial cystitis, dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence
   - **f.** **Mirabegron** activates the β3 adrenergic receptor in the detrusor muscle in the bladder, which leads to muscle relaxation and an increase in bladder capacity.

Drugs for Bladder over-activity (anticholinergic/antispasmodic)			
Scientific name	Dosage form	Trade name	concentration
Oxybutynin	Tab	Ditropan®	5 mg
	Syrup	Ditronin®	5 mg/5 ml
	Patch	Oxytrol® , Kentera®	3.9 mg/day
	Topical Gel	Gelnique®	3% , 10%
Solifenacin	Tab	Vesicare®	5 mg , 10 mg
Tolterodine	Tab	Detrol®, Detrusitol®	1 mg , 2 mg
	Cap	Detrol LA®, Detrusitol R®	2 mg , 4 mg
Fesoterodine	Tab ER	Toviaz®	4 mg , 8 mg
Darifenacin	Tab ER	Enablex® , Emselex®	7.5 mg , 15 mg
Propiverine	Tab	Detrunorm®	15 mg
Propantheline	Tab	Pro-Banthine®	15 mg
Trospium Chloride	Tab	Sanctura®, Madaus®, Regurin®	20 mg
	Cap	Sanctura XR®	60 mg
Flavoxate	Tab	Urispas® , Genurin®	100 mg , 200 mg
Mirabegron	Tab ER	Myrbetriq® , Betmiga®	25 mg , 50 mg

Drugs for Bladder over-activity (Tricyclic antidepressants)			
Scientific name	Dosage form	Trade name	concentration
Imipramine	Tab , Cap	Tofranil®	10 mg , 25 mg & 75 mg (Cap)
Desipramine	Tab	Norpramin®	10 mg , 25 mg , 50 mg
Doxepin	Tab , Cap	Sinequan®	10 mg , 25 mg , 50 mg
Nortriptyline	Cap	Pamelor® , Aventyl®	10 mg , 25 mg , 50 mg

*** Only these TCAs above are FDA approved for the treatment of U-UI.**

2. **Urethral under-activity** or **Stress Urinary incontinence (S-UI)** occurs during activities such as exercise, lifting, coughing, and sneezing, the urethral sphincter no longer resists the flow of urine from the bladder during periods of physical activity.
   a. **The goal of treatment of S-UI** is to improve urethral closure **by stimulating the α-adrenergic receptors** in the smooth muscle of the bladder neck and proximal urethra, enhancing supportive structures underlying the urethral epithelium, or enhancing serotonin and norepinephrine effects in the micturition reflex pathways.
   b. **Generally managed by non-drug methods** (specific types of exercise).
   c. **Duloxetine** (SSRI) is licensed for the treatment of moderate to severe stress incontinence in women; Even though not FDA approved, **duloxetine is first-line therapy**; most adverse events diminish with time, Also **Imipramine** can be used for S-UI.
   d. **α -Adrenergic agonists** is used for S-UI as **Pseudoephedrine** (15–60 mg three times daily) with food, water, or milk and **Phenylephrine** (10 mg four times daily)
      - Contraindications include hypertension, tachy-arrhythmias, coronary artery disease, myocardial infarction, hyperthyroidism, renal failure, narrow-angle glaucoma.

Drugs for Bladder Under-activity			
Scientific name	Dosage form	Trade name	concentration
Duloxetine	Cap	Cymbalta®	30 mg , 60 mg
Pseudoephedrine	Tab	Sudafed®	30 mg , 60 mg , 120 mg
Phenylephrine	Tab	Contact D®	25 mg , 50 mg , 75 mg

8.3- Overflow incontinence

1. **It is a form of urinary incontinence,** characterized by the involuntary release of urine from an overly full urinary bladder, often in the absence of any urge to urinate.
2. This condition occurs in people who have a blockage of the bladder outlet (benign prostatic hyperplasia, prostate cancer, or narrowing of the urethra), or when the muscle that expels urine from the bladder is too weak to empty the bladder normally. Overflow incontinence may also be a side effect of certain medications.
3. It is usually treated with **Bethanechol,** (it stimulates parasympathetic receptors to increase bladder muscle tone, which in turn causes contraction and stimulates micturition); Used as 25–50 mg 3 or 4 times daily on an empty stomach, **(Short-term use only).**
   - Avoid use if patient has asthma or heart disease**.**
   - Never give I.V. or I.M. because of life-threatening cardiovascular reactions.
   - **Also, may be used for relieving urinary retention**, by increasing detrusor muscle contraction. However, it has only a limited role in the relief of urinary retention; its use has been superseded by catheterization.

Scientific name	Dosage form	Trade name	concentration
Bethanechol	Tab	Urecholine® , Myotonine®	5 mg , 10 mg , 25 mg , 50 mg

8.4- Nocturnal Enuresis

1. **Nocturnal enuresis (NE)**, also called **bedwetting**, is involuntary urination while asleep after the age at which bladder control usually begins; The etiology of NE is not fully understood, although there are three common causes: excessive urine volume, poor sleep arousal, and bladder contractions; also, may be related to low amounts of antidiuretic hormone (ADH).
   - Some recent studies relate NE to stress.
   - Urinary tract infections (UTIs) is also linked to NE.
2. **Treatment is not appropriate in children under 5 years** and it is usually not needed in those aged less than 7 years and in cases where the child and parents are not anxious about the bedwetting; however, **children over 10 years usually require treatment**.
   - The most important reason for treating enuresis is to minimize the embarrassment and anxiety of the child and the frustration experienced by the parents; The knowledge that another family member had and outgrew the problem can be therapeutic.
3. An **enuresis alarm should be first-line treatment** for well-motivated, well-supported children aged over 7 years because alarms have a lower relapse rate than drug treatment when discontinued; (The alarm sounds when the first drop of urine contacts the probe).
4. **Desmopressin**: an analogue of vasopressin is used for nocturnal enuresis; it is given by oral or by sublingual administration, Particular care is needed to avoid fluid overload.
   - Should be administered 1 hour before bedtime, (it reduces urine production during sleep).
   - **Treatment should not be continued for longer than 3 months** without interrupting treatment for 1 week for full re-assessment.
   - **The nasal formulation of Desmopressin is no longer indicated for enuresis by the FDA,** due to reports of seizures in children using the nasal spray.
   - Patients being treated for primary nocturnal enuresis should be warned to limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards; and to stop taking Desmopressin during an episode of vomiting or diarrhea (until fluid balance normal).
   - **Side effects include:** Headache, facial flushing, nausea, hyponatremia, seizures.
5. **Tricyclic antidepressants** such as (**Imipramine)** are used but relapse is common after withdrawal; **Treatment should not normally exceed 3 months** unless a full physical examination is made and the child is fully re-assessed.
   - The **relapse rate is high** when the medication is discontinued.
   - The usual dose, taken 1-2 hours before bedtime, is 25 mg for patients aged 6-8 years and 50-75 mg for older children and adolescents.
6. An anticholinergic (**Oxybutynin**) might be helpful in some patients, especially those with overactive bladder, dysfunctional voiding, or neurogenic bladder; This drug reduces uninhibited detrusor contractions, **increase the threshold volume** at which an uninhibited detrusor contraction occurs, and **enlarge the functional bladder capacity**.
   - **Oxybutynin** is given in a dose of 2.5-5 mg administered at bedtime.
   - The combination of **Desmopressin** and **Oxybutynin** might be efficacious in children with overactive bladder or dysfunctional voiding who respond to anticholinergic therapy with improved daytime symptoms but who continue to wet at night.

Scientific name	Dosage form	Trade name	concentration
Vasopressin	Inj. Solu.	Pitressin®	20 units/ml
Desmopressin	Nasal Spray	Minirin® , Stimate®	0.1 mg/ml (5 ml), 1.5 mg/ml (2.5 ml)
	Tab	Minirin®	0.1 mg , 0.2 mg
	Inj. Solu.	Stimate®	4 mcg/ml

**** Desmopressin** 5 ml Nasal spray delivers 10 mcg per spray, while the 2.5 ml Nasal spray delivers 150 mcg per spray. **(i.e.: the 2.5 ml container is 15 times more potent than the 5 ml container) →** (good luck trying to convene your patients about this fact).

8.5- Drugs for Erectile Dysfunction (ED)

A. Human Male Sexual response cycle consist of 4 stages or phases; which all lead to normal sexual process; any dysfunction in any stage will lead to a **Sexual Dysfunction**:

1. **Excitement (Desire, Libido) phase:** in which the heart rate increase, breathing rate increase, blood pressure increase and the body temperature increase leading to flushing (sex flush); the penis becomes partially erected (and fully erected if there is enough sexual stimulations) and the testicles are drawn upward the body.
2. **Plateau (Arousal) phase:** the period between sexual excitement and orgasm, in which the urethral sphincter contract (to prevent urine from mixing with semen, and to prevent retrograde ejaculation), during this phase a viscous fluid is emitted from the urethra and the testicles are drawn closer to the body.
3. **Orgasmic phase:** accompanied by quick cycles of muscle contractions in the lower pelvic muscles, which surround both the anus and the sexual organs; orgasms are accompanied with euphoric sensation.
4. **Resolution phase:** if orgasm is achieved; resolution may last 10-15 minutes with sensation of calmness and relaxation, and if the orgasm is not achieved; irritability and discomfort can result, in which it can last for several hours.
   - Thus, masturbation can be harmful sometimes; due it doesn't give the body the time to go throw the natural physiological human male sexual response cycle; and it may not produce sufficient orgasm to feed the sexual hunger and thus the restoration phase will end with more irritability and discomfort.

B. Factors Effecting Libido in men:

1. **Hormones and Neurotransmitters:**
   - Dopamine increase libido, while Prolactin decrease libido, (Dopamine directly inhibits Prolactin release from the pituitary gland).
   - Testosterone and Norepinephrine both increase libido.
   - Oxytocin is responsible for the orgasm and sexual pleasure.
   - Serotonin decrease libido.
2. **Psychological Factors:** Lack of privacy, lack of intimacy (no love feelings), stress, fatigue, distraction, depression; all decrease libido.
3. **Physical Factors:** Hypothyroidism, obesity, anemia, heavy smoking; all decrease libido.

Notes:

1. Erectile dysfunction (ED) is the failure to achieve or maintain a penile erection suitable for sexual intercourse, Patients often refer to it as **Impotence**.

- It's different from low sexual desire (which is psychological related).
- May be due Hormonal abnormalities because of excess prolactin (hyperprolactinemia) or decreased testosterone concentrations (hypogonadism).
- Being overweight and getting too little exercise raise the chances for ED, Studies show that men who exercise regularly have a lower risk of ED.
- Stress, depression, low self-esteem, and anxiety can prevent the process that leads to an erection; these factors can also make the problem worse if ED is due a physical problem.

2. Normally, when a man is sexually aroused, the arteries in the penis relax and widen, allowing more blood than usual to flow into the organ, Impulses from the brain and genital nerves start the process of filling the penis tissues, and as these tissues expand and harden, the veins that carry blood out of the penis are compressed, reducing outflow and resulting in an erection.

- Thus, drugs that increase blood flow into the penis, can produce an erection.
- **Phosphodiesterase type-5 inhibitors (PDE-5 I)** not only increase the blood flow into the penis but also prevent the muscle wall from relaxing, so the blood does not drain out of the blood vessels and the penis remains erect.

3. **Treatment options include:**
   - **a)** Phosphodiesterase type-5 inhibitors (PDE-5 I).
   - **b)** Testosterone-Replacement Regimens.
   - **c)** Alprostadil Intracavernosal injection (inj. Directly to the penis).
   - **d)** Other agents, mainly vasodilators (some are not FDA approved)

First: Phosphodiesterase type-5 inhibitors (PDE-5 I)

1. These include: **Sildenafil**, **Tadalafil**, **Vardenafil** and **Avanafil**; licensed for the treatment of Erectile dysfunction (ED), they Inhibits PDE-5 in the penile tissue, preventing the breakdown of cyclic guanosine monophosphate, thus increasing smooth muscle relaxation in the corpora cavernosa and increasing penile rigidity.
   - **a.** They have **no effect on the penis in the absence of sexual stimulation**, (Adequate sexual stimulation is needed to trigger the events leading to erection).
   - **b.** Adverse effects are vasodilatation related which include: **Headache, hypotension, flushing**, **visual disturbances (blurred vision), difficulty discriminating blue from green**.
   - **c.** PDE-5 Inhibitors **may potentiate the hypotensive effects of nitrates**, and are therefore contraindicated in patients receiving such drugs.
   - **d.** Avoid use in CVD, hypotension, uncontrolled HT, MI, or stroke within 6 months.
   - **e.** Macrolides (Azithromycin Family) increases PDE-5 Inhibitors levels in blood stream.
2. They have different extra indications: **Sildenafil,** and **Tadalafil** are licensed for the **treatment of pulmonary arterial hypertension** (in both males and females), **Tadalafil** is also indicated for treatment of signs and symptoms of BPH.
3. The usual dose of **Sildenafil** is 50-100 mg about one hour before sexual intercourse, which its **effect last for 4-5 hours**; the dose may be increased or decreased depending on response, the maximum recommended dose is 100 mg, and it should not be taken more than once in 24 hr.
4. **Tadalafil** is a longer-acting drug, it can be used as required, but can also be used as a regular lower daily dose to allow for spontaneous (rather than scheduled) sexual activity or in those who have frequent sexual activity; (**effects may last up to 36 hours**).
5. **Vardenafil** is very similar to **Sildenafil**, its effect **lasts for 4-5 hours**; but it has the advantage of that it's being **useful in the treatment of Premature Ejaculation.**
6. **Avanafil** has the advantage that it has very fast onset of action compared with other PDE-5 inhibitors, (usually acts within 10 - 15 minutes), with a duration of effect for 6 hours.
7. The **Onset of effect** of Sildenafil may be delayed if taken with food; But Tadalafil and Vardenafil are not affected by food; **Dose to be taken** (Avanafil: 15–30 minutes, Sildenafil: 1 hour, Tadalafil: at least 30 minutes, and Vardenafil 25–60 minutes) before sexual activity.

Scientific name	Dosage form	Trade name	concentration
Sildenafil	Tab	Viagra®, Kamagra®, Novagra®	25 mg , 50 mg , 100 mg
	Oral Jelly	Kamagra®	50 mg , 100 mg
	Inj. Solu.	Revatio®	10 mg/12.5 ml
Tadalafil	Tab	Cialis®	5 mg , 10 mg , 20 mg
	Oro D tab		5 mg
Vardenafil	Tab	Levitra® , Fast-Fix®	5 mg , 10 mg , 20 mg
	Oro D tab	Staxyn®	10 mg
Avanafil	Tab	Stendra® , Spedra®	50 mg , 100 mg , 200 mg

Note:

- **Sildenafil in Gynecology:** tablet may be **administered intra-vaginally to reduce the menstrual cramps**; it dilates the blood vessels and increase blood flow to the uterus, which help to relieve pain.

Second: Testosterone-replacement regimens

1. These restore serum testosterone levels to the normal range (300–1,100 ng/dL; 10.4–38.2 nmol/L); **These regimens are indicated for symptomatic patients with hypogonadism** as confirmed by both a decreased libido and low serum testosterone concentrations.
    - **a.** Testosterone-replacement regimens correct secondary ED by improving libido, usually within days or weeks of starting therapy, they restore muscle strength and sexual drive and improve mood.
    - **b.** Testosterone can be replaced orally, parenterally, or transdermally.
2. Testosterone replacement **can cause sodium retention**, which can cause **weight gain** or exacerbate **hypertension**, **congestive heart failure, edema, gynecomastia**, serum lipoprotein changes, and polycythemia; **Exogenous testosterone can also exacerbate BPH and enhance prostate cancer growth.**
3. **Testosterone Injectable regimens are preferred** because they are effective, are inexpensive, and do not have the bioavailability problems or adverse hepatotoxic effects of oral regimens, Testosterone patches and gel are more expensive than other forms and should be reserved for patients who refuse injections.

Scientific name	Dosage form	Trade name	concentration
Testosterone	Inj. (I.M.)	Sustanon®	100 mg/ml , 250 mg/ml
	S.C Inj.	Depo-Testerone®	75 mg
	Tab , Cap	Striant®, Andriol Testocaps®	30 mg (tab), 40 mg (cap)
	Patch	Androderm®	4 mg/24 hr.
	Gel	Androgel®	1.62%
	Implant	Testopel	75 mg pellet
	Topical Solu.	Axiron	30 mg/actuation
	Nasal Gel	Natesto	5.5 mg/actuation
Methyl-Testosterone	Tab , Cap	Android® , Testred®	10 mg
Oxandrolone	Tab	Oxandrin®	2.5 mg , 10 mg

Third: Alprostadil injections

1. **Alprostadil (prostaglandin E1),** stimulates adenyl cyclase to increase production of cyclic adenosine monophosphate, a neurotransmitter that ultimately enhances blood flow to and blood filling of the corpora, it **has 2 dosage forms**:
    - **a) Intracavernosal Alprostadil injection** (inj. Directly to penis), is effective in 70% to 90% of patients, acts rapidly, with an onset of 5 to 15 minutes, the duration of action is dose related and within the usual dosage range lasts <1 hour.
        - The usual dose is 10 to 20 mcg up to a maximum of 60 mcg.
        - Should be injected 5 to 10 minutes before intercourse using a 0.5 in, 27- or 30-gauge needles or an auto-injector.
        - The maximum number of injections is one daily and three weekly.
    - **b) Intra-urethral Alprostadil pellet:** 125 mcg to 1,000 mcg - should be administered 5 to 10 minutes before intercourse, and effects lasts 30-60 min.
        - Before administration, the patient should empty his bladder and void completely; No more than two doses daily are recommended.
        - Associated with pain in 24% to 32% of patients.
        - Female partners may experience vaginal burning, itching, or pain, which is probably related to transfer of Alprostadil from the man's urethra to the woman's vagina during intercourse.
2. **Adverse effects include**: Penile pain, cavernosal scarring, priapism (erect penis do not return to normal flat), hypotension; Do not use with PDE-5 inhibitors.

3. **Alprostadil I.V. injection** is also used in maintaining a **patent ductus arteriosus in newborns**; this is primarily useful when there is threat of premature closure of the ductus arteriosus in an infant with ductal-dependent congenital heart disease.
4. **Topical Alprostadil cream** is only approved in Canada and used there as 1st line treatment for erectile dysfunction (its **applied into the urethra**, not by rubbing the external part of the penis).

Scientific name	Dosage form	Trade name	concentration
Alprostadil	Inj. Intracavernosal	Caverject®	10 mcg , 20 mcg , 40 mcg
	Inj. Solu.	Edex®	500 mcg/ml
	Intraurethral Pellet/Supp.	Muse®	125 mcg, 250 mcg, 500 mcg 1000 mcg
	Cream	Vitaros®	3 mg/g

Fourth: Other agents for ED

1. These include: **Trazodone** (α1 receptor antagonist + antidepressant related to SSRIs), **Yohimbine** (α2 receptor blocker), **Papaverine** (vasodilator), **Phentolamine** (α blocker), **Apomorphine** (narcotic analgesic), and other herbal combinations.
2. **Trazodone** has also antianxiety (anxiolytic/hypnotic) effects.
3. **Papaverine** is also used to **improve blood flow** in patients with circulation problems. It works by relaxing the blood vessels so that blood can flow more easily to the heart and through the body; **Papaverine** is also an antiarrhythmic medication (for visceral spams and vasospasms).
   - Some uses it for Erectile Dysfunctions as an intracavernous inj. (direct inj. To the penis!), It should not be injected into the penis; This practice has resulted in painful or prolonged erection that may require surgery to correct.
   - A topical gel is also available for Erectile Dysfunction treatment, which is safer and more efficient than the injectable dosage form.
4. **Phentolamine** is a short-acting α1-blocker (non-selective); usually used for the control of hypertensive emergencies, most notably due to Pheochromocytoma.
5. **Yohimbine**, a selective α2 receptor blocker, it increases norepinephrine; thus raises blood pressure and heart rate; its medically used for general sexual problems in both men and women, arouse sexual excitement, for erectile dysfunction (ED), sexual problems caused by selective-serotonin reuptake inhibitors (SSRIs); It acts by increasing blood flow and nerve impulses to the penis or vagina.
   - **Yohimbine** also has **fat burning effect**, it acts by promoting lipolysis.
6. **Apomorphine** when taken sublingually; It exerts its effect on hypothalamic centers involved in the triggering of the erection cascade (it's a dopaminergic agonist with affinity for dopamine receptor sites - mostly D2 - within the brain known to be involved in sexual function), it dissolves rapidly and results in an erection in responders in approximately 20 min.

Scientific name	Dosage form	Trade name	concentration
Trazodone	Tab	Desyrel®, Oleptro®	50 mg , 100 mg , 150 mg
Yohimbine	Tab	Yocon®, Aphrodyne®	5.4 mg
Papaverine	Cap ER	Para Time®	150 mg
	Inj. Solu.	Pavabid®	30 mg/ml
	Gel	TriMix®	2%
Phentolamine	Inj. Powder	Regitine®	5 mg
	Inj. Solu.	Oraverse®	0.4 mg/1.7 ml
Apomorphine	Sub lingual Tab	Ixense®, Uprima®	3 mg

Herbal Combinations for ED

Trade name	D. form	Scientific name(s)	concentration
Gentaplex® men	Cap	Lyophilized Fish Roe + Ginkgo Biloba	570 mg + 30 mg
Aphrofem® women	Cap	Lyophilized Fish Roe + Ginkgo Biloba	475 mg + 25 mg
Penamax®	Cap	Acetyl-L-carnitine + Propionyl-L-Carnitine + L-Arginine + Ginkgo Biloba + Butea Superba	1600 mg blend
Ultra T Male®	Tab	Fenugreek Extract + Grape-Apple Extracts + (Curcuma + Ginseng + Garlic Extracts) + Propionyl-L-Carnitine + Rhodiola Rosea + Tongkat Ali + Vit. C + Vit. E + Vit. B_6 + Ca + Magnesium + Zinc + Selenium	400 mg + 300 mg + 200 mg + 50 mg + 50 mg + 100 mg
Testrogain®	Cap	Acetyl-L-Carnitine + L-Methionine + Beta-Sitosterol + DHEA + Tribulus Terrestris + Saw Palmetto + Soy Bean + Vit. B_6 + Magnesium + Zinc	500 mg + 400 mg + 200 mg + 50 mg + 150 mg + 120 mg + 50mg + 2mg + 71mg

Notes:

1. **Fish Roe** is commercially known as **Caviar**, which is well known for its aphrodisiac effects.
2. **Ginkgo Biloba** dilates blood vessels (by increasing NO levels) to promote blood flow to the sexual organs, but might increase the risk of bleeding.
3. **Acetyl-L-carnitine** and **Propionyl-L-Carnitine** act by boosting energy metabolism.
4. **L-Arginine** which enhances blood circulation, by increasing the amount of nitric oxide in the body, they stimulate blood vessels to become larger (thus also used by bodybuilders). This improves blood flow, which could help a man get an erection
5. **Butea Superba** is an herb that helps to restore erectile function.
6. **Tribulus Terrestris** is claimed to increase testosterone levels; However, there is no strong evidence that it does that.
7. Many other combinations are found in the market, they may include multi-vitamins, Zinc, proteins, B-complexes, vitamin E …. Etc. **(all may be beneficial as secondary supplement).**

8.6- Drugs for Men Ejaculation Problems

First: Premature Ejaculation (PE):

1. **Premature ejaculation** occurs when a man ejaculates sooner during sexual intercourse than they or their partner would like, it occurs when a man experiences orgasm and expels semen soon after sexual activity (usually 1 min. after entering the vagina) and with minimal penile stimulation; Treatment options include: **Antidepressants, Dapoxetine, Vardenafil, Tramadol, Cabergoline** and **Topical anesthetic**
2. **Antidepressants** (A side effect of certain antidepressants is delayed orgasm), usually **SSRI** as **Sertraline**, **Paroxetine**, **Fluoxetine**, and others like **Clomipramine**.
   - These medications are **taken on demand pre-intercourse.**
   - Patients who can't tolerate antidepressants side effects can take **Clomipramine 25 mg** tab.
   - There is evidence that a **combination of Sildenafil with SSRI** is **better than SSRI alone**.
3. **Dapoxetine** is the first **SSRI** developed specially for the treatment of **premature ejaculation** (PE) in men 18–64 years old, **it was rejected by the FDA in 2011,** (and still non-FDA approved).
   - It's fast acting property makes it suitable for the treatment of PE but not as an antidepressant.
   - Must be **taken BEFORE 2 HOURS from intercourse** to work effectively.
   - Dapoxetine may increase the central nervous system depressant (CNS depressant) activities of Ethanol, thus **its contraindicated to drink alcohol and take Dapoxetine**.

- In a **study comparing Dapoxetine** and **Sertraline** on demand pre-intercourse; the sertraline group was better compared with the Dapoxetine group as regards ejaculation latency, ejaculation control, and patient satisfaction. [7]
- Combining **Dapoxetine with PDE-5 I** (as **Tadalafil**) for the treatment of ED accompanied by PE has better results in increasing latency than using either products alone.

4. In a study comparing **Vardenafil** and **Sertraline** for the treatment of PE, Vardenafil improved premature ejaculation more than Sertraline. [11, 12]
5. **Tramadol** (oral analgesic generally used to treat mild pain), it increased ejaculatory latency to 4-20 times in more than 90% of men used it.
6. **Cabergoline** has been found to raise a man's chances of sustaining multiple orgasms during sex, (enhance Erection and libido), But don't try this at home, it's not (FDA) approved.
7. **Topical anesthetic (desensitizing) creams** and **sprays** (containing **Lidocaine** or **Prilocaine** and **Vitamin E**), these dull the sensation on the penis to help delay ejaculation and applied a short time before intercourse (usually 15 to 20 minutes).
   - Their use is sometimes disliked due to the reduction of sensation in the penis as well as for the partner (due to the medication rubbing onto the partner).
   - If applied too much it may cause swelling and soreness.

Scientific name	D. form	Trade name	concentration
Dapoxetine	Tab	Priligy®, Longus®, D-Late®	30 mg , 60 mg
Sertraline	Tab	Zoloft® , Lustra®	50 mg , 100 mg
Vardenafil	Tab	Levitra® , Fast-Fix®	5 mg , 10 mg , 20 mg
	Oro D tab	Staxyn®	10 mg
Dapoxetine + Tadalafil	Tab	Tada Plus®, Bebos Plus®	60 mg + 20 mg
Sildenafil + Tramadol	Tab	Vegdol Plus®	100 mg + 100 mg
Sildenafil + Lidocaine	Cream	The Pilot	20 gm cream
Lidocaine	Gel , Spray	Xylocaine®	2% , 5%
Lidocaine + Prilocaine	Cream	EMLA®	(2.5% + 2.5%)\30 gm

Second: Delayed Ejaculation:

1. Also called **Retarded Ejaculation**; it is a man's inability for or persistent difficulty in achieving orgasm, despite typical sexual desire and sexual stimulation.
2. Generally, a man can reach orgasm within a few minutes of active thrusting during sexual intercourse, whereas a man with delayed ejaculation either does not have orgasms at all or cannot have an orgasm until after prolonged intercourse which might last for 30–45 min or more.
   - Some women may actually like a prolonged intercourse; but the majority finds it very tiring and exhausting and painful.
3. In some cases, delayed ejaculation presents the condition in which the man can climax and ejaculate only during masturbation, but not during sexual intercourse.
4. Causes for delayed ejaculation is multifactorial, including physical, Psychological and lifestyle factors, or even due some medications or diseases.
5. All the available drugs for delayed ejaculation are not FDA approved for that cause; all are used as off-label; these drugs include:
   a. **Amantadine** (antiparkinsonian + antiviral); has benefit in treating delayed ejaculation by potentiating dopaminergic actions, used 100-400 mg on demand before intercourse.
   b. **Bupropion** (antidepressant, used for smoking cessation); when given as 150 mg once daily for 2 months, it improves overall ejaculation time.
   c. **Cyproheptadine** (antihistamine, the famous appetite stimulant); has been associated with improvements in delayed ejaculation, used 8-12 mg on demand (2-3 tabs), 1-2 hours before intercourse.
   d. **Oxytocin** 24 IU intranasal used minutes just before intercourse is useful for treatment of delayed ejaculation.

Third: Retrograde Ejaculation:

1. Retrograde ejaculation occurs when semen which would, in most cases, be ejaculated via the urethra is redirected to the urinary bladder.
2. Normally, the sphincter of the bladder contracts before ejaculation, sealing the bladder which besides inhibiting the release of urine also prevents a reflux of seminal fluids into the male bladder during ejaculation; the semen is forced to exit via the urethra, the path of least resistance.
3. When the bladder sphincter does not function properly, retrograde ejaculation may occur; the retrograde-ejaculated semen, which goes into the bladder, is excreted with the next urination.
   - Retrograde ejaculation is sometimes referred to as a (dry orgasm), it can cause male infertility.
4. Drug treatment for Retrograde Ejaculation include: **Pseudoephedrine**, **Midodrine** or **Imipramine**; they all act by tightening the bladder neck muscles and preventing the semen from going backwards into the bladder; They are used 1-2 hours before intercourse.

8.7- Infertility in Men

1. Male factor infertility is often an outcome of **impaired sperm production or function**, which can originate from a variety of causes, Problems with male fertility can be caused by a number of health issues and medical treatments, some of these include:
   - **Varicocele:** A Varicocele is a swelling of the veins that drain the testicle; It's **the most common reversible cause of male infertility**; This may prevent normal cooling of the testicle by blocking proper blood drainage, leading to reduced sperm count and fewer moving sperm, treating the Varicocele can improve sperm numbers and function, and may potentially improve outcomes when using assisted reproductive techniques such as in vitro fertilization.
   - **Infection**: Some infections can interfere with sperm production or sperm health, or can cause scarring that blocks the passage of sperm, these include some sexually transmitted infections, including chlamydia and gonorrhea; inflammation of the prostate (prostatitis); and inflamed testicles due to mumps (mumps orchitis); Although some infections can result in permanent testicular damage, most often sperm can still be retrieved.
   - **Ejaculation issues**: **Retrograde ejaculation** occurs when semen enters the bladder during orgasm instead of emerging out the tip of the penis; various health conditions can cause retrograde ejaculation, including diabetes, spinal injuries, medications, and surgery of the bladder, prostate or urethra, some men with spinal cord injuries or certain diseases can't ejaculate semen, even though they still produce sperm, in these cases sperm can still be retrieved for use in assisted reproductive techniques.
   - **Antibodies that attack sperm:** Anti-sperm antibodies are immune system cells that mistakenly identify sperm as harmful invaders and attempt to eliminate them.
     - Sometimes a man's body makes antibodies that attack his own sperm; Antibodies are most often made because of injury, surgery or infection.
   - **Undescended testicles:** In some males, during fetal development one or both testicles fail to descend from the abdomen into the sac that normally contains the testicles (scrotum). Decreased fertility is more likely in men who have had this condition.
   - **Hormone imbalances:** Infertility can result from disorders of the testicles themselves or an abnormality affecting other hormonal systems including the hypothalamus, pituitary, thyroid and adrenal glands. Low testosterone (male hypogonadism) and other hormonal problems have a number of possible underlying causes.
   - **Sperm duct defects:** The tubes that carry sperm (sperm ducts) can be damaged by illness or injury, some men experience blockage in the part of the testicle that stores sperm (epididymis) or a blockage of one or both of the tubes that carry sperm out of the testicles; men with cystic fibrosis and some other inherited conditions may be born without sperm ducts altogether.

- **Problems with sexual intercourse:** These can include trouble keeping or maintaining an erection sufficient for sex (erectile dysfunction), premature ejaculation, painful intercourse, anatomical abnormalities such as having a urethral opening beneath the penis (hypospadias), or psychological or relationship problems that interfere with sex.
- **Celiac disease:** A digestive disorder caused by sensitivity to gluten, celiac disease can cause male infertility; Fertility may improve after adopting a gluten-free diet.
- **Certain medications**: Testosterone replacement therapy, long-term anabolic steroid use, cancer medications (chemotherapy), certain antifungal medications (Ketoconazole), some ulcer drugs (cimetidine) and certain other medications can impair sperm production.
- **Weight:** may play a role in male fertility due to elevated Estrogen and lower Testosterone levels observed in obese men.
- **Overheating the testicles:** Frequent use of saunas or hot tubs may temporarily lower your sperm count. Sitting for long periods, wearing tight clothing, the type of underwear you wear is likely to make a significant difference in male fertility.
- **Reactive Oxygen Species (ROS):** they are small molecules found in many bodily fluids, they are found in white blood cells and in the sperm cells in semen, ROS can help prepare the sperm for fertilization, but too much ROS can hurt other cells, Sperm are easily harmed by ROS. Recent studies have shown more ROS molecules in the semen of infertile men.

2. Treatment for men infertility depends on the underlying cause, which is usually multifactorial:

a. **Hypogonadism** (low Testosterone levels): the doctor may add **Androgens** or synthetic Testosterones such as **Mesterolone** (over dosing may cause testosterone to get even lower).
b. **Hyperprolactinemia**: treatment with **Cabergoline** or **Bromocriptine**.
c. **Retrograde ejaculation:** treatment with **Pseudoephedrine, Midodrine** or **Imipramine**.
d. **High Estrogen levels:** treatment with **Tamoxifen, Anastrozole** or **Letrozole**.
e. **Low FSH or LH levels**: treatment with **Gonadotropins**; usually 1500 or 5000 IU **hCG**.
f. **High (ROS) levels:** treatment with **antioxidants** (Vitamin E, Co-Q10, Selenium)
g. **Clomiphene** may be given for men with **Oligospermia** (it increases sperm production in men by increasing FSH and LH levels); dosed as 25-100 mg per day.
h. **Pentoxifylline** (peripheral vasodilator) may improve sperm count, motility and shape in patients using it for 3 to 6 months.
i. **Immunologic Infertility:** the doctor may add an **anti-inflammatory** drug (**prednisolone**) to lower anti-sperm antibodies and prevent immune system related infertility (prevent immune system damage); although success rates are not high, and in vitro fertilization (IVF) with Intracytoplasmic Sperm Injection (ICSI) is now preferred for fertility problems caused by the immune system.

3. Sometimes the male infertility is due to **low count** of sperms, or **abnormal morphology** of sperms, or **Low motility** of sperms and **abnormal Viscosity**:

- **Agents that increase sperm Count**: herbals (Fenugreek, Ginseng, Black seed, Maca Root, Witharia Somnifera, Mucuna Pruriens, Horny goat weed) and antioxidants (Selenium, Coenzyme Q10, Vitamin E, Asthaxanthin, L-Carnitine, L-Glutathione, Omega-3, Zinc).
- **Agents that enhance sperm Morphology**: Lycopene, Vitamins C & E, Coenzyme Q10, Folic acid, D-Ribose, L-Lysine.
- **Agents that enhance sperm Motility**: Pentoxifylline, N-Acetyl-Cysteine, L-Arginine, L-Carnitine, Myo-Inositol, L-Methionine, Quercetin, L-Citrulline (precursor of L-Arginine).
- **Agents that enhance sperm Viscosity**: N-Acetyl-Cysteine, Mucolytics (Bromhexine, Ambroxol).

Many Male Fertility blends contain a combination of these products, their results upon enhancing Sperm quality and quantity is seen after a duration of use for 3 months. (this is because the spermatogenesis cycle lasts for about 74 days).

8.8- Sexually Transmitted Diseases (STDs)

1. The term sexually transmitted disease (STD) is used to refer to an **infection passed from one person to another through sexual contact**, patient can contract an STD by having unprotected Vaginal, Anal, or Oral sex with someone who has the STD.
   - Vaginal and Anal sex aren't the only way STDs are transmitted; It's also possible to contract or transmit an STD through Oral sex, STDs can be passed from one person's genitals to another person's mouth or throat and vice versa.
2. That doesn't mean sex is the only way STDs are transmitted; Depending on the specific STD, infections may also be transmitted through sharing needles, sharing toothbrushes and Towels, unclean shaving devices or scissors, Tattoos and tooth medical devices.
3. It's possible to contract an STD without developing symptoms; but some STDs cause obvious symptoms, in men common symptoms include:
   - Pain or discomfort during sex or urination.
   - Sores, bumps, or rashes on or around the penis, testicles, anus, buttocks, thighs, or mouth.
   - Unusual discharge or bleeding from the penis.
   - Painful or swollen testicles.
4. Many different types of infections can be transmitted sexually; The most common STDs are described below (Herpes Simplex Virus (HSV) Infection, Syphilis, Chlamydia infection, Gonococcal Infection (Gonorrhea), Human Papillomavirus (HPV), Pubic Lice, Trichomoniasis and HIV); for HIV see chapter 5, Antivirals for more info.

First: Herpes Simplex Virus (HSV) Infection

1. Herpes is the shortened name for the herpes simplex virus (HSV), there are two main strains of the virus, **HSV-1** and **HSV-2**, both can be transmitted sexually.
2. HSV-1 primarily causes oral herpes, which is responsible for cold sores; However, HSV-1 can also be passed from one person's mouth to another person's genitals during oral sex, when this happens, HSV-1 can cause genital herpes; HSV-2 primarily causes genital herpes.
3. The most common symptom of herpes is **blistery sores**, in the case of genital herpes, these sores develop on or around the genitals; in oral herpes, they develop on or around the mouth.
   - Other Symptoms include itching, genital burning, vesicle formation, and ulcer formation.
   - From 50% to 80% of patients will have a recurrent infection.
4. **Treatment options**:
   - For Initial HSV infection: **Acyclovir** 400 mg orally three times daily for 7–10 days.
   - For Recurrent HSV infection: **Acyclovir** 800 mg orally twice daily for 5 days.
   - For Herpes encephalitis (HSV spread through neural routes): I.V. **Acyclovir** for 21 days.

Second: Syphilis

1. Syphilis is caused by bacteria (Treponema pallidum), it often goes unnoticed in its early stages.
2. The first symptom to appear is a **small round sore**, known as a chancre; it can develop on the genitals, anus, or mouth, it's painless but very infectious.
   - if left untreated, late-stage syphilis can lead to: loss of vision, loss of hearing, loss of memory, mental illness, infections of the brain or spinal cord, heart disease and death.
3. **Recommended treatment**:
   - Primary syphilis, Secondary syphilis: **Benzathine penicillin G** 2.4 million units I.M. in a single dose, or **Doxycycline** 100 mg orally twice daily for 2-4 weeks.
   - Tertiary syphilis: **Benzathine penicillin G** 2.4 million units I.M. every week for 3 weeks.
   - Neurosyphilis: **Ceftriaxone** 2 gm/day by I.M./I.V. for 10–14 days.

Third: Chlamydia infection

1. Caused by (Chlamydia trachomatis), many people with chlamydia have no noticeable symptoms, when symptoms do develop, they often include: pain or discomfort during sex or urination, green or yellow discharge from the penis and pain in the lower abdomen
2. If left untreated, chlamydia can lead to: infections of the urethra, prostate gland, or testicles, pelvic inflammatory disease and infertility.
3. **Treatment strategy**:
   - **Azithromycin** 1 gm in a single dose or **Doxycycline** 100 mg twice daily for 7 days.
   - Alternative Rx: **Ofloxacin** 300 mg twice for 7 days or **Levofloxacin** 500 mg once for 7 days.
   - Abstain from sexual intercourse for at least 7 days.

Fourth: Gonococcal Infection (Gonorrhea)

1. Caused by infection with the bacterium (Neisseria gonorrhea); also known as "the clap."
2. Many people with gonorrhea develop no symptoms; but when present, symptoms may include:
   - a white, yellow, beige, or green-colored discharge from the penis or vagina.
   - pain or discomfort during sex or urination.
   - more frequent urination than usual.
   - itching around the genitals and sore throat
3. **Treatment strategy**:
   - **Ceftriaxone** I.M. injection **or Cefixime** Capsule + treatment that covers chlamydia (**Azithromycin** 1 g single dose).
   - Alternative: **Gemifloxacin** 320 mg + **Azithromycin** 2 gm orally once.
   - Abstain from sexual intercourse for at least 7 days.

Fifth: Human Papillomavirus (HPV)

1. Human papillomavirus (HPV) is a virus that can be passed from one person to another through intimate **skin-to-skin** or **sexual contact**; there are many different strains of the virus, some are more dangerous than others; The most common symptom of HPV is **warts on the genitals, mouth, or throat**; Some strains of HPV infection can lead to cancer.
2. 90% of HPV infections (9 out of 10) **go away on their own** within two years, according to the CDC; But when the virus doesn't go away on its own, it can cause serious health problems; these include **genital warts** and **warts in the throat** (known as recurrent respiratory papillomatosis).
3. While most cases of HPV don't become cancerous, some strains of the virus are more likely to cause cancer than others. According to the National Cancer Institute, most cases of HPV-related cancer in the USA are caused by HPV 16 and HPV 18; These two strains of HPV account for 70 percent of all cervical cancer cases.
4. **There's no treatment for HPV**, HPV infections often clear up on their own, there's also a vaccine available to protect against some of the most dangerous strains, including HPV 16 and HPV 18.
   - Genital Warts are treated with **Imiquimod** 5% cream (Aldara®), 3 time per week for up to 16 weeks, or by **Podophyllotoxin** 0.5% solution or gel (Wartec®), twice daily for 3 days, then 4 days of no therapy and repeating this cycle for up 4 times if necessary.

Sixth: Pubic lice

1. Crabs is another name for pubic lice, they're tiny insects that can take up residence on the pubic hair; Like head lice and body lice, they feed on human blood.
2. Common symptoms of pubic lice include: itching around the genitals or anus, small pink or red bumps around the genitals or anus, low-grade fever; The patient might also be able to see the lice or their tiny white eggs around the roots of pubic hair.
3. If left untreated, pubic lice can spread to other people through skin-to-skin contact or shared clothing, bedding, or towels; also Scratched bites can also become infected. It's best to treat pubic lice infestations immediately.
4. Treatment as with head or Body lice; **Permethrin**, **Ivermectin**.

Seventh: Trichomoniasis

1. Also known as "trich." It's caused by a protozoan organism (Trichomonas vaginalis); that can be passed from one person to another through genital contact; it's more common in females.
2. According to the CDC, less than one-third of people with trich develop symptoms, but When symptoms do develop, they may include: discharge from the vagina or penis, burning or itching around the vagina or penis, pain or discomfort during urination or sex, frequent urination.
3. Treatment options: **Metronidazole** 2 gm orally or **Tinidazole** 2 gm orally in a single dose

8.9- Kidney Stones

1. Kidney stone disease, also known as **urolithiasis**, is when a solid piece of material (kidney stone) occurs in the urinary tract; **Kidney stones typically form in the kidney and leave the body in the urine stream**, a small stone may pass without causing symptoms; If a stone grows to more than 5 millimeters (0.2 in) it can cause blockage of the ureter resulting in severe pain in the lower back or abdomen; A stone may also result in blood in the urine, vomiting, or painful urination.
2. **There are four different types of kidney stones**. It's important to gain a basic understanding of each one so you can establish a plan to counteract them—which includes a healthy diet, extra hydration, and certain medications

A) Calcium stones

Calcium stones **make up the majority of all kidney stones at 80%;** There are two types of calcium stones, **calcium oxalate** (most common) and **calcium phosphate**—both of which can be seen on a plain x-ray; both formed in an acidic urine.

a. **Oxalates are a natural element in food**. But, when there's an overabundance of oxalates in the system, they can stick to calcium in the urine to form a calcium oxalate stone. **It's important if the patient is a calcium stone former, to consume fewer foods on the high oxalate list**, which unfortunately also includes healthy food options such as leafy greens (kale, spinach), beets, and nuts.
b. **Phosphate stones** are much less common and typically develop in patients with metabolic or hormonal disorders such as hyperparathyroidism and renal tubular acidosis.

B) Uric Acid Stones

Uric acid stones **make up approximately 10% of all kidney stones.** They're usually formed in people with a high animal protein diet and people who suffer from gout. **If the patient has gout, then he is 60 percent more likely to develop a kidney stone**! Like calcium stones, these stones are formed in acidic urine (pH less than 7) but are not as visible on a plain x-ray.

- Uric acid stones are the only stones that can be dissolved using a diet which in part consists of increased levels of citric acid and apple cider vinegar.

C) Cysteine Stones

Cysteine stones are the least common stones comprising only four percent of cases. The result of an inherited (genetic) disorder, **Cysteine stones occur when there's an excess of the amino acid Cysteine in the body**. These stones are recurring and typically larger in size.

D) Struvite Stones

Struvite, or **infectious stones, comprise 6 percent of all kidney stones**, which in contrast to most stones, form in an alkaline urine. Struvite stones are more common in women, infants, and the elderly, and are often associated with recurrent bacterial urinary tract infections.

- **It is common for Struvite stones to start as calcium stones and then colonize with bacteria** that develop the Struvite component of the stone.
- Usually patient is given **Acetohydroxamic Acid.**

3. There are some **uncommon stone types**; these include: **Calcium Carbonate**, **Calcium Citrate** and **Ammonium Urate** (this occurs due **laxative abuse**).
   - Also, some **drugs and their metabolite may cause renal stones when over-used and abused**, these include: Aminophylline, Ciprofloxacin, Phenazopyridine, Sulfamethoxazole, Phenytoin, Amoxicillin, and Guaifenesin.
4. **Diet is important to prevent the recurrence of renal stones**; the patient should be advised to stick to the following diet:
   - Calcium = 1.0 gm/day.
   - Protein = 1.0 gm/kg/day or less low purine content.
   - Sodium = 100 mEq/day
5. **Treatment strategy and options:**
   a. Prevention is by **drinking fluids as many as possible** such that more than two liters of urine are produced per day.
   b. In those with **Calcium stones: thiazide diuretics (Hydrochlorothiazide) and citrate** are effective**; Allopurinol is effective for those with high uric acid** levels in the blood or urine.
   c. It is recommended that soft drinks containing phosphoric acid (as Pepsi, Cola) be avoided.
   d. **Large stones** may be helped to pass with **Tamsulosin** (Speed the passage of stones in the ureter) appear to be effective for stones over 4 mm but less than 10 mm in size.
   e. **Urine alkalization:** increasing the pH of the urine, **Acetazolamide** is a medication that alkalinizes the urine.
   f. **Acetohydroxamic Acid** (which is an antibiotic indicated for chronic UTS caused by urea-splitting bacteria); given 250 mg 3-4 times daily.
   g. **Certain dietary supplements can cause alkalization of the urine**: These include **Sodium Bicarbonate, Potassium Citrate, Magnesium Citrate**, and **Bicitra** (a combination of citric acid monohydrate and sodium citrate dihydrate).
      - The mainstay for medical management of **uric acid stones is alkalization.**
      - Aside from alkalization of the urine, these supplements have the added **advantage of increasing the urinary citrate level**, which helps to **reduce the aggregation of calcium oxalate stones.**
      - They can **reduce the efficacy** of some antibiotics as **(Nitrofurantoin)** when co-administered together; since some antibiotics require acidic media to be active.

Notes:

1. **If the stone size is less than 5 mm = most of them will pass spontaneously;** with simple remedies and pain control**; but if > 5mm = less than 20% chance of passage and may need a referral to urologic intervention.**
2. Increasing the urine **pH to around 6.5 provides optimal conditions for dissolution of uric acid stones.** Increasing the urine **pH to a value higher than 7.0 increases the risk of calcium phosphate stone formation.**
3. Urine should be kept acidic all the time; **PPIs and H_2 blocker should be prohibited or used in less quantities** in those patients who are suffering from peptic ulcer; **Vitamin D should be stopped or used in very low quantity.**
4. One of the medical therapies for prevention of stones is **the thiazide and thiazide-like diuretics,** such as **Chlorthalidone** or **Indapamide**; These drugs inhibit the formation of calcium-containing stones by reducing urinary calcium excretion; Sodium restriction is necessary for clinical effect of thiazides, as sodium excess promotes calcium excretion.
5. For people with **hyperuricosuria** and **calcium stones**, **Allopurinol** is one of the few treatments that have been shown to **reduce kidney stone recurrences.**
6. Several agents, including alpha adrenergic blockers (such as **Tamsulosin**) and calcium channel blockers (such as **Nifedipine**), have been found to be effective to **speed the spontaneous passage of stones in the ureter.**

8.10- Alkalization of Urine

1. The alkalinizing action **may relieve the discomfort of cystitis** caused by lower urinary tract infections; Also used for the **(Prevention) of uric acid stones**.
2. Also, Alkalization of urine can be undertaken with potassium citrate, and Sodium bicarbonate is used as a urinary alkalinizing agent in some metabolic and renal disorders.
3. Some formulations contain a urinary antiseptic and/or antispasmodic.
   - **Hexamine** is hydrolyzed to **Formaldehyde** which exerts potent antimicrobial effect against Gram-positive and Gram-negative bacteria and fungi.
   - **Khellin** is an antispasmodic that relieves urinary smooth muscle spasm and hypermotility associated with infection.
4. **Piperazine** citrate, adjusts the pH of urine to the appropriate value that helps dissolve uric acid and prevents formation and deposition of urate calculi.

Trade name	Dosage form	Scientific name(s)	concentration
Citrogran®	Granules	$NaHCO_3$ + Tartaric acid + Citric acid + Sucrose	----------
Uralyt-U®	Powder	Potassium Sodium Hydrogen Citrate	3 gm per dose
Urosolvine®	Eff. Powder	Piperazine + Colchicine + Atropine	195mg + 0.3mg + 2mg
Uricol Plus®	Eff. Powder	Piperazine + Colchicine + Khellin	195mg + 0.3mg + 1.83mg
Sankol®	Oral drop	Herbal preparation	30 ml
Cystone®	Tab, Syrup	Herbal preparation	----------
Ural®	Powder (sachets)	Sodium bicarbonate + Citric acid + Sodium citrate + Tartaric acid	1.76 gm + 0.72 gm + 0.63 gm + 0.89 gm
Urical®	Sachets	Sodium bicarbonate + Citric acid + Sodium citrate + Tartaric acid	1.58 gm + 0.646 gm + 0.566 gm + 0.79 gm
Uri Care®	Sachets	Sodium bicarbonate + Khellin + Citric acid + Sodium citrate	2.81 gm + 0.62 gm + 0.5 gm + 1.2 mg
Uricol®, Pharocol®	Sachets	Hexamine + Piperazine + Khellin	500mg +190mg +1.83mg
Harntee 400 N®	Granules	Herbal Tea combination	----------
Kellagon®	Cap	Herbal preparation	----------
Proximol®	Effervescent granules	Halfa bar extract + Hexamine* + Piperazine	18.6 mg + 6 gm + 1 gm
Foncitril 4000®	Sachets	Citric acid + Potassium Citrate + Sodium Citrate	1.189 gm + 1.730 gm + 1.845 gm
Kalinor®	Effervescent Tab	Potassium Citrate + Potassium Carbonate + Citric acid	2.17 gm + 2.0 gm + 2.057 gm
Uro 3®	Sachets	Potassium Bicarbonate + Potassium Citrate + Mg Citrate + Phyllanthus + Horse tail + Celery + Golden Rod + Chrysanthellum + Vit. B_6	2 gm + 1 gm + 1 gm + 220 mg + 200 mg + 100 mg + 100 mg + 55 mg + 50 mg
Mega Renal-Pro®	Sachets	Potassium Citrate + Mg Citrate + Phyllanthus + Horse tail + Celery + Golden Rod + Chrysanthellum + Vit. B_6	1 gm + 1 gm + 220 mg + 200 mg + 100 mg + 100 mg + 55 mg + 50 mg
Lithostat®	Tab	Acetohydroxamic Acid	250 mg

* **Hexamine** is contraindicated with Sulpha drugs (as **Trimethoprim**).

8.11- Other Urologic drugs

A. Phenazopyridine exerts an analgesic effect on the mucosa of the urinary tract and is used to **provide symptomatic relief** of pain and irritability in conditions such as cystitis and prostatitis, and urethritis. It is given **after food**; it causes **discoloration** of urine.

- **If given with an antibacterial for the treatment of urinary-tract infections, treatment should usually not exceed 2 days**.
- (Urinary analgesics also may **mask signs and symptoms of UTIs** not responding to antimicrobial therapy).

B. Rowatinex® and **Rawachol®** are terpene mixtures

- **Rowatinex** is used for **urolithiasis** (kidney stones) **for the expulsion of calculi**.
- **Rawachol** is used for prevention of liver stones.
- They are given **before food**, **4 times per day (or 2 Caps. twice daily)**.

C. Cranberry is used for **prophylaxis of urinary tract infections** (only); it's not useful once the infection has happened, it acts by inhibiting adhesion of uropathogenic E. coli to the urinary tract.

- Administration of standard cranberry preparations is recommended by European Urological Association (EUA) for prophylaxis.
- It can contribute to nephrolithiasis progression and enhance anticoagulation action of indirect anticoagulant drugs.
- Available as Capsule, chewable tablet and oral solution.

D. Propolis (extracted from bees); is thought to have antibacterial, antiviral, antifungal, and anti-inflammatory properties; But scientific research on **Propolis** is limited; usually found in combination with other products.

Trade name	Dosage form	Scientific name(s)	concentration
Urisept®, Azo-Mond® Spasmo-Cibalgin®	Tab	Phenazopyridine	100 mg , 200 mg
Rowatinex®	Cap	Terpene mixture	----------
Rawachol®	Cap	Terpene mixture	----------
Alinan Uractiv®	Syrup	Cranberry + Propolis + Rosehip + Vit. C	10 mg + 12 mg + 15 mg + 20 mg (per 5 ml)

References

1- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition.
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Rosemary R Berardi., Handbook of Nonprescription Drugs 18th Ed.
4- Community Pharmacy: Symptoms, Diagnosis and Treatment, By Paul Rutter 4th Ed.
5- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th ed.
6- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition.
7- https://journals.lww.com/humanandrology/Abstract/2016/12000/
8- ACCP Updates in Therapeutics® 2021: Pharmacotherapy Preparatory Review
9- JAMA Intern Med. 2018 Aug 1;178(8):1051-1057
10- Blume-Peytavi U, Whiting DA, Trüeb RM (26 June 2008). Hair Growth and Disorders. Springer Science & Business Media. p. 369. ISBN 978-3-540-46911-7.
11- https://www.questia.com/magazine/1G1-149202880
12- https://www.ncbi.nlm.nih.gov/pubmed/19400851

PAIN, PAINKILLERS AND MUSCULOSKELETAL SYSTEM

Chapter Nine: Pain, Painkillers and Musculoskeletal

9.1- Analgesics (Non-Narcotics)

a. Paracetamol, Nefopam, Flupirtine
b. Aspirin
c. NSAIDs
   - Some Combination Products
   - NSAIDs as eye drops
d. Selective cyclo-oxygenase (COX-2) inhibitors
   - Some Combination Products

9.2-Analgesics (Narcotics - Opioids)

a. Natural Opiates
b. Semi-Synthetic Opioids
c. Full Synthetic Opioids

9.3-Analgesics Combinations

- Special analgesic combinations

9.4-Muscle Relaxants

- Muscle Relaxants Combinations

9.5-Neuropathic pain

- Drugs used for Neuropathic pain
- Vitamin B_{12} types
- Special combinations indicated for Neuropathic Pain

9.6-Rubefacients, Topical NSAIDs, and Capsaicin

- Topical NSAIDs
- Combination products
- Topical Rubefacients
- Other Topical products for Pain Relief

9.7-Opioid Antagonists

9.8-Anti-Migraine drugs

a. Treatment of acute migraine
b. Prophylaxis of Migraine
c. Combination products for Migraine
d. Medical devices that is FDA approved for Migraine

9.9- Cannabinoid Analgesics

Chapter Nine: Pain, Painkillers and Musculoskeletal system

1. **Pain is an unpleasant sensory and emotional experience** that is associated with actual or potential tissue damage or described in terms of such damage.
2. Damage to body tissues as a result of disease or injury is detected by nerve endings that transmit signals to the brain; Interpretation of these sensations can be affected by a person's psychological state, so that **pain is worsened by anxiety and fear**, thus reassuring explanation of the cause of discomfort can make pain easier to bear and may even relieve it altogether.
3. Pain is usually **classified into:**
   a) **Acute pain** lasts 30 days longer than the usual healing process for that type of injury, and occurs after muscle strains and tissue injury, such as trauma or surgery.
   b) **Chronic pain** is persistent or episodic pain of a duration or intensity that adversely affects the function or well-being of the patient and can persist after the resolution of an injury. Some define it as lasting more than 6 months.
   c) **Neuropathic pain** is a result of an injury or malfunction of the nervous system; it is described as aching, throbbing, burning, shooting, stinging, and tenderness of the skin.
   d) **Migraine pain** is characterized by a severe headache generally associated with nausea and light and sound sensitivity.
4. Analgesics are divided into the **Opioids (Narcotics)** (with similar properties to drugs derived from opium, such as morphine) and **Non-Opioids (Non-Narcotics)**.
   - Non-opioids include all the other analgesics, including paracetamol, Nefopam, and non-steroidal anti-inflammatory drugs (NSAIDs); The non-opioids are less powerful as painkillers than opioids.

9.1- Analgesics (Non-Narcotics):

These include aspirin, Acetaminophen (Paracetamol), Nefopam, non-steroidal anti-inflammatory drugs (NSAIDs), selective cyclo-oxygenase 2 (COX-2) inhibitors.
These act as **pain killers (analgesics), anti-pyretic, anti-inflammatory** (except Paracetamol).

A) Paracetamol, Nefopam and Flupirtine

1. Paracetamol has **analgesic** and **antipyretic** effects **but has no anti-inflammatory effect,** Paracetamol is a suitable analgesic for children.
2. **Over-dosage is particularly dangerous as it may cause hepatic damage**.
3. Patient should be advised not to take **more than 1 gm** (usually 2 tablets of 500 mg) **at any one time,** and **not more than 8 tablets (4 gm) in 24 hours**.
4. A new statement from **FDA** states that Paracetamol combination drugs must contain at maximum 325 mg of Paracetamol only. (To avoid hepatic damage).
5. **Nefopam** is a new non-narcotic analgesic that may have a place in the relief of persistent pain unresponsive to other non-opioid analgesics.
6. **Flupirtine** is a non-opioid analgesic with **neuroprotective** and **muscle relaxant effect,** it works as a selective activator of neuronal K ± channels - by indirect antagonism to NMDA-receptors, activating the descending pain modulation mechanisms and GABAergic processes.

Scientific name	Dosage form	Trade name	concentration
Paracetamol	Tab	Panadol®, Emidol®, Adol®	500 mg
	Caplet	Panadol Joint® , Directol Extra®	625 mg
	Cap	Doliprane®, Kernadol®	500 mg , 1000 mg
	Syrup	Tempra®, Antipyrol®	125 mg/5ml , 250 mg/5 ml
	Amp.	Hayamol®	300 mg , 600 mg
	Supp.	Ultramol®, Panatol®, Doliprane®	125 mg , 250 mg 150 mg , 300 mg
	Oral Drops	Tempra® , Adol®	120 mg/5 ml

Nefopam	Tab	Accupan®	30 mg
	Amp		20 mg/2 ml
Flupirtine	Cap	Katadolon®	100 mg

B) Aspirin

1. Also considered as **NSAID**, two 325-mg tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.
2. **Aspirin** is used in low doses (75 mg to 160 mg) as platelet aggregation inhibitor, and for the prophylaxis of myocardial infarction (MI).
3. **Aspirin** is used off-label as a Mouth Gargle (300 mg in water) for Sore Throat and Tonsillitis.
4. Aspirin is given for pregnant to prevent Pre-eclampsia in those with anti-phospholipid syndrome.

Scientific name	Dosage form	Trade name	concentration
Aspirin	Tab	(Various)	75 mg , 81 mg , 100 mg , 325 mg , 500 mg
	Effervescent Tab	Aspin-C®	100 mg
	Powder (oral)	Aspegic®	500 mg , 1000 mg
	Vial (powder)	Aspegic®	500 mg , 1000 mg

* **Aspegic®** Formulated as DL-Lysine Acetylsalicylate.

C) Non-steroidal anti-inflammatory drugs (NSAIDs):

1. **NSAIDs have analgesic, anti-inflammatory, and antipyretic properties**. NSAIDs are used for the relief of mild to moderate pain, minor febrile conditions, and for acute and chronic inflammatory disorders such as osteoarthritis, and rheumatoid arthritis.
   - Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individual response and tolerance to these drugs, about 60% of patients will respond to any NSAID; of the others, those who do not respond to one may well respond to another.
   - Pain relief starts soon after taking the first dose and a full analgesic effect should normally be obtained within a week, whereas an anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to 3 weeks.
2. **NSAIDs** are prostaglandin inhibitors and prevent peripheral nociception by vasoactive substances such as prostaglandins and bradykinins. Most NSAIDs inhibit both **COX-1, which produces prostaglandins that are believed to be cytoprotective of the stomach lining**, and **COX-2, which produces prostaglandins responsible for pain and inflammation.**
3. **Some NSAIDs are applied topically** for the relief of muscular and rheumatic pain, and some are **used in ophthalmic preparations** for ocular inflammatory disorders [(1)].
4. The adverse effects of NSAIDs are generally **gastrointestinal disturbances,** such as gastrointestinal discomfort; These are usually mild and reversible; although in some patient's **NSAID may cause peptic ulceration and severe gastrointestinal bleeding**.
5. NSAIDs are **contra-indicated** in patients with **Active peptic ulceration.**
6. **To reduce the risk of gastrointestinal effects:**
   - NSAIDs may be **taken with or after food or milk**.
   - Taking **H2-antagonists, or proton pump inhibitors** such as omeprazole.
   - Using **enteric-coated formulations**.
   - Using some specific NSAIDs like **Celecoxib** (called selective COX-2 inhibitors) where the risk of serious upper gastro-intestinal side effects is lower.
7. NSAIDs should be used with **caution in patients with asthma** (cause respiratory depression), **and hypertension** (they cause sodium and water retention).

8. **The Use of more than one NSAID together should be avoided because of the increased risk of adverse effects.**
9. Owing to an association with **Reye's syndrom**e, **Aspirin and NSAIDs should not be given to children under 16 years,** unless specifically indicated; (Reye's syndrome may occur when aspirin and other salicylates are given during viral infections)
10. **NSAIDs** are classified as FDA pregnancy **category C** risk during the first and second trimesters and **category D during the third trimester.**

Scientific name	Dosage form	Trade name	concentration
Diclofenac Na+	Tab	Voltaren®, Refen®, Diclogesic®	25 mg , 50 mg , 100 mg
	Cap	Olfen®	75 mg , 100 mg
	Cap SR	Zorvolex®	18 mg , 35 mg
	Powder (oral)	Voltafast®, Olfen Despersable®	50 mg , 75 mg
	Amp	Almiral®, Olfen®	75 mg
	Supp.	Voltamed®	12.5 mg , 25 mg , 50 , 100 mg
	Skin Gel	Voltarin®, Voltamed®	10 mg/gm (50 gm tube)
	Skin Patch	Voltaheat® , Olfen®	140 mg/day
	Spray	Votrarin Emugel®	1% (75 ml)
Diclofenac K+	Tab	Cataflam®, Zipsor®	50 mg , 100 mg
Ibuprofen	Tab	Advil® , Brufen® , Apifen®	200 mg , 400 mg , 600 mg
	Oral Susp.	Profinal® , Mufen®	100 mg/5 ml
	I.V. Solu.	Caldolor® , Neoprofen®	100 mg/ml
Mefenamic acid	Cap/Tab	Ponstan® , Mefex®	250 mg , 500 mg
	Oral Susp.	Mefen®	50 mg/5 ml
Tolfenamic acid	Cap , Tab	Flocur®	20 mg
Ketoprofen	Tab/Cap	Profenid®	50 mg , 75 mg , 100 mg
	Cap ER	Bi-Profenid®	200 mg
	Amp	Profenid®, Isofenal®	100 mg/2 ml
	Oral Syrup	Toprec®	1 mg/ml (150 ml Bottle)
	Skin Gel	Profenid Gel® , Fastum®	2.5% (60 gm tube)
Dexketoprofen	Tab , Eff. Tab	Keral® , Dexday®	25 mg , 50 mg
Indomethacin	Cap	Indocin®	25 mg , 50 mg
	Supp.	Indocid®	50 mg , 100 mg
	Spray	Elmetacin®	1%
Aceclofenac	Tab	Preservex®, Loflam®	100 mg
Acemetacin	Cap	Emflex®, Rantudil®	60 mg , 90 mg
Naproxen	Tab	Aleve®, Naprox®	250 mg , 500 mg
Flurbiprofen	Tab	Ansaid® , Froben®, Maximus®	50 mg , 100 mg
Dexibuprofen	Tab	Seractil®	300 mg , 400 mg
Fenoprofen	Cap	Nalfon® , Fenopron®	200 mg , 400 mg
Loxoprofen	Tab	Loxonin® , Roxonin® , Oxeno®	60 mg , 120 mg
Oxaprozin	Tab	Daypro®	600 mg
Tiaprofenic acid	Tab	Surgam®	100 mg , 300 mg
Etofenamate	Amp	Flexo®	1 gm/2 ml
	Skin Gel	Dolo-Denk Gel®	10%
Nabumetone	Tab	Relafen®	500 mg , 750 mg
Etodolac	Tab	Dolarit®	400 mg
	Tab MR	Etopan XL®, Lodine SR®	600 mg

Ketorolac	Tab	Tradol®	10 mg
	Inj. Solu.	Ketro® , Tradol®	15 mg/ml , 30 mg/ml
Nimesulide	Tab , Supp.	Coxtal®, Nimalox® , Ache-off®	100 mg (both)
	Amp	Relaxonim®	75 mg/2 ml
Piroxicam	Cap	Felden®	10 mg , 20 mg
	Tab (subling.)	Felden Flash®	20 mg
	Amp	Flexase® , Felden®	20 mg/2 ml , 20 mg/ml
	Skin Gel	Felden Gel® , Picam®	5 mg/gm (60 gm tube)
	Supp.		20 mg
Meloxicam	Tab	Mobic®, Neoxicam®	7.5 mg , 15 mg
	Cap SR	Vivlodex®	5 mg , 10 mg
	Amp , Supp.	Mobic®	15 mg/1.5 ml , 15 mg (Supp)
Tenoxicam	Tab	Admiral® , Tilcotil®	20 mg
	Vial (powder)	Mobiflex® , Trocmetam®	20 mg
Lornoxicam	Tab	Quando® , Xefo®	8 mg , 16 mg
	Vial (powder)	Xefo®	8 mg
Metamizol	Tab , Inj.	Novalgin®, Nolotil®	500 mg , 575 mg

Some Extra Notes:

1. **NSAIDs within a group tend to have similar characteristics and tolerability;** There is little difference in clinical efficacy among the NSAIDs when used at equivalent doses, differences among compounds usually relate to dosing regimens (related to the compound's elimination half-life), route of administration, and tolerability profile.
2. **Naproxen is the only NSAID that does not appear to increase the risk of CV events**; therefore, its use is preferred in patients with CV risk factors per the ACG guidelines; However, in Feb. 2014, FDA panel voted against label changes that would indicate a lower CV risk.
   - Naproxen onset of action for analgesia is 1 hour, duration of effect is about 7 hours.
   - Onset of action for anti-inflammatory effect is 2 weeks.
3. **Diclofenac** has potent anti-inflammatory effect with medium analgesic effect, but its associated with the **highest risk of heart attack** and **stroke** among non-selective NSAIDs.
4. **Aceclofenac** is the glycolic ester of **Diclofenac**, it's very similar to Diclofenac in potency and activity; but has the advantage of **having lower side effects profile**, (4-folds lesser than Diclofenac).
5. The CHMP has **recommended restrictions on the use of Piroxicam** because of the increased risk of gastro-intestinal side effects and serious skin reactions; The CHMP has advised that:
   - Piroxicam **should not be used as first-line treatment.**
   - Piroxicam dose **should not exceed 20 mg daily.**
   - Treatment should be reviewed 2 weeks after initiating, and periodically thereafter.
6. **Meloxicam** has **dose dependent COX 2 selectivity** (7.5 mg is more COX 2 selective than 15 mg), and short term 7.5 mg daily is less likely than Naproxen or Diclofenac to be associated serious GI complications; but it may cause elevates in liver function tests in about 15% of patients.
7. **Nimesulide has been withdrawn from market in many countries,** due to concerns about the risk of hepatotoxicity; the use of **Nimesulide in children under the age of 12 is C.I**.
   - Nimesulide exerts COX-2 selectivity similar to celecoxib.
8. **Ibuprofen** onset of analgesia is 30 minutes and Duration is about 4-6 hours.
   - At low dose it has low risk of causing GI side effects, but this advantage is lost at high doses.
   - **The safest option for breastfeeding women** (has a short half-life, and excreted in very small amount in breast milk).
   - It's used for the **treatment of acne,** because of its anti-inflammatory properties, and has been sold in Japan as a topical form for adult acne.
   - Ibuprofen may be useful in the **treatment of severe orthostatic hypotension.**
   - **Dexibuprofen** is the active enantiomer of Ibuprofen; It has similar properties to **Ibuprofen.**

9. **Oxaprozin** also has a mild **Uricosuric properties** and is used in the treatment of gout.
   - It has a **rapid onset** of action, and a **very long duration** of action (half-life 50-60 hours).
10. **Acemetacin** is a pro-drug, which is converted into **Indomethacin.**
11. **Tiaprofenic acid** can **cause severe cystitis,** thus it should not be given to patients with urinary-tract disorders and should be stopped if urinary symptoms develop.
12. **Sulindac,** an analog of **Indomethacin,** is unique among the NSAIDs in not inhibiting prostaglandin synthesis in the kidneys, thus it may be one of the safest drugs for treating osteoarthritis in elderly.
    - Have **similar anti-inflammatory** potency with **Indomethacin;** but **less toxic.**
13. **Indomethacin** is **very potent anti-inflammatory and analgesic**, but has high cardiovascular risk and significant GI toxicity; it should not be used by children <14 years.
    - **Ankylosing Spondylitis** responds better to **Indomethacin;** It is probably related to its stronger inhibition of prostaglandin synthesis.
14. **Ketoprofen** has the advantage that (unlike other NSAIDs) it **inhibits the synthesis of leukotrienes and leukocyte migration** into inflamed joints, in addition to inhibiting the biosynthesis of prostaglandins; it also stabilizes the lysosomal membrane during inflammation, resulting in decreased tissue destruction.
15. **Metamizol** is a potent analgesic and antipyretic, but week anti-inflammatory drug.
    - **Metamizol was banned in the USA and some European countries** due to several reported cases of agranulocytosis; but it has been extensively used in India and other countries.
16. **Etodolac** has the **Lowest risk of gastrointestinal damage** in the NSAIDs group; Although Etodolac is no more potent than other NSAIDs.
17. **Flurbiprofen** has very **high analgesic effect** compared to other NSAIDs, 536-fold more potent than Aspirin and 26 times more potent than Ibuprofen.
18. **Ketorolac** is the most COX-1 selective NSAID, it's the **most potent and most effective NSAID analgesic,** with efficacy comparable to opioids; The analgesic effect of 30 mg of ketorolac is similar to 10 mg of morphine; (thus recommended for 5-day use only).
    - But it has **the highest incidence of side effects**; This drug is about five times more gastro toxic than other NSAIDs; and the risk of adverse effects is higher when ketorolac is used in higher doses, in elderly patients, and for more than 5 days.
    - **Ketorolac is banned in France and Germany** since 1993, due to high risks of Gastrointestinal bleeding and renal failure.

Some Combination Products of NSAIDs

These combination below are designed to decrease the direct gastrointestinal side effects of NSAIDs by combining them with PPIs, H2 Blocker and Misoprostol.

Scientific name(s)	D. form	Trade name	concentration
Ketoprofen + Omeprazole	Cap	Axorid®	(100mg + 20mg), (200mg + 20mg)
Naproxen + Esomeprazole	Tab	Vimovo®	500 mg + 20 mg
Meloxicam + Esomeprazole	Tab	Rumonal Pro®	15 mg + 20 mg
Ibuprofen + Famotidine	Tab	Duexis®	800 mg + 26.6 mg
Diclofenac Na^+ + Misoprostol	Tab	Arthrotec® , Misofen®	50 mg + 200 mcg
Naproxen + Misoprostol	Tab	Napratec®	500 mg + 200 mcg

NSAIDs as eye drops

They are used to **suppress the optical mast cell responses to allergens** including (but not limited to) aerosolized dust particles and other allergens, also used as **ophthalmic analgesics** or in **allergic conjunctivitis to reduce the eye inflammation.**

- For more info, see chapter 12.

D) Selective cyclo-oxygenase 2 (COX-2) inhibitors:

1. These are **also NSAIDs,** but they are **selective for inhibition of COX-2 (responsible for inflammation and pain)**, this selectivity against COX-2 provides a therapeutic advantage over nonselective COX inhibitors, allowing the proper management of chronic inflammatory conditions. (6), They have been shown to be associated with **less GI bleeding** and **dyspepsia**.
   - **Contraindicated** in patients who are **allergic to sulfur. (Except Etoricoxib).**
2. They are associated with an **increased risk of serious (and potentially fatal) adverse cardiovascular thrombotic events**, including myocardial infarction and stroke.
   - **They Increase the risk of major cardiovascular problems by about 37%.**
   - Thus (Celecoxib, Etoricoxib, and Parecoxib) are **contra-indicated in ischemic heart disease, cerebrovascular disease, peripheral arterial disease,** and **mild to severe heart failure;** They should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, in patients with edema for any other reason, and in patients with other risk factors for cardiovascular events.
   - Although; a shocking trail (discussed below) shows that **CV risk is not a COX-2 inhibitor class effect**, and CV risk was the same in Celecoxib compared with Naproxen and Ibuprofen.
   - And due that trail; an FDA advisory panel in 2018 concluded that **Celecoxib poses no greater risk for causing heart attacks and strokes than the commonly-used NSAIDs Ibuprofen or Naproxen** and recommended that the FDA consider changing its advice to physicians regarding celecoxib's safety. (7)
3. **Celecoxib** and **Etoricoxib** are licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; but **Etoricoxib** is also licensed for the relief of pain from acute gout; as follows:
   - **Etoricoxib** tablet 60 mg – 90 mg once daily for Osteoarthritis, Rheumatoid arthritis, Ankylosing spondylitis and Acute pain conditions.
   - **Etoricoxib** tablet 120 mg once daily for Acute Gout, limited for use for 7 days only.
   - **Etoricoxib** tablet 90 mg once daily for postoperative dental pain surgery, for 3 days only.
   - **Etoricoxib** is approved in more than 80 countries worldwide, but **it's not approved by the US FDA**, and not allowed to be sold in the USA; as the (FDA) requires additional safety and efficacy data for Etoricoxib before it will issue approval. (Due to the other 3 withdrawals in this family).

Scientific name	Dosage form	Trade name	concentration
Celecoxib	Cap	Celebrex®, Coxib®	100 mg , 200 mg
Rofecoxib	Tab	Vioxx®, Ceoxx®	12.5 mg , 25 mg , 50mg
Valdecoxib	Tab	Bextra®	10 mg , 20 mg
Parecoxib	Vial (powder)	Dynastat®	40 mg
Lumiracoxib	Cap	Prexige®	100 mg
Etoricoxib	Tab	Arcoxia® , Atoxia® , Etoxia®	60 mg , 90 mg , 120 mg
Mavacoxib	Tab	Trocoxil®	75 mg

Notes:

1. **Rofecoxib** and **Valdecoxib** were **withdrawn from the market** on 2004, 2005 respectively; because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use.
2. **Parecoxib** is an **injectable** prodrug of **Valdecoxib**; it is approved through much of Europe for short term perioperative pain control, has no effect on platelet function and therefore does not promote bleeding during or after surgery.
   - The drug is not approved for use after cardiac surgery in Europe.
3. **Lumiracoxib** has been withdrawn from the market in several countries, mostly due to hepatotoxicity concerns; It has never been approved for use in the USA.
4. **Mavacoxib** was rejected several times as a human Drug; then it was approved as veterinary drug

Note1: PRECISION trail [8]

1. **P**rospective **R**andomized **E**valuation of **C**elecoxib **I**ntegrated **S**afety versus **I**buprofen **o**r **N**aproxen, a randomized controlled trial to prospectively examine the CV safety of long term NSAID use in arthritis patients with, or at high risk for CV disease.
2. The trail included (24,081) patients for (10 years); which used **Celecoxib** 100 mg BID, **Ibuprofen** 600 mg TID and **Naproxen** 375 mg BID.
3. The summery of the trail was (with mean drug exposure ±20 months):
   - **Celecoxib** demonstrated similar incidence of CV events compared to **Naproxen** and **Ibuprofen**, and the rate of hospitalization for hypertension was also significantly lower with **Celecoxib** compared to **Ibuprofen**.
   - **Celecoxib** treatment also resulted in lower rates of gastrointestinal events than did either comparator: **Ibuprofen** and **Naproxen**
   - **Celecoxib** was also demonstrated significantly lower rate of renal events than with **Ibuprofen**, and similar to **Naproxen**
   - CV risk is not COX-2 inhibitors class effect, and not all COX-2 inhibitors are the same.
4. This trial was funded and supported by Pfizer (the brand & originator of Celecoxib).

Note2: Some Combination Products of COX-2 Inhibitors

Scientific name(s)	D. form	Trade name	concentration
Celecoxib + Orphenadrine	Tab	Caditar Flex®	200 mg + 25 mg
Celecoxib + Pregabalin	Cap	Lyca-C®	200 mg + 75 mg
Etoricoxib + Paracetamol	Tab	Nucoxia-P®	60 mg + 500 mg
Etoricoxib + Pregabalin	Tab , Cap	Cilonerve®, Neurobem®	90 mg + 75 mg
Etoricoxib + Thiocolchicoside	Tab	Nucoxia-MR®	(60mg + 4mg), (60mg + 8mg)

*** Orphenadrine** and **Thiocolchicoside** are **muscle relaxants** (see below)**.**
*** Pregabalin** is an anticonvulsant that used for **neuropathic pain**.

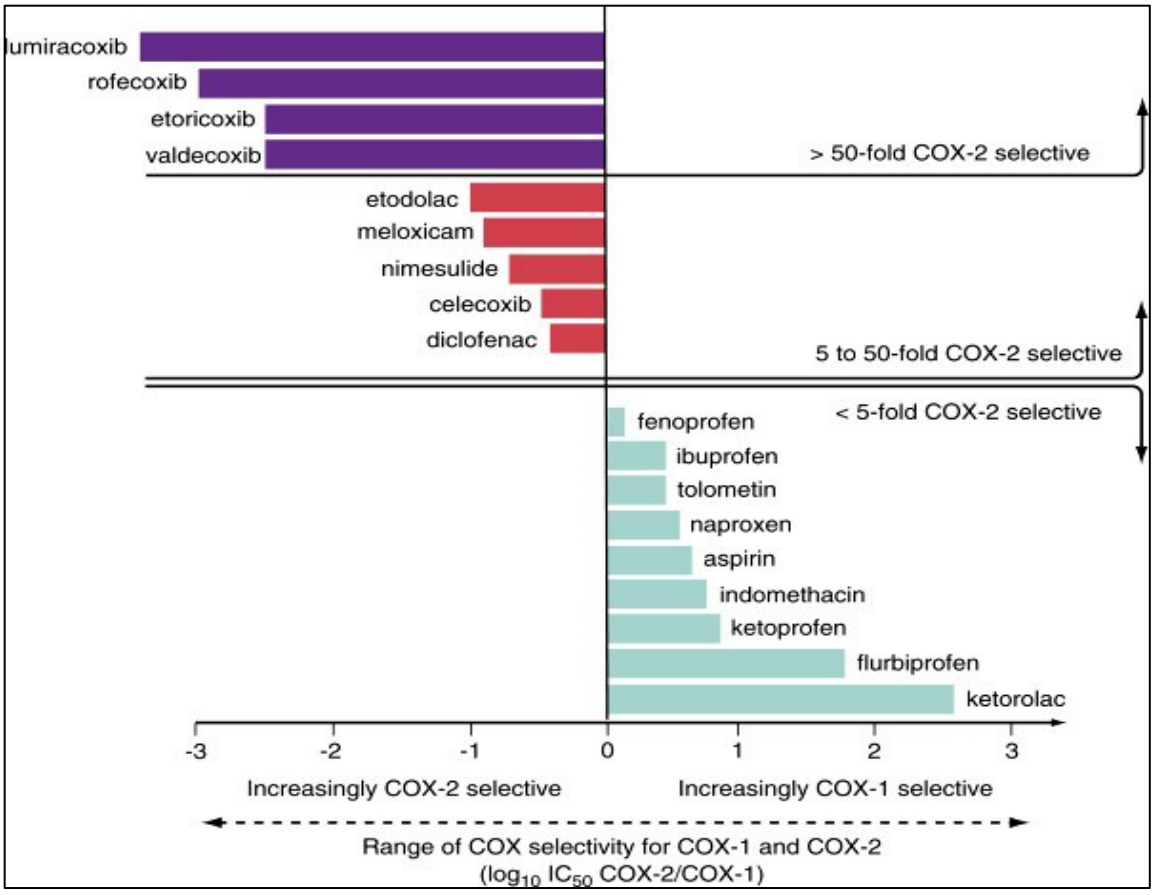
Note3: what to choose?! [9]

Too many NSAIDs are available; both traditional and new COX-2 selective, which one is better than others? Are they all the same? To answer these questions, see the notes below:

1. The **analgesic benefit** and **anti-inflammatory properties** of NSAIDs are **COX-2 dependent** (this means the more COX-2 selective the more anti-inflammatory effect).
2. **Oral** NSAIDs have **no significant differences** in general **analgesic potency**.
3. The gastrointestinal (GI) side effects from NSAIDs are directly related to inhibition of COX-1, thus Selective COX-2 inhibitors showed the least likelihood of GI side effects including perforation, bleeding, or obstruction.
   - **Diclofenac** showed a 2-fold increase in GI side effects, while **Ibuprofen** and **Naproxen** showed a 4-fold increase than **Celecoxib**.
4. Nearly all NSAID regimens displayed a 2-fold increase in the risk of hospitalization due to heart failure, possibly related to sodium retention.
   - **Naproxen** did not show the increased risk of major coronary or vascular events.
   - In a large, country-wide observational study in Denmark, researchers found a correlation between NSAID use and death rate, with COX-2 selective inhibitors having an increased hazard ratio for death; **Ibuprofen** used in quantities greater than 1,200 mg were associated with an increased hazard ratio for the composite end-point of myocardial infarction (MI) and death, as was **Diclofenac** dosages greater than 100 mg.
   - In 2015, the US FDA strengthened its warning that NSAIDs (both selective and non-selective) can cause adverse cardiovascular outcomes, include M.I., stroke, and heart failure.
5. Prolonged NSAID use can limit prostaglandins synthesis below the required level, resulting in acute kidney injury; elevated risks were noted for selective and partially selective NSAIDs (**Diclofenac**, **Meloxicam**, **Celecoxib**).

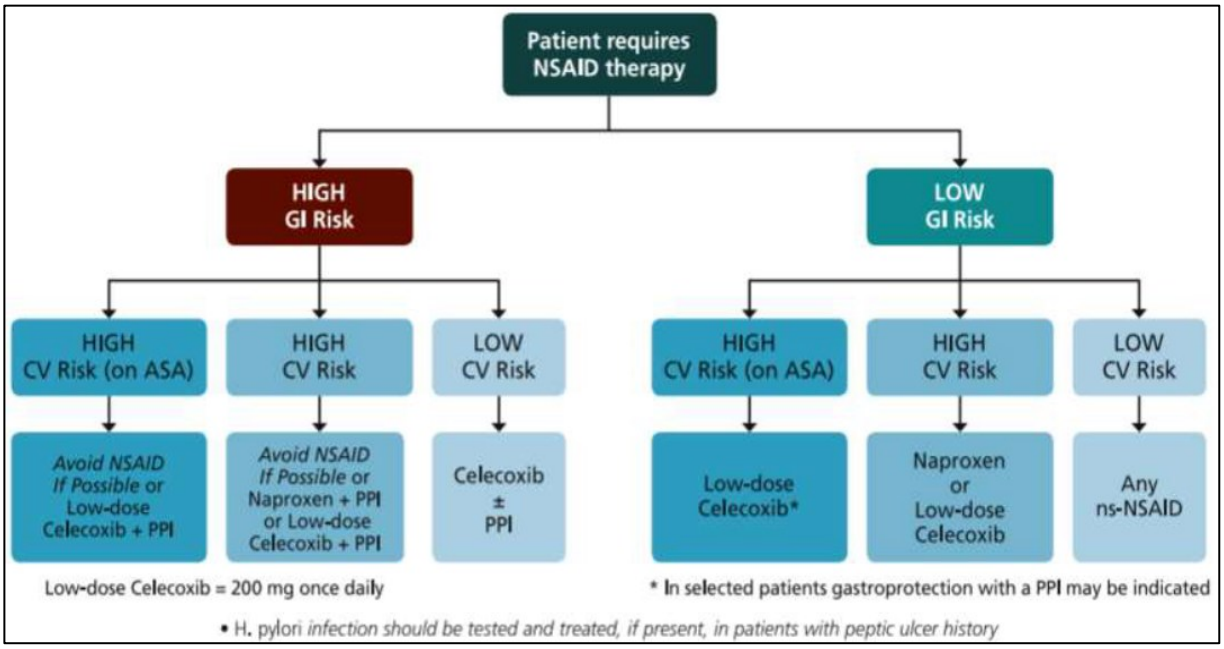
Note4: it's all about COX-2 selectivity

1. The more COX-2 selective the more potent anti-inflammatory (also more CV side effect??)
2. The less COX-2 selective the more potent analgesic (also more GI side effects??)
3. The table below shows NSAIDs Classification by COX selectivity, done by (in vitro assessment of COX-1/COX-2 activity):



Note5: I feel lost, need an easier approach

1. If you feel you don't have any time to look and read about all the NSAIDs notes above, and in the textbooks, or by Googling; below a simple table to help you choose a NSAID:



9.2- Analgesics (Narcotics - Opioids):

1. These drugs are related to **opium**, an extract of poppy seeds; They act directly on several sites in the central nervous system to block the transmission of pain signals, because they act directly on the parts of the brain where pain is perceived, **opioids are the strongest analgesics** and are therefore used to treat the pain arising from surgery, serious injury, and cancer.
   - The use of these powerful opioids is strictly controlled because the **euphoria** produced can lead to abuse and addiction; but when these opioids are given under medical supervision to treat severe pain, the risk of addiction is negligible.
2. Opioid analgesics are usually used to relieve moderate to severe pain, **(the Repeated administration may cause dependence and tolerance)**.
3. **Opioids** such as **(Codeine** or **Dextropropoxyphene)** are used in the treatment of less severe pain, and are often combined with non-opioid analgesics such as aspirin, or Paracetamol.
4. More potent opioids such as **Morphine** are used in severe acute and chronic pain.
5. **Tramadol** produces **fewer of the typical opioid side-effects** (notably, less respiratory depression, less constipation and less addiction potential [2], (However, **Tramadol is abused by many addicts,** locally and worldwide); **Tramadol** is a **serotonin releaser**, **reuptake inhibitor of norepinephrine (SNRI)** and a **weak μ-opioid receptor agonist**.
   - **Tramadol** painkilling action starts in less than 1 hour, but wears off after about 4 hours.
   - In the USA, the doctor can only prescribe Tramadol in maximum of five refills for the same patient, and a new prescription is required every 6 months.
   - **Tramadol** is used off-label for the treatment of **premature ejaculation (PE)**.
6. The most **common side-effects include nausea and vomiting** (particularly in initial stages), and **constipation** [2]; also, opioid (Narcotic) analgesics may prevent clear thought and cloud consciousness; thus, the Narcotic addict is very dangerous.
   - Other possible adverse effects **depressed breathing**; when they are taken in overdose, these drugs may induce a deep coma and lead to fatal breathing difficulties.
7. **Opioids should be used with caution in patients with impaired respiratory function** (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack), also **avoided in obstructive or inflammatory bowel disorders**.
8. **Long-term use of opioid analgesics can cause hypogonadism and adrenal insufficiency** in both men and women. This is thought to be dose related and can lead to amenorrhea, reduced libido, infertility, depression, and erectile dysfunction.
9. Also, Long-term use of opioid analgesics has also been associated with a state of **abnormal pain sensitivity (hyperalgesia)**, which is more diffuse and less defined than normal pain.
10. Can be classified into:
    a. **Natural opiates:** alkaloids contained in the resin of the opium poppy, as **Morphine, Codeine**.
    b. **Semi-synthetic opioids:** created from either the natural opiates or morphine esters, such as **hydromorphone, hydrocodone, oxycodone, Oxymorphone, buprenorphine.**
    c. **Fully synthetic opioids**: such as **Fentanyl, Pethidine, Levorphanol, Methadone, Tramadol** and **Dextropropoxyphene.**
11. A combination of opioid and non-opioid analgesics is used to treat postoperative pain, the use of intra-operative opioids affects the prescribing of postoperative analgesics, a postoperative opioid analgesic should be given with care since it may potentiate any residual respiratory depression.
12. **Opioid analgesics are relatively ineffective in dental pain**, also they often cause nausea and vomiting which limits its value in dental pain.
13. Other opioids include **(Loperamide, Difenoxin, Diphenoxylate)**, are used mainly in the treatment of diarrhea (see chapter 2, section 6, for more details).

Natural Opiates			
Scientific name	Dosage form	Trade name	concentration
Morphine	Tab ER	Arymo ER®	15 mg , 30 mg
	Inj. Susp. (ER)	Depodur®, Kadian®	10 mg/ml
	Inj. Solu.	Avinza®	0.5 mg/ml , 1 mg/ml
	Inj. Solu.	Infumorph®	200 mg/20 ml , 500 mg/20 ml
Codeine *	Tab	Codam®	15 mg , 30 mg , 60 mg
	Inj. Solu.		15 mg/ml , 30 mg/ml

* **Codeine** is also used **in the treatment of dry cough** as an **antitussive**, and also used as **antidiarrheal** (off-label).

Semi-Synthetic Opioids			
Scientific name	Dosage form	Trade name	concentration
Hydromorphone	Tab	Dilaudid® , Exalgo®	2 mg , 4 mg , 8 mg , 12 mg , 16 mg
	Inj. Solu.		2 mg/ml , 4 mg/ml , 10 mg/ml
Hydrocodone	Cap	Zohydro®	10 mg , 15 mg , 20 mg , 40 mg
Oxycodone *	Tab	Roxicodone® , Oxecta®	10 mg , 15 mg , 20 mg , 30 mg
Oxymorphone	Tab	Opana® , Opana ER®	5 mg , 10 mg , 15 mg , 20 mg
Buprenorphine **	Tab (subling.)	Buprenex® , Temgesic®	2 mg , 8 mg
	Inj. Solu.	Subutex®	0.3 mg/ml
	Skin Patch	Butrans®	5 mcg , 10 mcg , 20 mcg (per hr.)

* **Oxycodone is pregnancy (B) risk factor,** but becomes **(D)** with high doses or long-term use.
**** Buprenorphine's** high-dose sublingual tablet preparations indicated for detoxification and long-term replacement therapy in opioid dependency **(opioid addiction treatment)**, and the drug is now used predominantly for this purpose.

Fully Synthetic Opioids			
Scientific name	Dosage form	Trade name	concentration
Fentanyl or (Fentanil)	Inj. Solu.	Sublimaze®	0.05 mg/ml
	Intra-nasal	Lazanda® (Contains only 8 sprays/bottle)	100 mcg/0.1 ml , 400 mcg/0.1 ml
	Skin Patch	Duragesic®	12.5 mcg , 25 mcg , 50 mcg
Remi-Fentanyl	Vial (Solu.)	Ultiva®	1 mg , 2 mg , 5 mg
Sufentanil	Tab , SubLing	Dsuvia	30 mcg
	Inj. Solu.	Sufenta	0.05 mg/ml
Pethidine (or) Meperidine **(in USA)**	Tab , Inj. Solu.	Demerol®	50 mg , 100 mg (tab) 25 mg/ml , 50 mg/ml (inj.)
Levorphanol	Tab	Levo-Dromoran®	2 mg
Methadone	Tab	Dolophine®	5 mg , 10 mg
	Inj. Solu.		10 mg/ml
Dextropropoxyphene	Tab	Darvon® , Darvocet®	65 mg , 100 mg
Nalbuphine	Inj. Solu.	Nubain®	10 mg/ml , 20 mg/ml
Butorphanol	Inj. Solu.	Stadol®	1 mg/ml , 2 mg/ml
	Nasal Spray		10 mg/ml
Pentazocine	Inj. Solu.	Talwin®	30 mg/ml
Tramadol	Tab , Cap	Tramal® , Ultram® , Topalgic®	50 mg , 100 mg , 200 mg
	Inj. (Amp)	Zydol®, Trabar®	50 mg/ml , 100 mg/2 ml
Tapentadol	Tab	Palexia®	50 mg , 100 mg , 200 mg

Extra Notes:

1. **Dextropropoxyphene has been taken off the market in Europe, USA in 2010**, due to concerns of fatal overdoses and heart arrhythmias, it's still used in our market.
2. **Nalbuphine** is indicated for the relief of moderate to severe pain. It can also be used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia during labor, and as a **treatment for morphine induced pruritus.**
3. **Butorphanol** is used in **management of migraine** using the intranasal spray formulation. It may also be used parenterally for management of moderate-to-severe pain, as a supplement for balanced general anesthesia, and **management of pain during labor**.
   a. **Butorphanol** is **more effective** in reducing pain in women than in men.
   b. Recently was discontinued by the manufacturer; It's now only available in generic.
4. **Tapentadol** produces analgesia by two mechanisms. It is an opioid-receptor agonist and it also inhibits noradrenaline reuptake.

9.3- A) Analgesics Combinations

1. Analgesics are frequently used in combination, such as the **Paracetamol** and **codeine** preparations found in many non-prescription pain relievers.
2. The use of **Paracetamol, Aspirin, Ibuprofen, Naproxen** and other **NSAIDS** concurrently with weak to mid-range Narcotics has synergistic effects by combatting pain at multiple sites of action.

Trade name	D. form	Scientific name(s)	concentration
Antidol®, Pain Stop®	Cap	Dextropropoxyphene + Paracetamol	32.5 mg + 325 mg
Relief®	Tab	Diclofenac Na + Paracetamol + Chlorpheniramine	50 mg + 500 mg + 100 mg
No-Pain®, Ibex®, Novafen®	Cap	Paracetamol + Ibuprofen + Caffeine	325 mg + 200 mg + 30 mg
Dologan Denk	Tab	Paracetamol + Ibuprofen + Caffeine	250 mg + 250 mg + 50 mg
Cilopan®	Tab	Paracetamol + Nefopam	325 mg + 30 mg
Megafen®	Tab	Paracetamol + Ibuprofen	325 mg + 200 mg
	Susp.	Paracetamol + Ibuprofen	162.5 mg + 100 mg
Pain Leave®, Relief Extra®	Tab	Paracetamol + Diclofenac Na + Chlorpheniramine + Mg-Trisilicate	500 mg + 50 mg + 4 mg + 100 mg
Stopain®, Panalgrine®	Tab	Paracetamol + Caffeine + Propyphenazone	300 mg + 50 mg + 150 mg
Saridon®	Tab	Paracetamol + Caffeine + Propyphenazone	250 mg + 50 mg + 150 mg
Excedrin®	Tab	Paracetamol + Aspirin + Caffeine	250 mg + 250 mg + 65 mg
Citramon®	Tab	Paracetamol + Aspirin + Caffeine	200 mg + 220 mg + 27 mg
Diclomol®	Tab	Paracetamol + Diclofenac Na	500 mg + 50 mg
Actinac Plus®, Pyxinac Plus®	Tab	Paracetamol + Aceclofenac	500 mg + 100 mg
Nimo Plus®	Tab	Paracetamol + Nimesulide	500 mg + 100 mg
Azur®, Zerlor®, Panlor®	Tab	Paracetamol + Caffeine+ Codeine	350 mg + 50 mg + 30 mg
Panamax®	Tab	Paracetamol + Caffeine+ Codeine	500 mg + 30 mg + 10 mg
Synalgos®	Tab	Aspirin + Caffeine + Codeine	356 mg + 30 mg + 16 mg
Co-Codamol®	Tab	Paracetamol + Codeine	500 mg + 8 mg
Talacen®	Tab	Paracetamol + Pentazocine	650 mg + 25 mg

Ultracet®, Zafin®	Cap, Tab	Paracetamol + Tramadol HCL	325 mg + 37.5 mg
Sudamed Plus®, Sudafed®	Tab	Paracetamol + Diclofenac Na + Tramadol HCL	350 mg + 50 mg + 25 mg
Mega-Relief Forte®	Cap	Paracetamol + Diclofenac Na + Tramadol HCL + Codeine	350 mg + 50 mg + 25 mg + 8 mg
Advil PM®	Tab, Cap	Ibuprofen + Diphenhydramine	200 mg + 25 mg
Combunox®	Tab	Ibuprofen + Oxycodone	400 mg + 5 mg
Ibudone®, Vicoprofen®	Tab	Ibuprofen + Hydrocodone	(200 mg + 2.5 mg), (200 mg + 5 mg)
Percodan®,Oxycodan®	Tab	Aspirin + Oxycodone	325 mg + 5 mg
Midol Max®, Pamprin®	Tab, Cap	Paracetamol + Pamabrom * + Pyrilamine **	500 mg + 25 mg + 15 mg
Pamprin PMS®	Tab, Cap	Paracetamol + Pamabrom + Pyridoxine	500 mg + 25 mg + 50 mg

*** Pamabrom** is a diuretic. ** **Pyrilamine** is an antihistamine.

9.3- B) Special analgesic combinations: (may be useful for Neuropathic pain)

Trade name	Dosage form	Scientific name(s)	concentration
Difen B_{12}®	Tab	Diclofenac K + Betamethasone + Cyanocobalamin (Vit. B_{12})	50 mg + 0.3 mg + 5 mg
	(Amp + Vial) To be Mixed	Diclofenac K + Betamethasone + Hydroxocobalamin (Vit. B_{12})	75 mg + 2.63 mg + 10 mg
Dioxaflex B_{12}®, Panclo B_{12}®, Rodinac B_{12}®	Tab	Diclofenac Na + Betamethasone + Cyanocobalamin (Vit. B_{12})	50 mg + 0.3 mg + 5 mg
	1 Amp (only)	Diclofenac Na + Betamethasone + Hydroxocobalamin (Vit. B_{12})	75 mg + 2 mg + 10 mg
Difen Flex®, Oxadisten®	Tab	Diclofenac Na + Pridinol*	(50 mg + 4 mg)
	Amp	Diclofenac Na + Pridinol*	(75 mg + 2.2 mg)
Mio Virobron®, Bronax Flex®	Tab	Meloxicam + Pridinol*	15 mg + 4 mg
Tremecox®	Cap	Meloxicam + Gabapentin*	15 mg + 300 mg
Dorsal®	Tab	Meloxicam + Carisoprodol*	15 mg + 100 mg
Flexicamin®	Tab	Piroxicam + Carisoprodol*	10 mg + 350 mg
Flexicamin B_{12}®, Flogiatrin B_{12}®	Tab	Piroxicam + Carisoprodol* + Dexamethasone + Vit. B_6 + Vit. B_{12} (Hydroxo B_{12})	10 mg + 350 mg + 1 mg + 150 mg + 2.5 mg
	(2 Amp) To be mixed	Piroxicam + Dexamethasone + Vit. B_6 + Vit. B_{12} (Hydroxocobalamin)	(20 mg) Piroxicam only Amp (2 mg + 250 mg + 10 mg)
Pirocomplex®	Amp	Piroxicam + Prednisolone + Hydroxocobalamin	20 mg + 7.5 mg + 10 mg
Delta-Tomanil B_{12}	Tab	Diclofenac Na + Prednisolone + Cyanocobalamin	50 mg + 1.25 mg + 2.5 mg
	Amp	Diclofenac Na + Prednisolone + Hydroxocobalamin	75 mg + 7.5mg + 10 mg
Buta-Rut B_{12}®	Tab	Piroxicam + Vit. B_{12}	20 mg + 0.5 mg

Dolotol 12®	(Amp + Vial)	Aspirin Lysine + Glycine + Lidocaine Hydrochloride + Vit. B_1 + Vit. B_{12} + Vit. B_6	1.8 mg + 200 mg + 30 mg + 100 mg + 1 mg + 100 mg
Diclo-Neurobion®	(2 Amp) To be mixed	(Diclofenac Na + Vit. B_{12}), (Vit. B_1 + Vit. B_6 + Lidocaine)	(75 mg + 5 mg) (100 mg + 100 mg + 20 mg)
Caditar Flex®	Tab	Celecoxib + Orphenadrine *	200 mg + 25 mg
Lyca-C®	Cap	Celecoxib + Pregabalin	200 mg + 75 mg
Lavica-M plus®	Cap	Celecoxib + Pregabalin + Vit. B_{12}	200 mg + 75 mg + 750 mcg
Nucoxia-P®	Tab	Etoricoxib + Paracetamol	60 mg + 500 mg
Cilonerve®, Neurobem®, Neurocoxib®	Tab , Cap	Etoricoxib + Pregabalin *	90 mg + 75 mg
Prega Plus®, Atox P®	Tab	Etoricoxib + Pregabalin + Vit. B_{12}	90 mg + 75 mg + 750 mcg
Nucoxia-MR®	Tab	Etoricoxib + Thiocolchicoside *	(60mg + 4mg),(60mg + 8mg)
Gabamin®	Tab	Gabapentin + Mecobalamin (B_{12})	300 mg + 500 mcg
Nidesef®	Cap	Gabapentin + Tramadol	300 mg + 25 mg

*** Carisoprodol** and **Pridinol** are **Muscle relaxants,** (Centrally acting).
*** Orphenadrine** and **Thiocolchicoside** are **muscle relaxants** (see below)**.**
*** Gabapentin** and **Pregabalin** are anticonvulsants that used for **neuropathic pain**.

9.4- Muscle Relaxants

1. Muscle spasm is the involuntary, painful contraction of a muscle or a group of muscles that can **stiffen an arm or leg** or make it almost impossible to straighten the back.
- There are various causes: it can follow an injury, or come on without warning; it may also be brought on by a disorder like osteoarthritis, as the pain in the affected joint triggering abnormal tension in a nearby muscle.
- **Lower limbs (legs) muscle spasms are commonly mistaken with DVTs** (deep vein thrombosis); in such cases (pain in the gulf or lower extremities); DVT should be ruled out first before starting any muscular relaxant.

Table 1. Difference Between Spasticity and Spasms

Description	Spasticity[4,10,13]	Spasms[3,5]
Definition	• Velocity-dependent increase in muscle tone caused by the increased excitability of the muscle stretch reflex	• Involuntary muscle contractions
Etiology	• Central • Disorder of upper motor neurons	• Peripheral • Muscle sprain or injury • Nerve compression (eg, spinal stenosis)
Symptoms	• Stiffness • Hypertonicity • Hyperreflexia	• Jerks • Twitches • Cramps
Causes	• Multiple sclerosis • Cerebral palsy • Spinal cord injury • Traumatic brain injury • Motor neuron disease • Post-stroke syndrome	• Musculoskeletal pain • Fibromyalgia • Sciatica • Mechanical low back pain • Herniated disk • Spinal stenosis • Myofascial pain
FDA-approved agents[a]	• Botulinum toxin[b] • Baclofen • Dantrolene[c] • Diazepam[d] • Riluzole[e] • Tizanidine	• Carisoprodol • Chlorzoxazone • Cyclobenzaprine • Metaxalone • Methocarbamol • Orphenadrine

2. **Muscle Relaxants** are group of drugs which affects **skeletal muscle** function and decreases the muscle tone; they may be used to alleviate symptoms such as **muscle spasms, pain, reduce spasticity** in a variety of neurological conditions and in hyperreflexia.
3. **These drugs do not act directly on the muscles; rather they act centrally (in the brain)** and are more of a total body relaxant, they generally **work by either enhancing the level of inhibition, or reducing the level of excitation**, Inhibition is enhanced by mimicking or enhancing the actions of endogenous inhibitory substances, such as GABA.
   - Because of the enhancement of inhibition in the CNS, most spasmolytic agents have the side effects of **sedation, drowsiness** and may cause **dependence** with long-term use**;** several of these agents also have **abuse potential.**
   - Muscle relaxants are very powerful drugs which may produce negative effects, including heart failure and paralysis.
4. They include: **Baclofen, Tizanidine, Dantrolene, Methocarbamol, Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Tolperisone** and **Orphenadrine.**
5. **(Diazepam, Gabapentin,** and **Pregabalin)** all have muscular relaxant activity.

Scientific name	D. form	Trade name	concentration
Baclofen	Tab	Lioresal® , Lioraz ®	10 mg , 25 mg
	Intrathecal Inj.	Gablofen®	500 mcg/ml , 1000 mcg/ml 2000 mcg/ml
Tizanidine	Tab	Sirdalud® , Zanaflex®	2 mg , 4 mg
Chlorzoxazone	Tab	Lorzon®	375 mg , 500 mg , 750 mg
Cyclobenzaprine	Tab	Flexeril® , Amrix®	5 mg , 7.5 mg , 10 mg
	Cap	Fexmid®	15 mg , 30 mg
Dantrolene	Cap	Dantrium®	25 mg , 50 mg , 100 mg
	Inj. Powder	Revonto®	20 mg
Metaxalone	Tab	Skelaxin®	800 mg
Thiocolchicoside	Tab , Cap	Coltramyl®, Muscoril®, Muscoflex	4 mg
Methocarbamol	Tab	Robaxin®	500 mg , 750 mg
	Inj. Solu.		100 mg/ml
Orphenadrine	Tab	Norflex®	100 mg
	Amp	Norflex®	30 mg/ml
Tolperisone	Tab	Mydocalm®	150 mg
Pridinol	Tab	Blokium®	4 mg
Eperisone	Tab	Myonal®	50 mg
Carisoprodol	Tab	Soma®	250 mg , 350 mg

Extra Notes:

1. When **Baclofen** is administered by **intrathecal Injection,** it may cause CNS depression accompanied with cardiovascular collapse and respiratory failure.
2. **Tizanidine** can be very strong even at the 2 mg dose and **may cause hypotension**, so caution is advised when it is used in patients who have a history of orthostatic hypotension.
3. **Orphenadrine** is an **anticholinergic drug**; it is closely related to **diphenhydramine (antihistamine),** thus used against pain and muscle spasm of various etiologies.
   - May have a **slight Euphoria effect (mood enhancement):** thus some countries started to withdraw it from its public markets**, it's useful in Neuropathic pain.**
4. **Eperisone** acts by **relaxing both skeletal muscles and vascular smooth muscles.**
5. **Carisoprodol** is a potent centrally acting skeletal muscle relaxant; causes heavy sedating, relaxant, and anxiolytic effects; thus, it can produce psychological and physical dependence; it **has been taken off in some markets due to problems with dependence, abuse and side effects.**
   - **Abused** by many addicts in our market. (Don't give by Hand)

Note1: Muscle Relaxants Combinations:

Trade name	D. form	Scientific name(s)	concentration
Norgesic®, Kanagesic® Myogesic®, Muscerol®	Tab	Paracetamol + Orphenadrine	450 mg + 35 mg
Norgesic Forte®	Tab	Orphenadrine + Aspirin + Caffeine	(25 mg + 385 mg + 30 mg), (50 mg + 770 mg + 60 mg)
Myolgin®, Relaxon® Paraxone®	Cap	Paracetamol + Chlorzoxazone	300 mg + 250 mg
Myofen®	Cap	Ibuprofen + Chlorzoxazone	200 mg + 250 mg
Flexofan®	Cap	Ketoprofen + Chlorzoxazone	50 mg + 250 mg
Leodex Plus®	Tab	Dexketoprofen + Thiocolchicoside	25 mg + 4 mg
Dolozox®	Tab	Paracetamol + Diclofenac K + Chlorzoxazone	325 + 50 mg + 250 mg
Relaxofine®	Tab	Ibuprofen + Nimesulide + Chlorzoxazone	200 mg + 100 mg + 250 mg
Dimra®	Tab	Diclofenac K + Methocarbamol	50 mg + 500 mg
Distem®	Tab	Paracetamol + Methocarbamol	300 mg + 380 mg
Somadril®	Tab	Paracetamol + Caffeine + Carisoprodol	160 mg + 32 mg + 200 mg
Soma Forte®	Tab	Carisoprodol + Aspirin + Codeine	200 mg + 325 mg + 16 mg

Note2: Orphenadrine or Chlorzoxazone

Which one of these common muscle relaxants is better than the other?

- **Orphenadrine** has an additional **analgesic effect**; (plus its muscle relaxant effect); although side effects are like diphenhydramine's antihistaminic and anticholinergic effects, including dry mouth, blurred vision, and urinary retention; (thus not preferred in elderly pt. and Glaucoma).
  - Onset of Action is 1 hour; duration is about 6 hours.
- **Chlorzoxazone** muscle relaxant effect is related to its **sedative properties**; it acts primarily at the level of the spinal cord and subcortical areas of the brain; (thus preferred in pt. with anxiety).
  - Onset of Action is 0.5 – 1 hour; duration is about 3 – 4 hours.

Note3: Tolperisone & European Medicines Agency (EMA) [10]

1. The EMA has recommended **restricting the use of Tolperisone**; After review and a subsequent re-examination in 2012, the Agency concluded the **safety and adverse reaction risks of this drug outweigh the benefits**, and that there is **weak support for its efficacy**, in all but one indication (muscle stiffness or spasticity after stroke), and specifically, due to the prevalence of hypersensitivity symptoms such as flushing, rash, severe skin itchiness (with raised lumps), wheezing, difficulty breathing, and swallowing, fast heartbeat and fast decrease in blood pressure (basically anaphylaxis).
2. Their recommendations included **ceasing advertising in Europe and ceasing injections**, updating patient information leaflets, changing to another medicine for existing users, and for prescribers to only use it stroke patients when administered by mouth, not injection.

Note4: Botox for muscle spasms

1. **Botulinum Toxin** (BTX) is produced from Clostridium botulinum and is injected locally to **inhibit presynaptic release of Acetylcholine** (Ach) in the neuromuscular junction, resulting in paralysis of the muscle; the onset of effect varies depending on the indication but is typically 14 days for spasticity and cervical dystonia, the effect typically lasts approximately 3 months.
2. The effect diminishes when motor neurons develop new nerve terminals that start releasing Ach; resistance to the paralytic effect could develop with repeated injections due to development of antibodies against the toxin.
3. Adverse effects include rash and muscle weakness at the injection site and flu-like symptoms.

9.5- Neuropathic pain

1. Neuropathic pain occurs as a result **of damage to neural tissue**; it may be continuous and/or episodic (paroxysmal); Neuropathic pain may be divided into **peripheral neuropathic pain**, **central neuropathic pain**, or **mixed** (peripheral and central).

2. Central neuropathic pain is found in spinal cord injury, multiple sclerosis and some strokes; Aside from diabetes (diabetic neuropathy) and other metabolic conditions, the common causes of painful peripheral neuropathies are herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, and toxins.
   - Neuropathic pain is common in cancer as a **direct result of cancer** on peripheral nerves (e.g., compression by a tumor), or as a **side effect of chemotherapy** (chemotherapy-induced peripheral neuropathy)

3. **Fibromyalgia** is a neuropathic disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood issues. Researchers believe that fibromyalgia amplifies painful sensations by affecting the way brain processes pain signals.
   - Only 3 drugs are FDA approved for the treatment of Fibromyalgia: (**Pregabalin**, **Duloxetine** and **Milnacipran**. (for more info on Fibromyalgia see chapter 10, section 7)

4. Neuropathic pain can be **very difficult to treat, with only some 40-60% of patients achieving partial relief;** it is generally managed with a tricyclic antidepressant as (**Amitriptyline**) or with certain antiepileptic drugs (**Gabapentin, Pregabalin** and **Carbamazepine**), or with SSRIs as (**Paroxetine**, **Fluoxetine**, **Citalopram**), and SNRIs antidepressants as **(Duloxetine**, **Venlafaxine)**. [2] (see chapter 4 for more info)
   - **Duloxetine** is recommended as a first line agent for the **treatment of chemotherapy-induced neuropathy** by the American Society of Clinical Oncology.

5. Neuropathic pain may respond to **Opioid analgesics (Narcotics)**; especially **Tramadol** and **Oxycodone** (centrally-acting narcotic analgesics); they are combined with other treatments when patients do not respond to first-line treatments.

6. Some Doctors also use **vitamin B-Complex** as 2ndry supplement for relieving neuropathic pain (**especially Vit. B_{12}**); although it's useful only in neurological diseases caused by its deficiency.

7. **Alpha Lipoic acid** (**ALA**) supplements can help with neuropathy (nerve damage) caused by diabetes or cancer treatment; it seems to reduce symptoms like pain, tingling, and prickling in the feet and legs, when given at a dosage of 600 mg once daily over a period of three weeks, it leads to a significant and clinically relevant reduction in neuropathic pain. [11]

8. In neuropathies, both neurons and Schwann cells may be affected; the involvement of Schwann cells causes demyelination of the axons, which leads to the failure of nerve transmission, Axon functionality is recovered through the remyelination process, where the synthesis of phospholipids and sphingolipids plays a crucial role; **Nucleotides** such as **CMP (Cytidine monophosphate)** and **UMP (Uridine monophosphate)** are basic substrates in the synthesis of these compounds and exogenous supplementation of CMP and UMP ensures the proper supply of substrates required to enable regenerative processes to accelerate.

9. **Topical drugs for Diabetic Neuropathy (DN):**
   - **Topical Capsaicin**: is the topical treatment used most often in painful DN, it produces the activation and subsequent P substance depletion of C fiber nerve endings; Multiple controlled studies collected in a meta-analysis have shown that the topical application of Capsaicin is effective in the treatment of pain related to DN.
   - **Topical Nitrates**: the application of an **Isosorbide Dinitrate spray** or **Isosorbide Trinitrate patches** have been shown to decrease the pain and burning associated with DN.

Antiepileptic drugs			
Scientific name	Dosage form	Trade name	concentration
Gabapentin	Cap	Neurontin® , Gabamed®	100 mg , 300 mg , 400 mg
Pregabalin	Cap	Lyrica®	75 mg , 150 mg
Carbamazepine	Tab , Tab ER	Tegretol® , Taver® , Tegral®	200 mg , 400 mg
Tricyclic antidepressants (TCAs)			
Amitriptyline	Tab	Deprezole®, Elavil® , Levate®	10 mg , 25 mg , 50 mg
Imipramine	Tab , Cap	Tofranil®	10 mg , 25 mg & 75 mg
Clomipramine	Tab , Cap	Anafranil®	25 mg , 50 mg
Maprotiline	Tab	Ludiomil®	25 mg , 50 mg , 75 mg
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Fluoxetine	Cap	Prozac®	20 mg , 40 mg
	Cap DR	Sarafem®	90 mg
Paroxetine	Tab	Seroxat® , Paxil® , Pexeva®	10 mg , 20 mg , 40 mg
	Cap	Seroxat CR®	30 mg
Citalopram	Tab	Celexa® , Cipramil®	10 mg , 20 mg , 40 mg
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)			
Duloxetine	Cap , Cap CR	Cymbalta®	30 mg , 60 mg
Venlafaxine	Tab	Effexor®	25 mg , 50 mg
	Cap	Effexor XR®	75 mg , 150 mg
Narcotics (Opioids)			
Tramadol	Tab , Cap	Tramal® , Ultram® , Topalgic®	50 mg , 100 mg , 200 mg
	Inj. (Amp)	Zydol®, Trabar®	50 mg/ml , 100 mg/2 ml
Oxycodone	Tab	Roxicodone® , Oxecta®	10 mg , 15 mg , 20 mg , 30

Nucleotides + Combinations			
Cytidine + Uridine	Cap	**Nucleo CMP®**	5 mg + 1.33 mg
	Amp		10 mg + 6 mg
Uridine + Folic acid + Vit. B_{12}	Cap	Keltican®	75 mg + 0.4 mg + 3 mcg
Uridine + Vit. B_{12} + L-Methylfolate + Pyrroloquinoline + Magnesium	Tab	**Neural Plactive®**	200mg + 2.5mcg + 400mcg + 20 mg + 56 mg
Uridine + Folic acid + Vit. B_1 + Vit. B_3 + Vit. B_6 +Vit. B_{12}	Tab	**Biolevox Neuro®**	50 mg + 400 mcg +4mg + 20mg + 6mg + 10mcg
Cytidine + Uridine + Folic acid + Alpha Lipoic acid + Vit. B_1 + B_3 + Vit B_6 + B_{12} + N-Acetyl Cysteine	Tab	**Axonal®**	50 mg + 30 mg + 400 mcg + 200 mg + 58 mg + 20 mg + 58mg + 100mcg + 300mg

Other Drugs for Neuropathy			
Alpha Lipoic acid	Cap	Lipoic Forte®	600 mg
	Tab	ALA®	100 mg , 200 mg
Capsaicin	Cream	Zostrix® , Sorex®	0.025% , 0.075%
Isosorbide Dinitrate	Spray	Isoket®	1.25 mg/spray
Isosorbide Trinitrate	Patch	Deponit®	5 mg , 10 mg

Note1: Vit. B_{12} comes in 3 types:

Scientific name	D. form	Trade name	concentration
Cyanocobalamin	Tab	Cobalamine®	100 mcg , 250 , 500 , 1000 mcg
	Amp	Cobalamine®	1000 mcg/ml
	Amp (Oral)	B_{12} Gerda®	1000 mcg/4 ml

Cyanocobalamin	Oral Vial	Maddovit B_{12}®	25 mcg/7 ml
	Nasal Spray	Nascobal® , CaloMist®	25 mcg/spray
Methylcobalamin	Amp	Methycobal®	500 mcg
	Tab	Methycobal®, Mecobalamine®	250 mcg , 500 mcg
Hydroxocobalamin	Amp	Cobalin-H®	1000 mcg/ml
	Vial	Cyanokit®	5 gm/vial

Notes:

1. **Cyanocobalamin** turns inside the body to **(Methylcobalamin)** then to **(Hydroxocobalamin) which is the active form of B_{12}**
   a. **Methylcobalamin** ampule and tablets should be protected from light and moisture, (Light decreases the active ingredient content and may turn reddish with exposure to moisture.)
   b. **Cyanocobalamin** is the least expensive and least painful type at the injection site, and is used once a week **I.M. ONLY**, but it is the least efficient.
2. **Methylcobalamin,** also called **(Mecobalamin);** is **more efficient than Cyanocobalamin** because it does not need to switch to another form inside the body.
   a. It has a better absorption profile.
   b. More painful at the injection site and **can be given I.M, I.V.**
   c. **The best choice for smokers,** due to their inability to convert **Cyanocobalamin** to **Methylcobalamin** because of the presence of the heavy metals & toxins in the liver.
   d. Its methyl group stimulates Serotonin production in CNS; (thus has a mood supporting effect).
   e. High doses can be effective in the treatment of Multiple Sclerosis.
3. **Hydroxocobalamin** is the most bioactive form, and is the most type commonly used.
   a. It's better to be given I.V., due to its very painful at injection site unless mixed with local anesthetic, stay inside the body for a longer period, which reduces the no. of injections.
   b. The (5 gm vial) is used in the treatment of Cyanide poisoning as I.V infusion.

Note2: Special combinations for Neuropathic Pain:

Trade name	D. form	Scientific name(s)	Concentration
Neurobion® (merck)	Tab	Vit. B_1 + Vit. B_6 + Vit. B_{12}	100 mg + 200 mg + 200 mcg
	Amp	Vit. B_1 + Vit. B_6 + Vit. B_{12}	(100mg+100mg+1mg)/3 ml
Neurorubin® (Acino)	Tab	Vit. B_1 + Vit. B_6 + Vit. B_{12}	200 mg + 50 mg + 1000 mcg
	Amp	Vit. B_1 + Vit. B_6 + Vit. B_{12}	(100mg+100mg+1mg)/3 ml
Ancopir®	Tab	Vit. B_1 + Vit. B_6 + Vit. B_{12}	200 mg + 100 mg + 0.3 mg
	Amp	Vit. B_1 + Vit. B_6 + Vit. B_{12} + Lidocaine	200 mg + 50 mg + 1 mg + 10 mg (per 2 ml)
Benexol B_{12}®, Apikobal®	Tab	Vit. B_1 + Vit. B_6 + Vit. B_{12}	250 mg + 250 mg + 1 mg
Livabion®	Amp	Vit. B_1 + Vit. B_6 + Vit. B_{12} + Folic Acid + Nicotinamide	5 mg + 4 mg + 2500 mcg + 1 mg + 20 mg
Inzitan®	Amp	Dexamethasone + Vit. B_{12} + Vit. B_1 + Lidocaine	4 mg + 250 mcg + 50 mg + 60 mg (per 2 ml)
Gavindol®	Tab	Gabapentin + Vit. B_1 + Vit. B_{12}	300 mg + 100 mg + 20 mcg
Dicloneurovit forte®	Tab	Diclofenac + Vit. B_1 + B_6 + B_{12}	50 mg + 50 mg + 50 mg + 1 mg
Beneday®, Apikobal Plus®	Tab	Vit. B_1 + Vit. B_6 + Vit. B_{12} + Alpha Lipoic acid	250 mg + 250 mg + 1 mg + 300 mg

Notes:

1. **Neurobion®, Neurorubin®** are also indicated for muscle soreness and back pain with unknown etiology, and as an adjuvant in the treatment of neurotic pain (acute or chronic neuritis & polyneuritis); They **both should not be used as a replacement therapy** for Vitamin B deficiency, or deficiency due to pregnancy or malnutrition; because their concentrations are at the super-therapeutic doses range.
2. **Inzitan®** Indications include: myalgia, neuralgia, neuritis.

9.6- Rubefacients, Topical NSAIDs, and Capsaicin:

1. They may provide some relief of **pain in musculoskeletal conditions;** they act by causing dilation of the capillaries and an increase in blood circulation.
2. **Rubefacients** include: **Oil of Wintergreen, Methyl Salicylate, Eucalyptus Oil, Menthol** and **Capsaicin.**
3. **Topical NSAIDs** include: **Diclofenac Na⁺, Ibuprofen, Ketoprofen, Piroxicam, Etofenamate, Indomethacin, Felbinac, Trolamine** or **(Triethanolamine)** and **Nimesulide.**
4. **Camphor** is readily absorbed through the skin and produces a feeling of cooling similar to that of menthol, and acts as **slight local anesthetic** and **antimicrobial substance**. There are anti-itch gels and cooling gels with camphor as the active ingredient. Camphor is an active ingredient (along with menthol) in vapor-steam products.
5. **Capsaicin** is the active component of chili peppers, produces a sensation of burning in any tissue with which it comes into contact**; it is used as an analgesic** in topical ointments, and dermal patches to relieve pain.

Topical NSAIDs			
Scientific name	D. form	Trade name	concentration
Diclofenac Na⁺	Skin Gel	Voltarin®, Voltamed®	10 mg/gm (50 gm tube)
	Patch	Olfen®	
	Spray	Voltarin®	1% (75 ml)
Ibuprofen	Skin Gel	Ibugel® , Fenbid®	10% (100 gm tube)
Ketoprofen	Skin Gel	Profenid Gel® , Fastum®	2.5% (60 gm tube)
Piroxicam	Skin Gel	Felden Gel® , Picam®	5 mg/gm (60 gm tube)
Nimesulide	Skin Gel	Sulide®	50 mg/1 gm (20 gm tube)
Indomethacin	Spray	Elmetacin®	1%
Etofenamate	Skin Gel	Dolo-Denk Gel®	10% (20 gm tube)
Idrocilamide	Cream	Srilane®	5%
Felbinac **	Gel	Traxam®	3%
Trolamine **	Cream	Aspercreme®	10%
Combination Products			
Diclofenac + Pridinol*	Cream	Oxadisten®	1.45% + 0.34% (100 gm tube)
Diclofenac + Capsaicin	Cream	Diclofex DC®	1.5% + 0.025 %
Diclofenac + Menthol + Methyl Salicylate + Linseed Oil	Gel	Divon®, Relief G®	1.16% + 5% + 10% + 3%

* **Pridinol** is a muscle relaxant.

** **Felbinac = Biphenyl Acetic Acid = Biphenylylacetic Acid,** they are all the same drug.

** **Trolamine = Triethanolamine**, they are the same drug.

Topical Rubefacients			
Trade name	D. form	Scientific name(s)	concentration
Moov®	Gel , Spray	Menthol + Oil of Wintergreen + Camphor + Eucalyptus Oil	10% + 3% + 11% + 2%
Rheumalgin®	Cream	Methyl Salicylate + Menthol + Turpentine Oil + Camphor + Capsicum + Peppermint Oil	15 gm + 1 gm + 1 gm + 1 gm + 0.5 gm + 2 gm (per 100gm)
Deep Heat®	Cream	Methyl Salicylate + Menthol + Eucalyptus Oil + Turpentine	12.8% + 5.91% + 1.97% + 1.47%

Arthi-Flex®	Cream	Menthol + Eucalyptus Oil	4% + 1%
Directol Super Heat®	Gel	Menthol + Eucalyptus Oil + Capsicum + Gaultheria Oil	2.5% + 0.5% + 0.125% + 8%
Directol Super Ice®	Gel	Menthol + Eucalyptus Oil	2% + 0.5%
Radian®	Cream	Menthol + Camphor + Methyl Salicylate + Capsicum	2.54% + 1.43% + 0.42% + 0.005%
Muscle Rub®	Cream	Menthol + Methyl Salicylate	1% + 15%
Thera-Gesic®	Cream	Menthol + Methyl Salicylate	1% + 15%
Thera-Gesic Plus®	Cream	Menthol + Methyl Salicylate	4% + 25%
Rubicalm®	Cream	Diethylamine Salicylate + Menthol + Chlorbutol	12 gm + 0.1 gm + 0.5 gm
Joint-Flex®	Gel	Camphor + Other Non-Medical Subs.	3.1%

Note: Other Topical products for Pain Relief:

Trade name	D. form	Scientific name(s)	concentration
Reparil N®	Gel	Aescin + Diethylamine Salicylate	1 gm + 5 gm
Arceclox®	Cream	Celadrin + Menthol	7.5% + 1.25%
Gothaplast®	Plaster	Nonivamide	2.43 mg
Jointace Gel®	Gel	Glucosamine + Chondroitin + Menthol + Eucalyptus Oil + Other Oils	Blend of 40 gm tube

Notes:

1. **Diethylamine salicylate** (derivative of salicylic acid); has anti-inflammatory and painkilling actions acts as a counter-irritant.
2. **Aescin** is the main active component in horse chestnut, it has anti-inflammatory, vasoconstrictor and Vasoprotective effects; It induces endothelial nitric oxide synthesis by making endothelial cells more permeable to calcium ions, and also induces release of prostaglandin.
3. **Arceclox®** is also found as soft gel Capsules for the treatment of **Osteoarthritis.**
4. **Nonivamide** is a synthetic analogue of **Capsaicin** that is used in topical preparations for the relief of muscular and rheumatic pain; **Nonivamide** has also been used as a food flavor and in (pepper sprays) for law enforcement and self-defense.

9.7- Opioid Antagonists:

1. **Naloxone** and **Naltrexone** are commonly used opioid antagonist drugs which are competitive antagonists that bind to the opioid receptors with higher affinity than agonists but do not activate the receptors; this effectively blocks the receptor, preventing the body from responding to opiates and endorphins, **used in opioid dependence, alcohol withdrawal, and to reverse coma and respiratory depression with opioid overdose.**
   - **Naloxone** cannot be absorbed orally.
   - **Naltrexone** is active orally and has a longer duration of action than **Naloxone.**

Scientific name	Dosage form	Trade name	concentration
Naltrexone	Tab	Revia® , Depade®	50 mg
	Inj. (I.M.)	Vivitrol®	380 mg
Naloxone	Inj. (Vial)	Narcan®	0.4 mg/ml , 1 mg/mL
Nalmefene	Tab	Selincro®	18 mg
	Inj.	Revex®	1 mg/ml (10 ml)
Naloxone + Buprenorphine	Tab (sublingual)	Suboxone®	(0.5 mg + 2 mg) , (1 mg + 4 mg) , (2 mg + 8 mg)

9.8- Anti-Migraine drugs (6)

1. **Migraine** is a term applied to recurrent severe headaches affecting only one side of the head and probably caused by changes in the blood vessels around the brain and scalp; it may be **accompanied by nausea and vomiting** and preceded by warning signs, usually an impression of **flashing lights** or **numbness and tingling in the arms**, also the speech may be impaired.
2. The underlying cause of migraine is uncertain, but an attack may be triggered by a blow to the head, physical exertion, certain foods and drugs, or emotional factors such as excitement, tension, or shock; a family history of migraine also increases the chance of an individual suffering from it.
3. The symptoms of a migraine attack begin when blood vessels surrounding the brain constrict, producing the typical migraine warning signs (The constriction is thought to be due to certain chemicals found in food or produced by the body); The neurotransmitter serotonin causes large blood vessels in the brain to constrict.
   - **Pizotifen** and **Propranolol** block the effect of chemicals on blood vessels, preventing attacks.
4. The next stage of a Migraine attack occurs when blood vessels in the scalp and around the eyes dilate (widen); and as a result, chemicals called prostaglandins are released, producing pain.
   - **NSAIDs** and **Paracetamol** relieve this pain by blocking prostaglandins.
   - **Codeine** acts directly on the brain, altering pain perception
   - **Ergotamine** and **5HT1 agonists (Triptans)** relieve pain by narrowing dilated blood vessels.
5. **Analgesic rebound headache:** If patients use analgesics often (usually defined as more than 3 times weekly), they can develop analgesic rebound headache, Patients with this condition usually present with a chronic daily headache, for which they take simple or narcotic analgesics.
   - Treatment consists of the withdrawal of all analgesics (but not prophylactic medications).

A) Treatment of Acute Migraine

1. Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks, a simple analgesic such as **Aspirin, Paracetamol** (preferably in a soluble or dispersible form) or a **NSAIDs** is often effective.
   - The NSAID **Tolfenamic acid** is licensed specifically for the treatment of an acute attack of migraine; **Diclofenac K^+, Flurbiprofen, and Ibuprofen** are also licensed for use in migraine.
2. **Peristalsis is often reduced during Migraine attacks;** thus, the medication may not be sufficiently well absorbed to be effective; and that's why dispersible or effervescent preparations are therefore preferred.
3. Concomitant **anti-emetic treatment may be required** (as Cyclizine in Migril®), due to Migraine attack is usually associated with nausea).
4. If treatment with an analgesic is inadequate, an attack may be treated with a specific anti-migraine compound such as a 5HT1-receptor agonist (Triptan); like **Sumatriptan**.
5. The **value of Ergotamine** for migraine is **limited by its side-effects**; it is best avoided.
   - To avoid habituation, the frequency of administration of ergotamine should be limited to no more than twice a month; **It should never be prescribed prophylactically** but in the management of cluster headache a low dose.
6. **Triptans** and **Ergotamine** are **contra-indicated in ischemic heart disease, previous myocardial infarction, coronary vasospasm** (including Prinzmetal's angina), and uncontrolled or severe hypertension.
   a. Also C.I. in **pregnancy, Epilepsy, renal** and **hepatic impairment.**
   b. **Triptans** and **Ergotamine** should not be administered **within 24 hours** of each other.
   c. **Triptans** should not be given with **(Cabergoline, Bromocriptine),** co-administration will lead to **life threatening Vasospasm.**
   d. **Propranolol** increases serum concentrations of **Rizatriptan**; thus, a 5-mg dose should be used with propranolol, and the dose should not exceed 15 mg/day.

7. **The maximum recommended doses of Ergotamine preparations should not be exceeded** (they should not exceed the maximum dose per attack, the maximum dose per day as well as the maximum dose per week).
   a. **Excessive use of acute treatments for migraine** (opioid and non-opioid analgesics, 5HT1 receptor agonists, and ergotamine) is associated with **medication-overuse headache (analgesic-induced headache)**; therefore, increasing consumption of these medicines needs careful management.
   b. **Ergotamine** preparations can **cause dry gangrene of hand and feet,** also may **cause coronary vasospasm, (thus they are C.I. in patients with heart diseases).**
8. Orally disintegrating tablets are available for **Zolmitriptan** and **Rizatriptan** if patients do not have access to water; however, **they do not work faster** than oral tablets and are not absorbed sublingually. (12)
   - Triptans Dose may be repeated after 2 hours, don't use more than 2 doses within 24 hours.
   - Its not recommended to use Triptans more than 2-3 days each week.
9. **Butorphanol** is indicated for **Sever Migraine Pain**, using the intranasal spray formulation.
10. The FDA approved a new drug (**Lasmiditan**) for the acute (active but short-term) treatment of migraine with or without aura (a sensory phenomenon or visual disturbance) in adults; **Lasmiditan** is not indicated for the preventive treatment of migraine.

Scientific name	Dosage form	Trade name	concentration
Butorphanol	Inj. Solu.	Stadol®	1 mg/ml , 2 mg/ml
	Nasal Spray		10 mg/ml

5HT1-receptor agonist (Triptans)				
Scientific name	Dosage form	Trade name	concentration	**Max Day Dose**
Sumatriptan	Tab	Imitrex® , Imigran®	25 mg , 50 mg , 100 mg	Tab = 200 mg Inj. = 12 mg Nasal = 20 mg
	Inj. (S.C.)	Sumavel®	4 mg/0.5 ml , 6 mg/0.5 ml	
	Inj. Auto	Sumavel DosePro®	4 mg/0.5 ml , 6 mg/0.5 ml	
	Nasal Spray	Imitrex®	(5 mg , 20 mg)/actuation	
	Skin Patch	Zecuity®	6.5 mg / 4 hr.	
Zolmitriptan	Tab	Zomig®, Zomitan®	2.5 mg , 5 mg	Tab = 10 mg Nasal = 10 mg
	Nasal Spray		(2.5 mg , 5 mg)/spray	
Almotriptan	Tab	Almogran® , Axert®	6.25 mg , 12.5 mg	Tab = 25 mg
Eletriptan	Tab	Relpax®	20 mg , 40 mg	Tab = 80 mg
Frovatriptan	Tab	Frova® , Migard®	2.5 mg	Tab = 7.5 mg
Naratriptan	Tab	Amerge®, Naramig®	1 mg , 2.5 mg	Tab = 5 mg
Rizatriptan	Tab	Maxalt®	5 mg , 10 mg	Tab = 30 mg
	Melt Wafers		10 mg	
Lasmiditan	Tab	Reyvow®	100 mg , 200 mg	Tab = 200 mg

* **Frovatriptan** has the highest half-life (26 hours), compared with other Triptans (1-4 hours).

Ergotamines				
Scientific name	Dosage form	Trade name	concentration	**Max Dose**
Ergotamine	Tab	Cafergot®, Megral®	1 mg	6 mg/day 10 mg/week
	Subling. Tab	Bellergal S®	2 mg	
Dihydro-Ergotamine	Inj.	DHE®	1 mg/ml	3 mg/day 6 mg/week
	Nasal Spray	Migranal®	0.5 mg/actuation	

B) Prophylaxis of Migraine

1. If the migraine attacks are frequent, preventive treatment for migraine should be considered, drugs that are used for prophylaxis of migraine include**:**
   a) **Beta-blockers** (**Propranolol** is the most commonly used).
   b) **Tricyclic antidepressants** and **antiepileptics** (**Topiramate**, **sodium valproate**, **Valproic acid,** and **gabapentin**) are also effective for preventing migraine.
   c) **Pizotifen** (but it is of limited value and may cause weight gain).
   d) **Clonidine** (not recommended; it can aggravate depression and cause insomnia).
2. **Beta-Blockers (Propranolol, Nadolol, Timolol, Atenolol,** and **Metoprolol)** are the most widely used treatment for prevention of migraine. They are reported to reduce the frequency of attacks by 50% in 60% to 80% of patients; **β-Blockers with intrinsic sympathomimetic activity are ineffective.**
3. **Amitriptyline** appears to be the tricyclic antidepressant (TCA) of choice**,** but **Doxepin, Nortriptyline** have also been used**;** Their beneficial effects in migraine prophylaxis are independent of antidepressant activity and may be related to down regulation of central $5HT_2$ and adrenergic receptors.
4. **Topiramate** is approved by the FDA for **migraine prophylaxis.** The dose is initiated at 25 mg/day and increased slowly to minimize side effects; **Gabapentin** may also have a role in migraine prophylaxis.
5. **Flunarizine** is a drug classified as **a calcium antagonist** which is used for various indications; it's effective in the **prophylaxis of migraine**, **occlusive peripheral vascular disease**, **vertigo of central and peripheral origin**, and as an **adjuvant in the therapy of epilepsy.**
   - It has been shown to significantly **reduce headache frequency and severity** in both adults and children; It's is **contraindicated in patients with depression**, in the acute phase of a stroke, and in patients with extrapyramidal symptoms or Parkinson's disease; It is also contraindicated in hypotension, heart failure and arrhythmia.
6. **Botulinum toxin type A** is licensed for the **prophylaxis of headaches in adults with chronic migraine**; that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse.
7. **All the Migraine Prophylaxis agents are not effective** in relieving migraine attack once it's in progress.
8. **Prophylaxis of cluster headache** is considered if the attacks are frequent, last over 3 weeks, or if they cannot be treated effectively, **Verapamil or lithium** (both unlicensed use) are used for prophylaxis.
9. **Prednisolone** can be **used for short-term prophylaxis of episodic cluster headache** (unlicensed use) either as **monotherapy, or in combination with verapamil** during verapamil titration, the dose of prednisolone for monotherapy or adjunctive therapy is 60-100 mg once daily for 2–5 days followed by a dose reduction of 10 mg every 2–3 days until it is discontinued.
10. A new generation of **monoclonal antibodies** is available for **prophylaxis of migraine**; they are called **calcitonin gene-related peptides (CGRP) antagonists**.
    - During a migraine attack the cerebral nerves and blood vessels release substances including Calcitonin Gene-Related Peptide (CGRP); which is a neuropeptide that has been implicated in different pain processes, including migraine; it also functions as a vasodilator.
    - **CGRP antagonists** acts by inactivating the CGRP molecule (by binding to it), or by blocking its receptor, thus preventing migraine from developing.
    - These include: **Fremanezumab**, **Galcanezumab**, **Erenumab** and **Eptinezumab**; all given by S.C. inj. Once monthly; except **Eptinezumab** which is given by I.V. inj. Once every 3 months.
    - **Rimegepant**; A new **oral CGRP monoclonal antibody** is currently Pending FDA approval.

Drugs for Migraine Prophylaxis			
Scientific name	Dosage form	Trade name	concentration
Pizotifen	Tab	Sandomigraine®	0.5 mg
Propranolol	Tab	Inderal® , Becardin®	10 mg , 40 mg
	Cap	Innopran®	80 mg , 120 mg
	Inj.	Inderal®	1 mg/1 ml
Topiramate	Tab	Topamax®	25 mg , 50 mg , 100 mg
Flunarizine	Tab	Sibelium®	5 mg
Doxepin	Tab , Cap	Sinequan®	10 mg , 25 mg , 50 mg
Clonidine	Tab	Dixarit® , Catapres®	25 mcg
Botulinum Toxin A*	Inj. Powder	Botox®	50 units – 100 – 200 U/vial
CGRP monoclonal antibodies			
Fremanezumab	S.C. inj.	Ajovy®	225 mg/1.5 ml
Galcanezumab	Prefilled inj.	Emgality®	100 mg/ml , 120 mg/ml
Erenumab	Prefilled inj.	Aimovig®	70 mg/ml , 140 mg/ml
Eptinezumab	Inj. Solu.	Pending FDA approval	
Rimegepant	Tab		

* Also called **Onabotulinumtoxina.**

C) Combination products for Migraine

Scientific name	D. form	Trade name	concentration
Ergotamine + Caffeine	Tab	***Migraine®***	1 mg + 100 mg
	Supp.	Migergot®	2 mg + 100 mg
Ergotamine + Cyclizine + Caffeine	Tab	***Migril®***	2 mg + 50 mg + 100 mg
Ergotamine + Belladonna + Caffeine Meprobamate + Phenobarbital	Tab	***Asia Migraine®***	1 mg + 0.1 mg + 50 mg 150 mg + 10 mg
Ergotamine + Caffeine + Paracetamol + Domperidone	Tab	No-Migraine®	1 mg + 100 mg + 250 mg + 10 mg
Ergotamine + Caffeine + Meprobamate* + Analagin (Dipyrone) + Pentobarbital	Tab	Migra-nial®	1 mg + 50 mg + 150 mg + 200 mg + 10 mg
Ergotamine + Caffeine + Belladonna Extract + Paracetamol	Tab	Migranil®	1 mg + 100 mg + 10 mg + 250 mg
Sumatriptan + Naproxen	Tab	Treximet®	85 mg + 500 mg

*** Meprobamate** is an anxiolytic drug.

D) Medical devices that is FDA approved for Migraine

A relatively new concept in treating migraine is using neuromodulation devices instead of traditional headache medications; These devices are sometimes referred to as stimulators, although they often turn down brain activity rather than stimulate it.

Neuromodulation devices can be electrical, temperature-altering, or magnetic, and while they can be portable, some require surgical placement; there are several non-invasive neuromodulation devices that have been approved by the FDA for headache and are no longer considered experimental. Each of them is labeled by the FDA as "minimal risk," meaning no significant side effects are expected.

1. **Transcutaneous Supraorbital NeuroStimulator**: The first neuromodulation device receiving U.S. approval was a Transcutaneous Supraorbital NeuroStimulator (**tSNS**); Also called the **Cefaly** device, it is approved in Europe and Canada, too. This device, now in a smaller, revised stimulator called Cefaly 2, is temporarily placed on the forehead and turned on daily for 20 minutes to prevent migraine. The study leading to FDA approval showed a significant number of migraine patients who wore the device daily for the designated amount of time had at least a 50% decrease in headache days; The Cefaly device electrically activates forehead nerves and creates a buzzing sensation. The signal goes into the brain turning headache pathways down slowly over time. This results in fewer headache days. The Cefaly is currently being studied for whether it might stop migraine acutely on an as-needed basis as well.

2. **SpringTMS**: The second approved device is a **single-pulse transcranial magnetic stimulator**, called **SpringTMS** or **sTMS**, this is a magnet placed on the back of the head and turned on for a split-second pulse, which usually has no side effects. Two pulses of the magnet stopped migraine with aura in around 40% of patients, so the FDA approved it for treating the pain of migraine with aura; sTMS is in its third design, called the "mini," and has also been found to stop the pain of migraine without aura and prevent migraine. sTMS is currently before the FDA to decide if the approved use of the device can be broadened to include migraine prevention. The preventive approach involves pulsing the magnet four times twice a day, plus extra pulses on an as-needed basis. It is already being used for this in the United Kingdom.

3. **GammaCore:** The third FDA approved device is a **non-invasive vagal nerve stimulator** (**nVNS**), called **GammaCore**, and is also approved in Canada and Europe. This device is placed on the neck over a gel and turned on to electrically stimulate the vagus nerve for 90 seconds to two minutes, generally in two cycles, causing mild buzzing and twitching neck sensations. The FDA approved nVNS for stopping the pain of an acute cluster headache attack in patients with episodic cluster headache, and it has also shown promise in preventing cluster headache when given in 2 cycles 3 times per day, and in treating migraine. Further studies are underway exploring its future use.

4. **Nerivio Migra:** The FDA has cleared a noninvasive device to relieve acute migraine pain, **Nerivio Migra** is a "first-in-category product," according to Theranica, the company that makes it; It is worn on the upper arm and uses smartphone-controlled electronic pulses to relieve migraine pain; **The device is for the acute treatment of migraine with or without aura in adults who don't have chronic migraine**, The FDA approved the device on the basis of results of a randomized, double-blind, placebo-controlled study involving 252 patients who had 2-8 migraines per month.

5. **Cerena:** it is intended to be used when a patient feels a headache coming on or when the pain begins. It's the first medical device granted marketing by the FDA to relieve pain caused by migraine headaches that are preceded by an aura.
   - How does it work? Using both hands to hold the device against the back of the head, the patient presses a button to release a very short (less than one second) magnetic pulse to stimulate the brain's occipital cortex (the back part of the brain that processes visual information); Transcranial Magnetic Stimulator (TMS) technology, used in the Cerena device, has been studied for quite some time but has only recently been authorized for use.

6. There are several neuromodulation devices currently being studied, but they are without FDA approval; these include:
   a. **Caloric vestibular stimulator**, called the **Scion device**. The Scion device is worn for 20 minutes once or twice a day as a pair of headphones with small cones in the ears. The device heats and cools the vestibular nerves of the ear and has been shown to prevent migraine by three months of use. A second US study on this device is underway.
   b. There are also neuromodulation devices that require surgical placement and are not yet FDA approved for headache management. In Europe there is the **sphenopalatine ganglion (SPG) stimulator (Pulsante)**, a small device that is placed above the teeth and screwed in as a preventive treatment of cluster headache; This device does not have wires or batteries and cannot be seen when in place. It is activated by a rechargeable, programmable remote controller that the patient turns on and off. It is currently in a 2017 U.S. approval study.
   c. **Occipital nerve stimulators (ONS)** have been studied for prevention of migraine, but with mixed results. These are inserted in the back of the head and require a wire and battery placed in the chest or hip. ONS approval for headache in Europe was withdrawn in 2014 because of side effects.

9.9- Cannabinoid Analgesics

1. These are reserved for symptomatic relief of **neuropathic pain in Multiple Sclerosis** and as adjunctive **analgesic treatment in patients with advanced cancer** who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain, should not be prescribed to any other types of pain.

Trade name	D. form	Scientific name(s)	concentration
Sativex®	Buccal Spray	Tetrahydrocannabinol + Cannabidiol	(27 mg + 25 mg) per ml

References
1- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition.
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Rosemary R Berardi, Handbook of Nonprescription Drugs 17th Ed
4- Community Pharmacy: Symptoms, Diagnosis and Treatment, By Paul Rutter 2018 Ed.
5- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th
6- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 10th Edition.
7- Stein, Rob (25 April 2018). "FDA Panel Affirms Safety of Painkiller Celebrex". NPR. Retrieved 19 May 2018.
8- https://www.nejm.org/doi/10.1056/NEJMoa1611593
9- https://www.clinicalcorrelations.org/2018/02/01
10- https://www.ema.europa.eu/en/medicines/human/referrals/tolperisone
11- https://www.ncbi.nlm.nih.gov/pubmed/20421656
12- ACCP Updates in Therapeutics® 2021: Pharmacotherapy

RHEUMATOLOGY & NEUROLOGY

Chapter Ten: Rheumatology & Neurology

Part one: Rheumatology:

10.1- Glucosamine and Chondroitin

10.2- Intra-articular injections for OA and RA

a. Intra-articular corticosteroid
b. Intra-articular Hyaluronic acids

10.3- Disease Modifying Anti-Rheumatic Drugs (DMARDs)

- Other DMARDs (less frequently used)

10.4- Biological DMARDs

10.5- Drugs for Gout

a. Acute attacks of Gout
b. Prophylactic therapy of Gout
c. Other drugs that increase uric acid excretion

10.6- Other Rheum. Drugs

Part two: Neurology:

10.7- Fibromyalgia

10.8- Drugs for Multiple Sclerosis

10.9- Drugs that Enhance Neuromuscular Transmission

a. Anticholinesterases
b. Acetylcholine-release enhancers

10.10- Central monoamine depleting agent

10.11- Other Neurological Drugs

- For drugs used in Epilepsy; see chapter 4, section 4.
- For drugs used in Parkinsonism see chapter 4, section 5.
- For anti-Alzheimer drugs see chapter 4, section 7.
- For painkillers see chapter 9.
- For special analgesic combination that act on neuropathic pain see the previous chapter, (chapter 9, section 3 for analgesic combinations, and section 5 for neuropathic pain).

Chapter Ten: Rheumatology & Neurology

Part one: Rheumatology:

1. This part describes the following conditions: **Osteoarthritis (OA), Rheumatoid arthritis (RA), Gout** and **Hyperuricemia**, (For **Osteoporosis** see chapter 6, section 7)
2. Note that these conditions cause chronic pain, so most of the analgesics mentioned in the previous chapter (Chapter 9) can be used in these conditions to relief acute pain.

Simple Introduction:

1) **Osteoarthritis (OA)** is a common chronic condition of articular cartilage degeneration. Secondary changes can occur in the bone, leading to pain, decreased functioning, disability.
2) **Rheumatoid arthritis (RA)** is a chronic, systemic autoimmune disease that involves inflammation in the membrane lining of the joints and often affects internal organs, most patients exhibit a chronic fluctuating course of disease that can result in progressive joint destruction, deformity, and disability.
3) **Gout** is a disease that is characterized by recurrent painful acute attacks of urate crystal induced arthritis, it may include tophi-deposits of monosodium urate in and around the joints and cartilage and in the kidneys, as well as uric acid nephrolithiasis.

10.1- Glucosamine and Chondroitin

1. **Glucosamine sulfate** and **Chondroitin sulfate** is considered as dietary supplements. Both compounds are found naturally in the body and are essential to the formation of cartilage, the combination is believed to have a synergistic effect by:
   a. **Stimulating cartilage production** (by Glucosamine).
   b. **Inhibiting its destruction** (by Chondroitin).
2. They are used for mild to moderate **Osteoarthritis,** therapy should continue for several months; but their effectiveness is conflicted; some studies show a modest benefit, while other studies show no difference compared to placebo, although they still to date a supplement (not a drug).
3. Dosing should be at least **Glucosamine 1,500 mg/day** and **Chondroitin 1,200 mg/day** in divided doses, these are the least effective doses.
   - **Glucosamine** adverse effects are mild and include GI gas, bloating, and cramps.
   - The most common adverse effect of **Chondroitin** is nausea, prolonged bleeding time.
4. **Glucosamine** and **Chondroitin** come in many combinations products; sometimes combined with **Collagen, MSM (Methylsulfonylmethane),** Vitamin D_3, Calcium**, Gingko Biloba,** and many others; (All these are considered as a supplements by the FDA).

Trade name	Dosage form	Scientific name(s)	Conc. (per 2 servings)
Jointace® Original	Tab	Glucosamine + Chondroitin + Vit. D_3 + Other Vitamins	1000 mg + 400 mg + 20 mcg (per 2 Tabs)
Jointace® Omega-3	Cap	Glucosamine + Omega-3 + Cod Liver Oil + Other Vitamins	400 mg + 400 mg + 400 mg (per 2 Caps)
Jointace® Collagen	Tab	Glucosamine + Chondroitin + Collagen + Other Vitamins	1000 mg + 100 mg + 300 mg (per 2 Tabs)
Jointace® Rose Hip	Tab	Glucosamine + Chondroitin + Rose Hip + Other Vitamins	1000 mg + 200 mg + 300 mg
Arthi-Flex®	Tab	Glucosamine + Hyaluronic Acid + MSM (Methylsulfonylmethane) + Collagen + Other Vitamins	1500 mg + 80 mg + 1500 mg + 965 mg
FlexaMin Plus®	Tab	Glucosamine + Chondroitin + MSM + Collagen + Hyaluronic + Other Vitamins	1500 mg + 1200 mg (blend of 1300 mg)

Joint-Flex®	Tab	Glucosamine + Chondroitin + MSM + Hyaluronic Acid	1500 mg + 1200 mg + 500 mg + 30 mg
Chondro-Aid® Fort	Cap	Glucosamine + Chondroitin + Vit E + Selenium	1500 mg + 1200 mg
Chondro-Aid® Restructurant	Sachet	Collagen + Hyaluronic acid + Vit D + Vit C	10000 mg + 25 mg
Vita-Joint®	Tab	Glucosamine + MSM + Other Vitamins	1500 mg + 400 mg
NutroCare Joint-V®	Tab	Glucosamine + Chondroitin + Other Vitamins	1500 mg + 400 mg
Osteo Bi-Flex®	Caplet	Glucosamine + Chondroitin + MSM + Collagen + Hyaluronic + Other Vitamins	1500 mg + (blend of 1288 mg)
Revmatol®	Tab	Glucosamine + Chondroitin + MSM + Collagen type II + Vit. D + ginger root + Other Vit.	750 mg + 100 mg + 250 mg + 150 mg + 10 mcg + 50 mg
Bioflex®	Cap	Glucosamine + Chondroitin + MSM + Boswellia Extract	375 mg + 300 mg + 125 mg + 50 mg
	Effervescent Tab	Glucosamine + Chondroitin + MSM + Boswellia Extract	750 mg + 600 mg + 300 mg + 20 mg
	Topical Gel	Glucosamine + Chondroitin + MSM + Collagen + others	0.02% + 0.02% + 0.02% + 0.2%
Dorofen®, Glucofen®	Cap , Tab	Glucosamine + Gingko Biloba	500 mg + 50 mg
Dolo Mecanyl®	Sachets	Glucosamine + Meloxicam	1500 mg + 15 mg

10.2- Intra-articular injections for OA and RA

First: Intra-articular corticosteroid injections:

Methylprednisolone or **Triamcinolone** may be **useful when only a few joints are affected** in case of osteoarthritis and rheumatoid arthritis; they are also injected locally in some other conditions, they can provide excellent pain relief particularly when a joint effusion is present.

- Average doses for injection of large joints in adults are: Methylprednisolone 20 - 40 mg, or Triamcinolone 10 - 20 mg.
- They should be limited to **3 or 4 injection per year.**

Scientific name	Dosage form	Trade name	concentration
Methylprednisolone	Prefilled Inj. Inj. Solu. (vial)	Depo-Medrol®	40 mg/ml , 80 mg/ml
Triamcinolone (Acetonide)	Inj. Solu. (vial)	Kenalog®	20 mg/ml , 40 mg/ml 200 mg/5 ml
Triamcinolone (Acetonide) ER	Vial (single dose)	Zilretta®	32 mg/vial
Triamcinolone (Hexacetonide)	Inj. Solu. (vial)	Aristospan®	20 mg/ml , 25 mg/5 ml , 100 mg/5 ml
Betamethasone	Inj. Solu. (vial)	Betneso®	4 mg/ml
Dexamethasone	Inj. Solu. (vial)	Depo-Dexa®	4 mg/ml
Hydrocortisone	Inj. Solu. (vial)	Hydrocortistab®	25 mg/ml

*** Triamcinolone** has 2 salts; **Acetonide** and **Hexacetonide**, the last has the **advantage of long acting** (it remains in the joint for 21 days); while other steroids last about 8-14 days.

Second: Intra-articular Hyaluronic acid injection:

1. These are intended to **improve elasticity and viscosity of synovial fluid**; they are indicated for the treatment of knee 0steoarithritis (OA) when treatment failures to other therapies.
2. There are several types of hyaluronic acid injections, (also called viscosupplementation), they are made from either rooster or chicken combs, or are derived from bacteria, and are injected directly into the joint. It may take more than one injection for the pain to go away.
3. Typically, the patient will receive a series of three to five shots one week apart over three to five weeks; on average, **it takes about five weeks to experience the full benefits of HA injection**.
   - Also, there is formulation that is designed to be given every 3 or 6 months.
4. In contrast, **relief from corticosteroid injections occurs within days**, though this relief diminishes significantly after about a month or two.
5. The theory behind these injections is that because people with OA have a lower than normal amount of Hyaluronic acid (HA) in their joints, adding HA to the joint will improve symptoms by helping to cushion the joint; The injection seems to work by temporarily restoring the thickness of the joint fluid, allowing better joint lubrication and perhaps directly affecting pain receptors.
   - Some Research shows that HA may also interfere with prostaglandins and cytokines (naturally occurring compounds that promote inflammation in the body); other research has shown that HA may actually help encourage the joint to make new cartilage since hyaluronic acid is a major building block of cartilage.
6. The evidence regarding HA is mixed, with **many studies show no benefit over placebo**, physicians may try this therapy in case it may work in a particular patient, for example as a temporizing measure before considering surgery.
7. **Some studies have shown that HA injections can reduce pain for up to six months, but others have shown more limited results**, with 30 to 40 percent of those receiving the injections showing no improvement; A recent study, presented last year at the EULAR conference, found that there were certain characteristics that make a person less likely to show improvement with HA injections, including obesity, severe arthritis, being older than 65, and/or having HA or corticosteroid shots in the past.
8. The American Academy of Orthopedic Surgeons (AAOS) **no longer recommends HA injections** for knee OA because it says that there isn't enough evidence the therapy provides "clinically important improvement."

Scientific name	Dosage form	Trade name	concentration
Sodium Hyaluronate	Intra-articular Inj.	Hyalgan®, Euflexxa®	10 mg/ml , 20 mg/ml
Hylan polymers	Intra-articular Inj.	Synvisc®, Synvisc-One®	8 mg/ml (2 ml, 6 ml Inj.)
Hyaluronan	Intra-articular Inj.	Orthovisc®	30 mg/2 ml
Hyaluronic Acid	Intra-articular Inj.	Hyalone®	60 mg/4 ml
	Intra-articular Inj.	Durolane®	60 mg/3 ml
	Intra-articular Inj.	Monovisc®	88 mg/4 ml
Combination Products			
Hyaluronic acid + Triamcinolone (Hexacetonide)	Intra-articular Inj.	Cingal®	(88 mg + 18 mg)/4 ml

**** Most benefits are seen after the last dose (in the last week).**

10.3- Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

1. Also called **Non-Biological DMARDs,** these drugs **affect the immune response** and can suppress the disease process in **Rheumatoid Arthritis (RA)** which is the main indication of them; Examples: **Penicillamine**, **Hydroxychloroquine**, **Chloroquine**, **Methotrexate, Leflunomide** and **Sulfasalazine**.
2. They usually **need 3 months to produce a notable therapeutic effect,** thus combination therapy with NSAIDs and Corticosteroids is established until then.

Scientific name	Dosage form	Trade name	concentration
Methotrexate	Tab	Rheumatrex® , MTX®	2.5 mg , 5 mg , 10 mg
	Inj. Solu.	Trexall®	25 mg/ml
Azathioprine	Tab	Imuran®	50 mg , 75 mg , 100 mg
	Inj. Powder		100 mg/Vial
Hydroxychloroquine	Tab	Plaquenil®	200 mg
Chloroquine	Tab	Aralen®	250 mg , 500 mg
Penicillamine	Tab	Cuprimine® , Distamine®	250 mg
	Cap	Depen® , Artamin®	125 mg , 250 mg
Sulfasalazine	Tab	Salazopyrin® , Azulfidine®	500 mg
Leflunomide	Tab	Arava® , Vamid®	10 mg , 20 mg , 100 mg

Notes:

1. **Methotrexate** is an antimetabolite and anti-folate drug; it is used in treatment of **Cancer, autoimmune diseases** as **Rheumatoid Arthritis (RA), Ectopic Pregnancy,** and for the **induction of medical abortions,** it acts by inhibiting the metabolism of folic acid.
   a. Used as a treatment for autoimmune diseases, including **Rheumatoid Arthritis**, Juvenile dermatomyositis, **Psoriasis, Psoriatic Arthritis**, Lupus, Sarcoidosis, **Crohn's disease, Eczema**, and many forms of vasculitis.
   b. It's Considered as the **1st line DMARD for the treatment of RA.**
   c. Usually given once weekly for RA, also can be combined with other DMARDs or Biologicals.
   d. **Methotrexate** is used (generally in combination with misoprostol) to terminate pregnancies during the early stages (**as an abortifacient**), it is also used to treat ectopic pregnancies.
   e. MTX is **contraindicated in pregnant and nursing women**, chronic liver disease, immunodeficiency, pleural or peritoneal effusions, leukopenia, and thrombocytopenia.
   f. **Usually Co-administered with Folic acid**, to reduce the side effects (given all the other days of the week except the day of MTX administration)
2. **Hydroxychloroquine** and **Chloroquine** are also **Anti-Malarials, they can cause ocular (eye) toxicity**, and therefore the patient should be asked about visual symptoms and monitor visual acuity annually using the standard reading chart, **C.I. in patients with G6PD.**
3. **Penicillamine** is also a **chelating agent** used in **Arsenic and Lead poisoning** and some other Heavy metals, also used in the treatment of **Wilson's disease.**
4. **Sulfasalazine** is also used in the treatment of **Ulcerative Colitis** and **Crohn's Disease.**
5. **Leflunomide** loading dose of 100 mg/day for the first 3 days may result in a therapeutic response within the first month; the usual maintenance dose of 20 mg/day may be lowered to 10 mg/day in cases of GI intolerance, complaints of hair loss, or other dose related toxicity.
   a. May cause liver toxicity and is contraindicated in patients with liver disease.
   b. may cause bone marrow toxicity; a complete blood cell count with platelets is recommended monthly for 6 months, then every 6 to 8 weeks thereafter.
   c. It is teratogenic and should be **avoided during pregnancy;** in fact; women should wait to become pregnant for at least 2 years after discontinuation of treatment (to increase its elimination, take Cholestyramine 8 gm TID for 11 days).

Note: Other DMARDs (less frequently used)

Scientific name	Dosage form	Trade name	concentration
Cyclosporine	Cap	Sandimmune® , Gengraf®	25 mg , 50 mg , 100 mg
	Inj. Solu.	Neoral®	50 mg/ml
Cyclophosphamide	Tab	Cytoxan®	25 mg , 50 mg
	Inj. Powder		500 mg , 1 gm
Aurothiomalate Na	Inj. Solu.	Myocrisin®	20 mg/ml
Auranofin	Cap	Ridaura®	3 mg
Anakinra	Prefilled Inj.	Kineret®	100 mg/0.67 ml

**** All these are used as Immunosuppressant's.**

Combination therapy with two or more Non-Biologic DMARDs may be effective when single DMARDs treatment is unsuccessful, recommended combinations include:
(1) MTX plus Hydroxychloroquine (2) MTX plus Leflunomide (3) MTX plus Sulfasalazine.

10.4- Biological DMARDs

1. Also called **Cytokine modulators,** they act as **Immunosuppressant's.**
2. **They can reduce or prevent joint damage, preserve joint integrity and function** in patient with moderate to severe **Rheumatoid Arthritis (RA)**; Biologic DMARDs are effective for patients who fail treatment with other DMARDs.
3. They include: the anti-TNF agents (Etanercept, Infliximab, Adalimumab, Certolizumab, and Golimumab), Abatacept, Tocilizumab, and Rituximab.
4. These drugs **carry an increased risk for infection,** Tuberculin skin testing is recommended prior to treatment so that latent tuberculosis can be detected; These agents should be **avoided in patients with preexisting infection** and in those at high risk for developing Infection, and **treatment should be discontinued temporarily if an infection develops.**

Scientific name	Dosage form	Trade name	concentration
Etanercept	Inj. Solu.	Enbrel®	50 mg/ml
	Inj. Power		25 mg/vial
Infliximab	Inj. Powder	Remicade®	100 mg/vial
Adalimumab	Prefilled Inj.	Humira®	40 mg/0.8 ml
Certolizumab	Inj. Powder	Cimzia®	200 mg/vial
Golimumab	Prefilled Inj.	Simponi®	50 mg/0.5 ml , 100 mg/0.5 ml
Belimumab	Inj. Powder	Benlysta®	120 mg , 400 mg (per vial)
Anakinra	Prefilled Inj.	Kineret®	100 mg
Abatacept	Prefilled Inj.	Orencia®	125 mg/Inj.
	I.V. infusion		250 mg/vial
Tocilizumab	Inj. Solu.	Actemra®	20 mg/ml
	Prefilled Inj.	RoActemra®	162 mg/0.9 ml
Rituximab	Inj. Solu.	Rituxan®	10 mg/ml
Ustekinumab	Inj. Solu.	Stelara®	45 mg/0.5 ml
Sarilumab	Prefilled Inj.	Kevzara®	150 mg/1.14 ml , 250 mg/1.14 ml

Notes:

1. **Etanercept** is also used in the treatment of Psoriasis.
2. **Infliximab, Adalimumab, Certolizumab** and **Golimumab** are also **used in the treatment of Psoriasis** (Psoriatic Arthritis and Plaque Arthritis), **severe cases of Crohn's Disease and Ulcerative Colitis**, Ankylosing Spondylitis.
3. **Rituximab** is also used in the **management of NH Lymphoma, CL Leukemia.**

10.5- Drugs for Gout

1. **Gout** is a disorder that arises when the blood contains **increased levels of uric acid**, which is a by-product of normal body metabolism, when its concentration in the blood is excessive, uric acid crystals may form in various parts of the body, especially in the joints of the foot (most often the big toe), the knee, and the hand, causing intense pain and inflammation known as gout.
2. Crystals may form as white masses, known as tophi, in soft tissue, and in the kidneys as stones. Attacks of gout can recur, and may lead to damaged joints and deformity known as gouty arthritis. Kidney stones can cause kidney damage; An **excess of uric acid** can be caused either by **increased production** or by **decreased elimination** by the kidneys, which remove it from the body; the disorder tends to run in families and is far more common in men than women, the risk of attack is increased by high alcohol intake, the consumption of certain foods (red meat, sardines, anchovies, yeast extract, and offal such as liver, brains, and sweetbreads), and obesity.
3. An attack may be triggered by drugs such as thiazide diuretics, or excessive alcohol drinking; Changes in diet and a reduction in the consumption of alcohol is an important part of treatment.

First: Acute attacks of Gout:

1. These are usually treated with **high doses of NSAIDs**, FDA approved NSAIDs for Gout include: (Indomethacin, Naproxen and Sulindac); although other NSAIDs are also useful and effective.
   a. **Etoricoxib** 120 mg is indicated for the relief of acute attack of Gout, used for 7 days only.
   b. **Colchicine** is an alternative in patients in whom NSAIDs are contraindicated.
   c. **Aspirin is not indicated in gout** (using small doses may trigger Gout attacks).
   d. **Urate-lowering drugs (Allopurinol** and **Febuxostat)** should not be given until the acute attack is controlled, as these drugs may prolong the attack by causing a change in uric acid equilibrium**,** Urate-lowering agents can begin within 1 to 2 weeks after the resolution.
   e. **Corticosteroid intra-articular injections** are also useful, **Systemic corticosteroid** therapy is another option, when either NSAIDs or colchicine cannot be given or haven't been effective.
2. **Colchicine** impairs leukocyte migration to inflamed areas and disrupts urate deposition and the subsequent inflammatory response; **(it has no effect on serum urate levels).**
   a. It relieves the pain and the inflammation within 12-24 hours of use.
   b. It causes a **dose related side effects** (GI side effects) including diarrhea.
   c. Should be **avoided** in patients with **peptic ulcer disease** and other GI disorders.
   d. **Chronic colchicine therapy may result in neuro-myopathy** (numbness, paresthesias, and/or weakness), **it is best to limit colchicine therapy to 6-month duration;** also, chronic use **may cause alopecia**, and neutropenia.
   e. In a shocking study; in patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a **lower risk of ischemic cardiovascular events** than placebo. [5]
3. **Canakinumab** (recombinant monoclonal antibody) can be used for the symptomatic treatment of frequent Gouty arthritis attacks (at least 3 in the previous 12 months); it is licensed for use in patients whose condition has not responded adequately to treatment with NSAIDs or colchicine, or who are intolerant of them.
   - It may cause increased risk of infections and Neutropenia.

Second: Prophylactic therapy of Gout:

There are 3 families that is used for prophylaxis:

1. **Urate-reducing drugs** include the xanthine oxidase inhibitors: (Allopurinol, Febuxostat) which reduce uric acid production, and **Selective uric acid reabsorption inhibitor** (SURI): Lesinurad.
2. **Uricosuric agents** (Probenecid**,** Benzbromarone and Sulfinpyrazone); which increases renal uric acid excretion; Both families are also used as a prophylaxis against uric acid stone.
3. **Recombinant Urate oxidase enzymes** (Pegloticase, Rasburicase); or called **Uricase enzymes**, which act by oxidizing Uric acid to Allantoin (which is inactive, nontoxic, and easily excreted).
   - Urate Oxidase is not found in the human body; although it's found in nearly all organisms (except in the humans; the perfect design?).

Notes:

1. **Allopurinol** is given in a once **daily dose** of 100 mg, and then increased gradually to 300 mg/day.
   - The 300 mg **once daily** is the most commonly prescribed dose, but this may be an inadequate dose; a dose of up to 800 mg/day (in two to three divided doses) may be needed to achieve the desired 6 mg/dL serum uric acid level.
   - Side effects occurring in 3% to 5% of patients **include rash (Allopurinol sensitivity)**, **diarrhea, drug fever**, **leukopenia or thrombocytopenia.**
   - **It has a drug-drug interaction profile with ACEIs and ARBs.**
   - It's currently been studied for the **treatment of Schizophrenia** (refractory aggression).

4. **Febuxostat:**
   - It has a **Higher incidence** of cardiovascular thromboembolic events than with Allopurinol; FDA issued a new Black boxed warning for Febuxostat: stating that patients who take the drug could be at an **increased risk of death**, especially death from heart-related issues.
   - Indicated for patients who have **Allopurinol sensitivity.**
   - No dosage adjustment needed in renal or hepatic failure.
   - **No drug interaction with ACEIs or ARBs.**

5. **Pegloticase** is a form of uricase (urate oxidase), **which catalyzes the oxidation of uric acid to Allantoin**, which is water soluble and easily excreted.
   - It needs to be given by IV infusion every 2 to 4 weeks.
   - Duration of effect is 12 days, (half-life 14 days).
   - Patients need to be closely monitored for anaphylaxis and infusion reactions; thus, Pre-treatment with antihistamines and corticosteroids is a must.
   - May cause a life-threatening Hemolysis in patients with G6PD deficiency.

6. **Rasburicase** is licensed for the prophylaxis and treatment of acute hyperuricemia.
   - Its FDA approved for the treatment of hyperuricemia caused by Tumor Lysis Syndrome (TLS).
   - Also has a risk of anaphylaxis and infusion reactions, and G6PD hemolysis risk.

7. **Lesinurad** is a selective uric acid reabsorption inhibitor (SURI), it's indicated to be used with a Xanthine oxidase inhibitor (i.e.: it should not be used as a monotherapy).
   A) Has a **Black-Box warning of the possible risk of causing acute renal failure.**

Scientific name	Dosage form	Trade name	concentration
Colchicine	Tab	Colcrys®	0.5 mg , 0.6 mg , 1 mg
Allopurinol	Tab	Zyloric® , Hyporic®, Zyloprim®	100 mg , 300 mg
	Inj. Powder		500 mg/vial
Febuxostat	Tab , Cap	Uloric® , Adenuric®, Feburic®	40 mg , 80 mg
Pegloticase	Inj. Solu.	Krystexxa®	8 mg/ml
Canakinumab	Inj. Powder	ILaris®	180 mg/vial
Rasburicase	Inj. Powder	Fasturtec®, Elitek®	1.5 mg , 7.5 mg (per vial)
Lesinurad	Tab	Zurampic®	200 mg
Uricosuric Drugs			
Probenecid	Tab	Benemid®	500 mg
Benzbromarone	Tab	Desuric®	80 mg
Sulfinpyrazone	Tab , Cap	Anturane®	100 mg , 200 mg

Combination Products			
Colchicine + Probenecid	Tab	Colcrys Plus®	0.5 mg + 500 mg
Colchicine + Allopurinol	Cap	Colpuril®	0.5 mg + 100 mg
Colchicine + Opium powder + Tiemonium methylsulfate	Tab	Colchimax®	1 mg + 12.5 mg + 50 mg
Lesinurad + Allopurinol	Tab	Duzallo®	200 mg + 300 mg
Allopurinol + Benzbromarone	Tab	Harpagin® , Allo-Comp® Lanolone®	100 mg + 20 mg

Note: Other drugs that increase uric acid excretion:

These include **Guaifenesin** (an expectorant), **Losartan, Fenofibrate**, **Oxaprozin**, and **Vit. C**.

a. **Losartan**, an angiotensin II receptor blocker (ARB), might be a useful anti-hypertensive agent in the patient who has both hyperuricemia and hypertension because **this agent can lower serum uric acid levels by inhibiting the uptake of uric acid**, this effect is minimal or not seen in other ARBs.
b. **Fenofibrate** is used to treat elevated cholesterol and triglyceride levels; **It has been shown to decrease serum uric levels by increasing renal uric acid clearance** and would be a useful agent in the patient with both hyperlipidemia and hyperuricemia.
c. **Oxaprozin** (a NSAID) also has **Uricosuric properties** and is used in the treatment of gout.
d. **Vitamin C** may lower the serum uric acid level, a study noted a 0.5 mg/dL decrease in serum uric acid when 500 mg Vit. C was given daily.

10.6- Other Rheum Drugs:

These below some of the drugs that are un-categorized, their short notes are below:

Trade name	Dosage form	Scientific name(s)	concentration
CH-Alpha®	Oral Vials	Collagen Hydrolysate	10 gm/vial
CH-Alpha Plus®	Oral Vials	Collagen Hydrolysate + Vit. C + Rose hips Extract + Selenium	10 gm/vial
Benlysta®	I.V. Solu.	Belimumab	120 mg/vial , 400 mg/vial
Swiss Microlactin®	Cap	Microlactin	500 mg
Xeljanz®	Tab	Tofacitinib	5 mg
Arceclox®	Cap , Cream	Celadrin (cap) Celadrin + Menthol (Cream)	525 mg (Cap) 7.5% + 1.25% (Cream)
Limbrel®	Cap	Flavocoxid + citrated zinc	250 mg , 500 mg
Semazin®	Cap	Serratiopeptidase	----------
Diora®, Zondar®	Cap	Diacerein	50 mg
Verboril®	Cap SR	Diacerein	50 mg , 100 mg
Reparil®	Tab	Aescin	20 mg , 40 mg
Piascledine 300®	Cap	Avocado oil + Soybean oil	100 mg + 200 mg

Notes:

1. **CH-Alpha®** Contains **Bioactive Collagen Peptides** that keeps joints flexible through the natural regeneration of joint cartilage.
2. **Belimumab** is a human monoclonal antibody that inhibits B-cell activating factor, indicated in **Systemic lupus erythematosus, Rheumatoid arthritis, Sjögren's Syndrome.**
3. **MicroLactin®** is a patented milk protein concentrate (Hyperimmune milk) that helps relieve joint pain that results from osteoarthritis; Results is seen in as little as 2 weeks, (it's a form of milk that is acquired by giving lactating cows immunostimulants, which produces a larger amount of antibodies in their secreted milk.
4. **Tofacitinib (Xeljanz®)** is currently approved for the **treatment of Rheumatoid arthritis (RA)** in the United States and Russia, and is being studied for treatment of psoriasis, inflammatory bowel disease, and other immunological diseases, as well as for the prevention of organ transplant rejection**.**
5. **Arceclox®** decreases inflammation and lubricates cell membranes throughout the body, restoring fluids that cushion bones and joints to promote flexibility and mobility.
6. **Limbrel®** is a Medical food product indicated for the clinical dietary **management of the metabolic processes of osteoarthritis** (weakly inhibit COX-1 and COX-2).
7. **Semazin®** has anti-inflammatory and anti-swelling effects.
8. **Diacerein** is used in the treatment of osteoarthritis, it works by inhibiting interleukin-1.
9. **Aescin** has Anti-exudative, Anti-inflammatory and Anti-edema effects.
10. **Piascledine®** is indicated for the symptomatic slow-acting treatment of hip and knee osteoarthritis, taken 1 cap daily with food; for about 3 to 6 months.

Part two: Neurology:

1. This part describes the following: **Fibromyalgia, Multiple sclerosis, Drugs that enhance Neuromuscular transmission** and **Central monoamine depleting agent**
   - For drugs used in Epilepsy; see chapter 4, section 4.
   - For drugs used in Parkinsonism see chapter 4, section 5.
   - For anti-Alzheimer drugs see chapter 4, section 7.
   - For painkillers see chapter 9.
   - For special analgesic combination that act on neuropathic pain see the previous chapter, (chapter 9, section 3 for analgesic combinations, and section 5 for neuropathic pain).

10.7- Fibromyalgia

1. **Fibromyalgia** is classed as a disorder of pain processing **due to abnormalities in how pain signals are processed in the central nervous system**, it is characterized by chronic widespread pain, and Differences in psychological and autonomic nervous system profiles among affected individuals may indicate the existence of fibromyalgia subtypes.
2. The defining symptoms of fibromyalgia are chronic widespread pain, fatigue, sleep disturbance, and heightened pain in response to tactile pressure (allodynia), other symptoms may include tingling of the skin (paresthesias), prolonged muscle spasms, weakness in the limbs, nerve pain, muscle twitching, palpitations, and functional bowel disturbances
3. **A 2007 review divides individuals with fibromyalgia into 4 groups:**
   1. **Extreme sensitivity to pain but no associated psychiatric conditions** (may respond to medications that block the 5-HT3 receptor)
   2. **Fibromyalgia and comorbid, pain-related depression** (may respond to antidepressants)
   3. **Depression with concomitant fibromyalgia syndrome** (may respond to antidepressants)
   4. **Fibromyalgia due to somatization** (may respond to psychotherapy)

Drugs usually used for Fibromyalgia include**: (Duloxetine, Pregabalin** and **Milnacipran)** [4]

Scientific name	Dosage form	Trade name	concentration
Duloxetine	Cap , Cap CR	Cymbalta®	30 mg , 60 mg
Pregabalin	Cap	Lyrica®	75 mg , 150 mg
Milnacipran	Tab	Savella®	12.5 mg , 25 mg , 50 mg

Note: For antidepressant drugs see chapter 4, for Neuropathic pain see chapter 9

10.8- Drugs for Multiple Sclerosis:

1. Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS), etiology of multiple sclerosis (MS) is unknown, and currently there is no cure, characterized by central nervous system demyelination and axonal damage, and appears to be autoimmune in nature.
2. Treatment of MS falls into three broad categories: symptomatic therapy, treatment of acute attacks, and disease-modifying therapies (DMTs) to alter the natural course of the disease:
   A) Symptomatic therapy (see the table 64-4 below)
   B) Acute exacerbations or relapses of MS can be disabling. When this is the case, acute exacerbations and relapses are treated with **high-dose glucocorticoids**, such as methylprednisolone 500 to 1,000 mg/day by I.V. route, onset of response within 3- 5 days.
   C) Treatment of relapsing-remitting MS with the disease-modifying therapies (DMTs) **Interferon-B** (see chapter 14 for Interferons), **Glatiramer, Natalizumab**, **Mitoxantrone**, **Fingolimod, Fampridine, Dalfampridine, Teriflunomide** and **Dimethyl Fumarate;** can reduce annual relapse rate, lessen severity of relapses ,slow progression of changes on magnetic resonance imaging scans, slow progression of disability, slow cognitive decline.
   D) Newer agents in the treatment of MS are the **Monoclonal antibodies** ex: (**Alemtuzumab, Daclizumab, Ocrelizumab**), these have a promising result but usually **very expensive** and has the disadvantageous of significantly **increasing the risk for opportunistic infections.**

Scientific name	Dosage form	Trade name	concentration
Glatiramer	Inj. Solu.	Copaxone®	20 mg/ml , 40 mg/ml
Natalizumab	Inj. Solu.	Tysabri®	300 mg/15 ml
Mitoxantrone	Inj. Solu.	Novantrone®	2 mg/ml
Fingolimod	Cap	Gilenya®	0.5 mg
Fampridine	Tab , Cap	Fampyra®, Neurelan®	10 mg
Dalfampridine	Tab ER	Ampyra®	10 mg
Teriflunomide	Tab	Aubagio®	7 mg , 14 mg
Dimethyl Fumarate	Cap	Tecfidera®	120 mg , 240 mg
Alemtuzumab	Vial	Lemtrada®, Campath®	12 mg/1.2 ml , 30 mg/ml
Daclizumab	Prefilled Inj.	Zinbryta®	150 mg/ml
Ocrelizumab	Vial	Ocrevus®	300 mg/ml
Siponimod	Tab	Mayzent®	0.25 mg , 2 mg

Extra Notes: (3)

1. **Natalizumab** is also indicated **for Crohn's disease and ulcerative colitis.**
2. **Mitoxantrone** is also used for **prostate cancer** and **acute non-lymphocytic Leukemia.**
3. **Fingolimod** may cause **first-dose bradycardia**, it's associated with increased risk of infections.
   - C.I. in patients with myocardial infarction, Angina, Stroke, heart failure.
4. **Dalfampridine** is indicated to **improve walking** in patients with MS **by ↑ walking speed**.
5. **Fampridine** is licensed for the **improvement of walking** in patients with multiple sclerosis who have a walking disability, it is also used for the treatment of spinal cord injury.
6. **Dimethyl Fumarate** is also used for **Friedreich's ataxia.**
7. **Alemtuzumab** is **also indicated for chronic lymphocytic leukemia** (CLL), and used off-label in **kidney transplantation**.
   a. It is a **monoclonal antibody** that binds to CD52, a protein present on the surface of mature lymphocytes, but not on the stem cells from which these lymphocytes are derived, then these CD52-bearing lymphocytes are targeted for destruction.
8. **Ocrelizumab** was approved by the FDA in March 2017 as a treatment for multiple sclerosis, and the first FDA approved drug for the primary progressive form of MS.
   a. At launch, the drug was **priced at $ 65,000** (annual cost, for two infusions per year).
   b. It is **an immunosuppressive drug**; it binds to CD20, which is selectively made by B cells, and when **Ocrelizumab** binds to CD20 it kills B cells by causing **antibody-dependent cell-mediated cytotoxicity** and to a lesser extent, complement-dependent cytotoxicity.

Symptomatic therapy: →

1. **Tremor**
   Cerebellar symptoms such as tremor can be troubling and difficult to control. Medications that can be helpful include **propranolol, Primidone,** and **isoniazid.**
2. **Major Depression**
   Major depression is common in patients with MS, and the risk of suicide may be increased markedly compared with healthy Subjects, Patients should be monitored closely for the development of major depressive symptomatology and treated accordingly.
   - **Interferon products** and **Natalizumab should be used cautiously in patients with significant depression.**

Table Treatment of Selected Primary Multiple Sclerosis Symptoms

Spasticity	Bladder Symptoms	Sensory Symptoms	Fatigue
Baclofen	Propantheline	Carbamazepine	Amantadine
Dantrolene	Oxybutynin	Phenytoin	Antidepressants
Diazepam	Dicyclomine	Amitriptyline or other TCAs	Modafinil
Tizanidine	DDAVP	Gabapentin	Methylphenidate
Tiagabine	Self-catheterization	Lamotrigine	Dextroamphetamine
Gabapentin	Imipramine or amitriptyline	Pregabalin	
Pregabalin	Prazosin		
Botulinum toxin type A	Botulinum toxin type A		
Dalfampridine	Solifenacin		
	Darifenacin		
	Trospium		
	Hyoscyamine		
	Fesoterodine		

3. **Sexual Dysfunction**
   Sexual dysfunction in both men and women are common in MS and counseling should be offered to both partners. **Sildenafil, Tadalafil** and **Vardenafil** are very effective for men with MS who have erectile dysfunction. Other options for men include **Alprostadil** injection or intra-urethra suppositories (MUSE). **(See chapter 8, section 5, for more info)**
   - **Sildenafil** is currently being studied in females with MS and sexual dysfunction; in patients needing antidepressant therapy for whom sexual dysfunction is a concern, **bupropion** is preferable to SSRIs as it has a much lower incidence of sexual side effects.

4. **Cognition**
   Cognitive dysfunction is common in MS, affecting up to 50% or more of patients. It generally manifests itself as word finding difficulties and problems with concentration and short-term memory; Cognitive dysfunction can be treated with stimulants or cholinesterase inhibitors.

5. **Emotional incontinence**; or **Pseudobulbar affect (PBA)**, is a type of emotional disturbance characterized by uncontrollable episodes of crying and/or laughing, or other emotional displays; PBA occurs secondary to a neurologic disorder (as MS) or brain injury. Patients may find themselves crying uncontrollably at something that is only moderately sad, being unable to stop themselves for several minutes, Episodes may also be mood-incongruent: a patient may laugh uncontrollably when angry or frustrated, for example. Sometimes, the episodes may switch between emotional states, resulting in the patient crying uncontrollably before dissolving into fits of laughter. (The last **Joker** movie 2019).
   - Antidepressants such as **Sertraline**, **Fluoxetine**, **Citalopram**, And **Amitriptyline** have been prescribed with some efficacy in the treatment of PBA.
   - **Dextromethorphan/Quinidine** combination is the first FDA-approved drug for the treatment of PBA; **Dextromethorphan** is used as a cough suppressant, **Quinidine** affects the way the heart beats, and is generally used in people with certain heart rhythm disorders. It is also used to treat malaria.

Scientific name	D. form	Trade name	concentration
Dextromethorphan + Quinidine	Tab	Nuedexta®	20 mg + 10 mg

10.9- Drugs that Enhance Neuromuscular Transmission

A) Anticholinesterases

1. Anticholinesterases are used as first-line treatment in ocular myasthenia gravis and as an adjunct to immunosuppressant therapy for generalized **myasthenia gravis**.
2. Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis; They prolong the action of acetylcholine by inhibiting the action of the enzyme acetylcholinesterase. Excessive dosage of these drugs can impair neuromuscular transmission and precipitate cholinergic crises by causing a depolarizing block. This may be difficult to distinguish from a worsening myasthenic state.
3. **Neostigmine** produces a therapeutic effect for up to 4 hours. Its pronounced muscarinic action is a disadvantage, and simultaneous administration of an Antimuscarinic drug such as **Atropine** or **Propantheline** may be required to prevent colic, excessive salivation or diarrhea.
   - It's indicated for the **treatment and diagnosis of Myasthenia Gravis.**
   - Also indicated for **post-op distention or urinary retention.**
4. **Pyridostigmine** is less powerful and slower in action than neostigmine but it has a longer duration of action, it is preferable to neostigmine because of its smoother action and the need for less frequent dosage.

Scientific name	Dosage form	Trade name	concentration
Neostigmine	Tab	Prostigmin®	15 mg
	Inj. Solu.		0.5 mg/ml , 1 mg/ml
Pyridostigmine	Tab	Mestinon® , Regonol®	60 mg , 180 mg (CR tab)
	Inj. Solu.		5 mg/ml

B) Acetylcholine-release Enhancers

1. **Amifampridine** is licensed for the symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS); a rare disorder of neuromuscular transmission
2. **Fampridine** is licensed for the improvement of walking in patients with multiple sclerosis who have a walking disability, it is also used for the treatment of spinal cord injury.

Scientific name	Dosage form	Trade name	concentration
Amifampridine	Tab	Firdapse®	10 mg
Fampridine	Tab , Cap	Fampyra® , Neurelan®	10 mg

10.10- Central monoamine depleting agent

1. These agents are used to **treat hyperkinetic movement disorders** and involuntary movements or **chorea** associated with **Huntington's disease** and **tardive dyskinesia**.
2. They include: **Tetrabenazine**, **Deutetrabenazine** and **Valbenazine**.

Scientific name	Dosage form	Trade name	concentration
Tetrabenazine	Tab	Xenazine®, Revocon®	12.5 mg , 25 mg
Deutetrabenazine	Tab	Austedo®	6 mg , 9 mg , 12 mg
Valbenazine	Cap	Ingrezza®	40 mg , 80 mg

10.11- Other Neurological Drugs

Scientific name	Dosage form	Trade name	concentration
Ataluren	Oral Susp.	Translarna®	125 mg, 250 mg, 1,000 mg
Riluzole	Tab	Rilutek®	50 mg
Edaravone	I.V. Solu.	Radicava®	30 mg/100 ml
	Amp	Aravon®	1.5 mg/ml (20 ml amp)
Elamipretide	Pending FDA approval		
Masitinib			
Nusinersen	Vial	Spinraza®	12 mg/5 ml

Notes:

1. **Ataluren** is indicated for **Duchene Muscular Dystrophy.**
2. **Riluzole** is an NMDA receptor antagonist, it's the only drug approved for the **spasmolytic treatment of ALS (Amyotrophic Lateral Sclerosis).**
   - Riluzole is also a neuroprotective agent with anticonvulsant properties.
   - Research and studies are ongoing for Riluzole in the treatment of severe mood, anxiety, and impulsive disorder
3. **Edaravone, Masitinib** are indicated for **Amyotrophic Lateral Sclerosis (ALS).**
   a. **Edaravone** is administered 60 mg IV infusion over 60 min qDay for 14 days; followed by a 14-day drug-free period.

   b. **Edaravone** was approved for ALS by the FDA in 2017 based on a small randomized controlled clinical trial with people who had early-stage ALS in Japan, who were administered the drug for 6 months; it had failed two earlier trials in people with all stages of ALS.
   c. **Edaravone** is used to help people recover from stroke in Japan.

4. **Elamipretide** is indicated for **primary mitochondrial myopathy**; which is characterized by muscle weakness in patients with genetic mitochondrial diseases.

5. **Nusinersen** is indicated for the treatment of **Spinal Muscular Atrophy (SMA).**
   a. Administered by **intrathecal** route, initially **4 loading doses** (first three doses at intervals of 14 days; then the 4th dose at interval of 30 days).
   b. Then a Maintenance dose once every 4 months.

References
1- Sean C. Sweetman. Martindale: 38th Edition.
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Comprehensive Pharmacy Review for NAPLEX, 8th Edition.
4- Pharmacotherapy: A Pathophysiologic Approach, 11th Ed.
5- https://www.nejm.org/doi/full/10.1056/NEJMoa1912388

CORTICOSTEROIDS

Chapter Eleven: Corticosteroids

First: Introduction:

1. Physiological effects of Glucocorticoids
2. Physiological effects of Mineralocorticoids
3. Corticosteroids side effects
4. Therapeutic uses of the corticosteroids

Second: Types of corticosteroids

- **A.** Inhaled corticosteroids
- **B.** Corticosteroids for Nasal Cavity
- **C.** Oral and Injectable Corticosteroids
- **D.** Intra-articular corticosteroid injections
- **E.** Topical Corticosteroids
  - Low Potency
  - Medium Potency
  - High Potency
  - Very High Potency
- **F.** Ophthalmic Corticosteroids
- **G.** Intra-vitreal Corticosteroids
- **H.** Otic Corticosteroids
- **I.** Rectal corticosteroids

Third: Corticosteroids related drugs

- **a.** Corticotropin
- **b.** Corticorelin
- **c.** Tetracosactide

Chapter Eleven: Corticosteroids

First: Introduction:

1. **Physiological effects of Glucocorticoids:**
   a. **Promote normal intermediary metabolism:** Glucocorticoids stimulates gluconeogenesis and stimulate protein catabolism and increase lipolysis (increase free fatty acids).
   b. **Decrease insulin sensitivity** in the muscles and adipose tissue.
   c. **Increase resistance to stress:** By raising plasma glucose levels, glucocorticoids provide the body with the energy it requires to combat stress caused, for example, by trauma, fright, infection, bleeding, or debilitating disease.
   d. They cause a modest **rise in blood pressure**, (they have positive inotropic effect throw stimulation of Na/K ATPase and Beta-adrenergic receptors); also, they **cause Na and water retention** (increase blood volume); they also **potentiate the vasoconstrictor effect of Norepinephrine and Angiotensin II.**
   e. **Alter blood cell levels in plasma:** Glucocorticoids cause a **decrease in eosinophil's, basophils, monocytes, and lymphocytes** by redistributing them from the circulation to lymphoid tissue. In contrast to this effect, glucocorticoids **increase the blood levels of hemoglobin, erythrocytes, platelets, and polymorph-nuclear leukocytes**. [Note: The decrease in circulating lymphocytes and macrophages compromises the body's ability to fight infections. However, this property is important in the treatment of leukemia].
   f. **Have anti-inflammatory action**; they **suppress phospholipase A2 activity** (thus decrease arachidonic acid synthesis, which in turn will cause a decrease in prostaglandins and leukotrienes synthesis); also, they **suppress cyclooxygenase (COX) activity**.
      - They **suppress proinflammatory cytokines** and other inflammatory mediators such as **tumor necrosis factor (TNF)** and **interleukins**.
      - They **suppress leukocytes and microphages migration**.
      - They **decrease capillary permeability**, which in turn **decrease inflammatory edema**.
   g. **Have anti-allergic action;** they **decrease tissue response to allergic mediators and decrease histamine release** throw stabilization of mast cells and basophils.
   h. **Have immunosuppressant effect;** they inhibit the function of macrophages, TNF, interleukins and prevents T-cells proliferation.
   i. **Affect other components of the endocrine system:** Feedback inhibition of corticotrophin production by elevated glucocorticoids causes inhibition of further synthesis of both glucocorticoid and thyroid-stimulating hormones.
   j. **Can have effects on other systems:** Adequate cortisol levels are essential for normal glomerular filtration (**they increase GFR**), also increase reabsorption of water, Na and CL.
      - High doses of glucocorticoids stimulate gastric acid and pepsin production and **may exacerbate ulcers.**
      - Effects on the central nervous system that influence mental status have been identified; they **decrease seizure threshold** and **increase intracranial pressure**.
      - Chronic glucocorticoid **therapy can cause severe bone loss and myopathy**; they **decrease the absorption of Calcium and Phosphate** from the intestine.
   k. They can **cause osteoporosis** throw several pathways; including **decreasing osteoblast** numbers and reducing its functionality, and by **increasing osteoclast** survival and activity.

2. **Physiological effects of Mineralocorticoids:**
   a. **Control the body's water volume and concentration of electrolytes**, especially sodium and potassium. Aldosterone acts on kidney tubules and collecting ducts, causing reabsorption of sodium, bicarbonate, and water.

b. Aldosterone decreases reabsorption of potassium, which, with H^+ is then lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands.
c. Elevated aldosterone levels may cause alkalosis and hypokalemia, whereas retention of sodium and water leads to an increase in blood volume and blood pressure.

3. The corticosteroids are used in **physiological doses for replacement therapy** in adrenal insufficiency. [3] **While the Pharmacological doses are used when anti-inflammatory or immunosuppressant effects are required** (for so many different diseases).

4. **The effects of different corticosteroids vary qualitatively as well as quantitatively**, and it may not be possible to substitute one for another in equal therapeutic amounts. Thus, whereas **cortisone and hydrocortisone have very appreciable mineralocorticoid** (or sodium-retaining) properties relative to their glucocorticoid (or anti-inflammatory) properties, prednisolone have considerably less, and others, such as betamethasone and dexamethasone, have none or virtually none.

5. As a rough guide, the approximate **equivalent doses** of the main corticosteroids in terms of their glucocorticoid (or anti-inflammatory) properties alone, are:
Betamethasone 0.75 Mg = Cortisone Acetate 25 Mg = Dexamethasone 0.75 Mg = Hydrocortisone 20 Mg = Methylprednisolone 4 Mg = Prednisolone 5 Mg = Prednisone 5 Mg = Triamcinolone 4 Mg [3].

a. The use of pharmacological doses of corticosteroids suppresses the endogenous secretion of steroids by the anterior pituitary.
b. The **adrenal suppression is less** when the corticosteroid **is given as a single dose in the morning, and even less if this morning dose is given on alternate days or less frequently**
c. **Sudden withdrawal** in dosage may **precipitate acute adrenocortical insufficiency**.
d. Gradual withdrawal of systemic corticosteroids is required for:
- Patient who received more than 40 mg prednisolone (or equivalent) daily for more than 1 week.
- Patient who received more than 3 weeks' treatment.

6. **Corticosteroids have numerous side effects** including nearly all body systems:
a. **Osteoporosis is the most common adverse effect:** due to the ability of glucocorticoids to suppress intestinal $Ca2^+$ absorption, inhibit bone formation, and decrease sex hormone synthesis; (Alternate-day dosing does not prevent osteoporosis; also, Patients are advised to take calcium and vitamin D supplements).
b. **The classic Cushing-like syndrome** (redistribution of body fat, puffy face, increased body hair growth, acne, insomnia, and increased appetite).
c. **Hyperglycemia** may develop and **lead to diabetes mellitus**. Diabetic patients should monitor their blood glucose and adjust their medications accordingly.
d. **Decreased growth in children, increased risk of infection, Emotional disturbances.**
e. **Peptic ulcers, Hypertension and Peripheral edema.**
f. Corticosteroids (**especially dexamethasone**) are frequently **abused in Iraq**. (Prolonged use glucocorticoids have a dramatic effect on body fat distribution, resulting in the characteristic **appearance of moon face**).

7. **Therapeutic uses of the corticosteroids:**
a. **Replacement therapy** for primary adrenocortical insufficiency **(Addison disease):** usually **Hydrocortisone** and **Fludrocortisone** are indicated in this condition.
b. **Replacement therapy** for secondary or tertiary adrenocortical insufficiency.
c. **Diagnosis of Cushing syndrome:** by **dexamethasone** suppression test.
d. **Relief of inflammatory symptoms:** they redness, swelling, heat, and tenderness that are commonly present at the inflammatory site, also stabilize mast cell and basophil membranes (thus, inhibiting histamine release) and diminishing the activation of the kinin system.

e. **Treatment of allergies:** treatment of the symptoms of bronchial asthma; allergic rhinitis; and drug, serum, and transfusion allergic reactions.
f. **Acceleration of lung maturation:** Respiratory distress syndrome is a problem in premature infants. Fetal cortisol is a regulator of lung maturation.; Consequently, a dose of **betamethasone** or **dexamethasone** is administered intramuscularly to the mother 48 hours prior to birth, followed by a second dose 24 hours before delivery.

A) Inhaled Corticosteroids (ICS):

1. An inhaled corticosteroid is used **regularly for prophylaxis of asthma**; they are **ineffective for acute asthmatic attack**.
2. May cause **oral candidiasis** (**oral fungal infection**) and this side effect can be **reduced by rinsing the mouth with water** after inhalation of a dose; or by using spacer device.

Scientific name	Dosage form	Trade name	concentration
Beclomethasone	Inhaler	Qvar®, Beclosone®, Becotid®	50 mcg , 100 , 250 mcg
Budesonide	Inhaler	Pulmicort®	200 mcg
	Nub. Solu.		200 mcg
	Inhale Cap	Miflonide®	200 mcg
Fluticasone	Aerosol	Flixotide® , Flovent®	110 mcg , 100 mcg (Diskus)
Ciclesonide	Inhaler	Alvesco®	80 mcg
Flunisolide	Aerosol	Aerospan®	80 mcg
Mometasone	Inhaler	Asmanex® , Twist-haler®	110 mcg , 220 mcg
Triamcinolone	Inhaler	Azmacort®	55 mcg , 100 mcg

* Comes in combination with long acting beta2 agonist for Rx of Asthma (see chapter 1).

B) Corticosteroids for Nasal Cavity:

1. Nasal preparations containing corticosteroids have a useful role in the **prophylaxis and treatment of allergic rhinitis**.
2. **Regular use is essential** for full benefit and it takes several days before full effect is reached.

Scientific name	Dosage form	Trade name	concentration
Betamethasone	Nasal drop	Methadin®	0.1 % (10 ml)
Beclomethasone	Nasal spray	Beconazse®	42 mcg/spray
Budesonide	Nasal spray	Rhinocort Aqua®, Cortinase®	32 mcg , 64 mcg (per Actuation)
Mometasone	Nasal spray	Nasonex®	50 mcg/spray
Triamcinolone	Nasal spray	Nasacort®	55 mcg/spray
Ciclesonide	Nasal spray	Omnaris®	50 mcg (per Actuation)
Flunisolide	Nasal spray	Aerospan nasal®	25 mcg (per Actuation)
Fluticasone	Nasal spray	Flonase® , Flixonase®	50 mcg/spray
Fluticasone + Azelastine *	Nasal spray	Dymista®	(50 mcg + 137 mcg)/spray

* **Azelastine is anti-histamine.**

C) Oral and Injectable Corticosteroids:

1. These are used in many diseases, as a **replacement therapy in adrenal insufficiency**, as **anti-inflammatory**, in autoimmune diseases such as **(Ulcerative Colitis, Crohn's disease),** as **Immunosuppresants** (in high doses) … etc.

TABLE 85-9 Relative Potencies of Glucocorticoids

Glucocorticoid	Anti-Inflammatory Potency	Equivalent Potency (mg)	Approximate Half-Life (min)	Sodium-Retaining Potency
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100–300	0
Dexamethasone	30	0.75	100–300	0

Scientific name	Dosage form	Trade name	concentration
Hydrocortisone	Tab	Cortef ®	5 mg , 10 mg , 20 mg
	Vial	Hyamol® , H.C.®	100 mg , 250 mg
Fludrocortisone	Tab	Florinef®	0.1 mg
Betamethasone	Tab	Celestone®	0.5 mg
	Amp	Celeston®, Betacort®	4 mg/ml , 6 mg/ml
Prednisolone	Tab	Deltacortil® , Predine®	5 mg , 20 mg
	Syr.	Xilone®	5 mg/5 ml , 15 mg/5 ml
Prednisone	Tab	Cortancyl® , Rayos®	20 mg , 50 mg
	Oral Solu.	Deltasone®	5 mg/5 ml
Dexamethasone	Tab	Decadron® , Dexon®	0.5 mg , 1 mg
	Tab DR	Baycadron®	4 mg , 6 mg
	Syr.	Dexon®, Orazone®	0.5 mg/5 ml
	Amp	Decadron®, Dexamed®	4 mg/ml , 8 mg/2 ml
Methylprednisolone	Tab	Medrol®	4 mg , 8 mg , 16 mg
	Inj. (vial)	Depo-Medrol®	40 mg/ml , 80 mg/ml
	Inj. (powder)	Solu-Medrol®	250 mg , 500 mg , 1 gm
Triamcinolone	Inj. (vial)	Kenacort A®, Trivaris®	20 mg/ml , 40 mg/ml
	Oral Gel	Kenalog®	1 mg/gm (10 gm tube)

Notes:

1. **Dexamethasone** has the strongest anti-inflammatory effect, while **Hydrocortisone** has the lowest anti-inflammatory effect.
2. **Triamcinolone** has the longest half-life (300 min); **Prednisone** has the lowest (60 min).
3. **Fludrocortisone is intended for use as a mineralocorticoid only**, (used only for Adrenocortical Insufficiency, Addison Disease) and used (off-label) in the treatment of severe orthostatic hypotension.
4. **Prednisolone is a pro drug**, its converted by the liver into **Prednisone**
   a. **Prednisone** is preferred in pregnancy because it minimizes steroid effects on the fetus.
   b. Many doesn't know that **there is a difference between Prednisolone** and **Prednisone.** (Don't be one of them)
5. **Triamcinolone Oral Gel** is used for the temporary relief of symptoms from mouth sores, oral inflammatory lesions and ulcerative lesions; it works by reducing the swelling, itching, and pain that can occur with mouth sores.

D) Intra-articular corticosteroid injections:

Methylprednisolone or **Triamcinolone** may be useful when only a few joints are affected in case of osteoarthritis and rheumatoid arthritis; they are also injected locally in some other conditions; they can provide excellent pain relief particularly when a joint effusion is present.

- They should be limited to 3 or 4 injection per year.
- (see chapter 10, section 2, for details)

E) Topical Corticosteroids:

1. Topical corticosteroids are effective in many inflammatory and proliferative skin diseases, used to help relieve redness, itching, swelling, or other discomfort caused by skin conditions including: **atopic dermatitis, psoriasis, seborrheic dermatitis, contact dermatitis, and nummular eczema.** [2-4]
2. **They come in different potencies (Low, Medium, High,** and **Very High);** Their Potencies are commonly classified according to the vasoconstrictor assay, based on the degree to which an agent causes cutaneous vasoconstriction on normal human subjects.
   - **Changing the salt form will also change the potency.**
3. Absorption of topical corticosteroids is highest on mucous membranes, followed by the scrotum, eyelid, face, chest, back, arms and legs, dorsa of hands and feet, and palms and soles.
4. **Chromic Topical therapy with Corticosteroids** can cause skin atrophy, ecchymosis, purple striae, dermatoses, and cataracts.
   - With chronic use, topical corticosteroids (especially the potent agents) show decreased efficacy, a phenomenon known as "tachyphylaxis".
   - They **mask** the symptoms of infections such as Tinea (fungal) and scabies.
   - **For more info see the dermatology chapter.**

F) Ophthalmic Corticosteroids:

1. Used to prevent permanent damage to the eye, which may occur with certain eye problems **(as Iritis, Keratitis** and **Conjunctivitis)**, they also **provide relief from redness, irritation, itching** and **allergic reactions** affecting the eye.
2. They should be **used with caution** for patients with the **Glaucoma & Cataract,** and they are **preferably not to be used more than about 7 – 10 days.**

Scientific name	Dosage form	Trade name	concentration
Betamethasone	Eye Drop	Methadin®	0.1 % (10 ml)
Dexamethasone	Eye Drop	Maxidex®	0.1%
	Eye Oint.		0.05%
Hydrocortisone	Eye Drop	Hyrocort®, Opticort®	1%
	Eye Oint.		1 %
Fluorometholone	Eye Drop	FML® , Flucon® , FML Forte®	0.1% , 0.25% (Forte)
Prednisolone	Eye Drop	Pred Mild® , Pred Forte®	0.12% , 1% (Forte)
Loteprednol	Eye Drop	Alrex® , Lotemax®	0.2% , 0.5%
	Eye Gel	Lotemax®	0.5%
Rimexolone	Eye Drop	Vexol®	1%
Difluprednate	Eye Drop	Durezol®	0.05%

**** For combination products with antibiotics see chapter 12, page 155.**

G) Intra-vitreal * Corticosteroids Injections:

1. Intra-vitreal injections are commonly used to treat retinal diseases such as diabetic retinopathy, macular degeneration, macular edema, and retinal vein occlusion.
2. **The medication is injected directly into the eye**, may be administered as frequently as once a month, depending on the condition being treated.

Scientific name	Dosage form	Trade name	concentration
Dexamethasone	Intra-vitreal Implant	Ozurdex®	0.7 mg (0.4 mg/0.1 ml)
Fluocinolone	Intra-vitreal Insert	Retisert®	0.59 mg
Triamcinolone	Intra-vitreal Inj.	Triesence®	4 mg/0.1 ml

*** For more details on this tech. see chapter 12, page 160.**

H) Otic Corticosteroids:

1. Used in the ear to relieve the redness, itching, and swelling caused by certain ear problems, used usually to treat inflammation, and eczema or dermatitis in the ears.
2. Generally ophthalmic (eye) preparations containing corticosteroids can be used in the ears. **They rarely found alone**, usually comes in combinations with antibiotics. (See chapter 13)

Scientific name	Dosage form	Trade name	concentration
Betamethasone	Ear drop	Methadin®	0.1 % (10 ml)
Dexamethasone	Ear drop	Dexonium®	10 mg/10 ml
Fluocinolone	Ear drop	Dermotic®	0.01%

I) Rectal corticosteroids:

1. Also called Gastrointestinal Corticosteroids, are **used to treat mild or moderate ulcerative colitis and Crohn's Disease.** They also may be used along with systemic (oral or injection) corticosteroids or other medicines to treat severe disease or mild to moderate disease that has spread too far to be treated effectively by medicine inserted into the rectum alone.
2. Rectal corticosteroids also are used to help relieve swelling, itching, and discomfort of some other rectal problems, including hemorrhoids and inflammation of the rectum.
3. Some of these medicines may be taken as pills. If the disease affects only the lower part of the colon, corticosteroids can be given by enema. For disease that only affects the rectum, suppositories and topical creams can be used.

Scientific name	Dosage form	Trade name	concentration
Budesonide	Rectal Enema	Entocort®	2 mg (0.02 mg/ml)
	Cap , Tab		3 mg (Cap) , 9 mg (Tab)
Hydrocortisone	Rectal Enema	Proctol® , Anusol HC®	100 mg/60 ml
	Rectal Supp.		25 mg , 30 mg
Hydrocortisone + Pramoxine *	Cream, Lotion , Rectal Foam	Procort® , Pramosone®	(1% + 1%), (2.5% + 1%)
Hydrocortisone + Lidocaine *	Rectal Gel	AnaMantle®	2.5% + 2%
Fluocinolone + Lidocaine*	Oint , cream , Supp.	Proctoheal®	0.1 mg + 20 mg

*** Pramoxine** and **Lidocaine** Are Local Anesthetics.

**** For Ulcerative Colitis and Crohn's disease: See chapter 2**

**** For Hemorrhoids: See chapter 2**

Third: Corticosteroids related drugs:

Scientific name	Dosage form	Trade name	concentration
Corticotropin	Inj. Solu.	Acthar Gel®	80 units/ml
Corticorelin	Inj. (I.V.)	Acthrel®	100 mcg/2 ml
Deflazacort	Tab	Emflaza®	6 mg , 18 mg , 30 mg
	Oral Susp.		22.75 mg/ml
Tetracosactide	Amp	Synacthen®	250 mcg/ml
	Amp	Synacthen Depot®	1 mg/ml

Notes:

1. **Corticotropin** is used to treat relapsing **multiple sclerosis** (MS), **infantile spasms**, and **nephrotic syndrome** (a collection of symptoms that indicate kidney damage), **dermatomyositis** (a chronic inflammatory disease of skin and muscle) and **polymyositis** (an autoimmune inflammatory disease of muscle).
   a. **Acthar Gel®** should never be given intravenously, also should not be used in patients with a skin condition called scleroderma, bone density loss (osteoporosis), infection throughout the body, eye infection (ocular herpes simplex), recent surgery, history of or a current stomach ulcer, heart problems, high blood pressure.
   b. May cause side effects similar to side effects that happen due to treatment with steroids

2. **Corticorelin** is used as a diagnostic test in adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome to differentiate between pituitary and ectopic production of ACTH.

3. **Deflazacort** is a glucocorticoid which has an **anti-inflammatory and immunosuppressant effects;** but it's indicated only for **Duchene muscular dystrophy (DMD).**

4. **Synacthen® (250 mcg Amp) is intended for administration for diagnostic purposes only** (Synacthen Test) as a single intramuscular or intravenous dose; it is not to be used for therapeutic administration. [2]
   - **While the Synacthen® Depot (1 mg Amp) is used to treat** Ulcerative Colitis, Crohn's disease, Steel disease, Rheumatoid Arthritis, Osteoarthritis and some inflammatory skin conditions like (Pemphigus, Sever Eczema, Psoriasis).

References

1- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition.
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Comprehensive Pharmacy Review for NAPLEX, 8th Edition
4- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Ed.
5- Lippincott's pharmacology 7 Ed.

OPHTHALMOLOGY

Chapter Twelve: Ophthalmology (The Eye)

12.1- Administration of drugs to the Eye (Teach the patient)

First: Anti-Glaucoma Eye Drops

- **A.** Beta-blockers eye drops
- **B.** Prostaglandin analogues drops
- **C.** α2 – agonists
- **D.** Carbonic Anhydrase Inhibitors
- **E.** Miotics or Cholinergic agents
- **F.** Kho kinase inhibitor
- **G.** Combination Products for Glaucoma

Second: Conjunctivitis

- **A. Eye Drops for Allergic/Irritant Conjunctivitis**
  - **1.** Anti-histamine Eye Drops
  - **2.** Mast cell stabilizer Eye Drops
  - **3.** Corticosteroids Eye Drops
  - **4.** NSAIDs Eye Drops
  - **5.** Decongestant or (Decongestant + Anti-histamine) Eye Drops
- **B. Drops for other types of Conjunctivitis**
  - **1.** Ophthalmic Quinolones
  - **2.** Ophthalmic Aminoglycosides
  - **3.** Ophthalmic Macrolides
  - **4.** Other Ophthalmic Antibacterials
  - **5.** Combination products of Antibacterial Eye Drops
  - **6.** Antibacterial Ophthalmic preparations combined with a corticosteroid
  - **7.** Special Eye Drop Combinations
  - **8.** Ophthalmic Antivirals
  - **9.** Ophthalmic Antifungals

Third: Lubricating Eye Drops (Tear's Deficiency)

- Drops with preservatives
- Drops free of preservatives
- In Form of Gel
- Eye lubricants + Decongestant

Fourth: Other Types of Ophthalmic Drops

- **A.** Drops that Extend the Iris (Mydriatics/Cycloplegics)
  - Combination products
- **B.** Anesthetic Eye Drops
  - Combination products
- **C.** Anti-Cataract Eye Drops
  - Combination products
- **D.** Other types of Eye Drops

Fifth: Intra-vitreal Eye Injections

Sixth: Other drugs for retinal disorders:

Chapter Twelve: Ophthalmology (The Eye)

12.1- Administration of drugs to the eye (Teach the patient)

1. Administration guideline for eye drops and ointments are shown in the tables below:

Administration Guidelines for Eye drops	Administration Guidelines for Eye ointment
1-If you have difficulty telling whether eye drops have touched your eye surface, refrigerate the solution before instilling it. Do not refrigerate suspensions. Always check the expiration date. 2-Wash hands thoroughly. Wash areas of the face around the eyes. Contact lenses should be removed unless the product is designed specifically for use with contact lenses. 3-Tilt head back. 4-Gently grasp lower outer eyelid below lashes, and pull eyelid away from eye to create a pouch. 5-Place dropper over eye by looking directly at it, as shown in the drawing  6-Just before applying a single drop, look up. 7-As soon as the drop is applied, release the eyelid slowly. Close eyes gently for 3 minutes by placing your head down as though looking at the floor (using gravity to pull the drop onto the cornea). Minimize blinking or squeezing of the eyelid. 8-Use a finger to put gentle pressure over the opening of the tear duct. 9-Blot excessive solution from around the eye.	1-Wash hands thoroughly. Wash areas of the face around the eyes. 2-If both drop and ointment therapy are indicated, instill the drops at least 10 minutes before the ointment so that the ointment does not become a barrier to the drops' penetrating the tear film or cornea. 3-Tilt head back. 4-Gently grasp lower outer eyelid below lashes, and pull eyelid away from eye as shown in the drawing  5-Place ointment tube over eye by looking directly at it. 6-With a sweeping motion, place one-fourth to one-half inch of ointment inside the lower eyelid by gently squeezing the tube, but avoid touching the tube tip to any tissue surface. 7-Release the eyelid slowly. 8-Close eyes gently for 1-2 minutes. 9-Blot excessive ointment from around the eye. 10-Vision may be temporarily blurred. Avoid activities that require good visual ability until vision clears.

2. one drop is all that is needed. Instillation of more than one drop should be discouraged because it may increase systemic side-effects.
3. When two different eye-drop preparations are used at the same time of day, dilution and overflow may occur when one immediately follows the other; The patient should therefore **leave an interval of at least 5 minutes between the two**.
4. If using a suspension, shake well before instilling, if using the suspension with another dosage form, **place the suspension drop last**, because it has prolonged retention time in the tear film [1] (most steroid eye drops present as a suspension).
5. If both **drop and ointment therapy are indicated**, **instill the drops at least 10 minutes before the ointment** so that the ointment does not become a barrier to the drops' penetrating the tear film or cornea.
6. Discard or replace eye drop bottles **30 days after the sterility safety seal is opened** (unless stated otherwise by manufacturer). The manufacturer's expiration date does not apply once the seal is broken.
7. Some eye drops (like **Latanoprost** (Xalatan®) need to **be stored at refrigerator.**
8. Patients should be warned not to drive or perform other skilled tasks until vision is clear after using eye drops or eye ointments.
9. It is common to **use drops during the day and then use eye ointment in the evening or at night** upon retiring when the blurring of vision will be less inconvenient.
10. **Contact lenses and drug treatment:** In general, patients should be counseled **not to place any ophthalmic solution, suspension, gel, or ointment into the eye when contact lenses are in place**; the lenses should be removed before drop instillation and not worn during the period of treatment.

First: Anti-Glaucoma Eye Drops

1. Drugs that **reduce intra-ocular pressure** by different mechanisms are available for managing glaucoma; **All are used topically (as Eye drops)** except **Acetazolamide** and **Methazolamide;** which are available as an oral tablet (and less commonly as an injection).
2. **Glaucoma** (high eye pressure); Occurs as a result of the imbalance between the secretion of fluid called (aqueous humour) – which its Concentration is about 4 cc inside the eye – and between the speed of its discharge, leading to its accumulation inside the eye suppressing the optic nerve, and if it continues to put pressure on the nerve → this will cause damage to the eye and lost vision.
   - In the most common type, called chronic (or open-angle) glaucoma, reduced drainage of fluid from the eye causes pressure inside the eye to build up slowly; Progressive reduction in the peripheral field of vision may take months or years to be noticed.
   - Acute (or closed-angle) glaucoma occurs when drainage of fluid is suddenly blocked by the iris. Fluid pressure usually builds up quite suddenly, blurring vision in the affected eye. The eye becomes red and painful, and a headache and sometimes vomiting also occur; The main attack is often preceded by milder warning attacks, such as seeing haloes around lights in the previous weeks or months.
3. Usually; the damage is gradual without any symptoms or pain, especially in the elderly and with increasing pressure patient may feel severe pain in the head, eye and blurred vision with redness and tears.
4. Drops work to reduce intraocular pressure to below 20 (normal range), and if it fails the doctor is resorted to the option of laser treatment.
5. **These drops reduce intraocular pressure in two ways:**
   a. **Slowing the production of fluid inside the eye** (Aqueous Fluid)
   b. **By improving the flow of fluid out of the eye** through the drainage angle (drainage).
6. The **treatment options for Glaucoma:**
   A) Beta-blockers eye drops: act by reducing the formation of the aqueous humour.
   B) Prostaglandin analogues: Improve Fluid discharge, thus reduce intraocular pressure.
   C) α2 - agonists: Reduce the secretion of fluid and also facilitate the process of discharge.
   D) Carbonic Anhydrase Inhibitors (CAI): reduce the formation of the aqueous humour.
   E) Miotics or Cholinergic agents: Improve liquid discharge cycle outside of the eye.
   F) Kho kinase inhibitor: increase trabecular outflow.
7. To get both benefits of reducing the formation of the aqueous humour and increasing its discharge → a combination of Beta-blocker plus Prostaglandin analogues or CAI is used.

A) Beta-blockers eye drops: (Reduce Formation of Fluid)

1. Beta blockers drops can be absorbed into the body and can affect the lungs, heart, and circulation. As a result, a Cardioselective beta blocker, such as Betaxolol, is prescribed with caution to people with asthma or certain circulatory disorders and, in some cases, such drugs are withheld altogether.
2. The amount of the drug absorbed into the body can be reduced by pressing on the lacrimal (tear) duct in the corner of the eye while applying the number of eye drops
3. Beta blocker drops are **usually given twice daily**.

Scientific name	Dosage form	Trade name	concentration
Betaxolol	Eye drop	Betoptic®, Eltaxol®	0.5% , 0.25%
Timolol	Eye drop	Lithimole®, Ophtamolol®, Timoptof®	0.5% , 0.25%
Carteolol	Eye drop	Ocupress® , Carteol®	1% , 2%
Levobunolol	Eye drop	Betagan®	0.5% , 0.25%
Metipranolol	Eye drop	OptiPranolol®	0.3%

B) Prostaglandin analogues drops: (Improve Fluid discharge)

1. Prostaglandin analogues are usually **applied once daily, preferably in the evening**, and should not be increased to twice daily, as this may decrease effectiveness.
2. Patients receiving Prostaglandin analogues drops should be instructed to refrigerate unopened medication, once opened Latanoprost can stored at room temperature for 6 weeks.
3. Prostaglandin analogues **may cause, darkening, thickening and lengthening of eye lashes** (reversible upon stopping treatment).
   - Some women actually uses it for this effect to have a more thickened eye lash.
   - Commercially; a topical gel of **Latanoprost** is available for eye lash thickening.
4. Before initiating treatment, patients should be warned of a possible change in eye color as an increase in the brown pigment in the iris can occur, which may be permanent; particular care is required in those with mixed colored irises and those receiving treatment to one eye only

Scientific name	Dosage form	Trade name	concentration
Latanoprost	Eye drop	Xalatan® , Latano®	0.005%
Bimatoprost	Eye drop	Lumigan® , Latisse®	0.01% , 0.03%
Travaprost	Eye drop	Travatan®	0.004%
Tafluprost	Eye drop	Taflotan® , Saflutan®	0.0015 %
Unoprostone	Eye drop	Rescula®	15%
Latanoprostene	Eye drop	Vyzulta®	0.024%

C) α2 – agonists: (Reduce secretion and facilitate discharge)

1. α2 – agonists are usually **given 3 times a day**.
2. **Brimonidine** is also formulated as a **gel** for the treatment of Facial Flushing **Rosacea**.
3. **Apraclonidine** usually used for maximum 1 month (short-term adjunctive treatment)

Scientific name	Dosage form	Trade name	concentration
Brimonidine	Eye drop	Alphagan®, Brimogan®, Brimo®	0.1% , 0.15% , 0.2%
Apraclonidine	Eye drop	Lopidine®, Iopidine®	0.5% , 1%

D) Carbonic Anhydrase Inhibitors (CAI): (reduce formation of fluid)

1. CAIs are usually **given 3 times a day**.
2. **Acetazolamide** is also used as a diuretic in CHF edema or drug induced edema.
3. **Acetazolamide**, **brinzolamide**, and **Dorzolamide** are contra-indicated if history of sulphonamide hypersensitivity.
   - **Acetazolamide** may cause troublesome adverse effects, including tingling of the hands and feet, the formation of kidney stones, and, rarely, kidney damage; thus, people with existing kidney problems are not usually given this drug.

Scientific name	Dosage form	Trade name	concentration
Dorzolamide	Eye drop	Trusopt® , Dorzoptic® , Xola®	2%
Brinzolamide	Eye drop	Azopt®	1%
Methazolamide	Tab	Neptazane®	25 mg , 50 mg
Acetazolamide	Tab	Cidamix®	125 mg , 250 mg
	Cap ER	Diamox Sequels®	500 mg
	Inj. (powder)	Diamox Sequels®	500 mg/vial

E) Miotics or Cholinergic agents: (Improve liquid discharge)

1. Miotics are usually given 3 times a day.
2. People receiving miotic eye drops are likely to notice darkening of vision and difficulty in seeing in the dark. Increased shortsightedness may be noticeable.

Scientific name	Dosage form	Trade name	concentration
Pilocarpine	Eye drop	Isopto Carpine® , Dropil®	10 mg (1%) , 20 mg (2%)
Carbachol	Eye drop	Miostat®	1.5 % , 3 %
	Intraocular Solu.		100 mcg/ml
Echothiophate	Eye drop	Phospholine®	0.125%

F) Kho Kinase inhibitor

Netarsudil is a Rho kinase inhibitor with norepinephrine transport inhibitory activity that reduces production of aqueous humour; it specifically targets the conventional trabecular pathway of aqueous humour outflow to act as an inhibitor to the rho kinase and norepinephrine transporters found there as opposed to affecting prostaglandin F2-alpha analog like mechanisms in the unconventional uveoscleral pathway that many other glaucoma medications demonstrate.

- **Netarsudil** is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Scientific name	Dosage form	Trade name	concentration
Netarsudil	Eye drop	Rhopressa®	0.02% (0.2 mg/ml)

Note: Combination Products for Glaucoma:

Those combine both the benefits of reducing the formation of the Aqueous Humor and increasing its discharge.

Scientific name(s)	D. form	Trade name	concentration
Beta-blocker + CAI			
Dorzolamide + Timolol	Eye drop	Cosopt® , Dorzoptic Plus® Xolamol®	2% + 0.5%
Brinzolamide + Timolol	Eye drop	Azarga®	(10 mg + 5 mg)/ml
Beta-blocker + α2–agonist			
Brimonidine + Timolol	Eye drop	Combigan®	0.2% + 0.5% , (2 mg+5 mg)/ml
Beta-blocker + Prostaglandin analog			
Latanoprost + Timolol	Eye drop	Xalacom® , Latancom®	(50 mcg + 5 mg)/ml
Bimatoprost + Timolol	Eye drop	Ganfort®	(0.3 mg + 5 mg)/ml
Travaprost + Timolol	Eye drop	Duotrav®	(40 mcg + 5 mg)/ml
Beta-blocker + Miotic			
Pilocarpine + Timolol	Eye drop	Fotil® , Fotil Forte®	(20 mg + 5 mg)/ml
α2–agonist + CAI			
Brimonidine + Brinzolamide	Eye drop	Simbrinza®	0.2% + 1%
Prostaglandin analog + Kho kinase inhibitor			
Latanoprost + Netarsudil	Eye drop	Rocklatan®	0.02% + 0.005%

** if the patient used a combination eye drop product of (Beta-blocker + α2–agonists or Prostaglandin analog) and still not reduced the eye pressure to normal levels → **the Physician can add oral CAI to the regimen.**

Second: Conjunctivitis

1. It's simply mean **inflammation of the conjunctiva** and is characterized by varying degrees of ocular redness, irritation, itching and discharge.
2. **It can be due 3 main causes: (bacterial, viral** and **allergic forms),** the table below will help to distinguish between those 3 main types:

Symptoms that help to distinguish between the different types of conjunctivitis			
	Bacterial	**Viral**	**Allergic**
Eyes affected	Both, but one eye often affected first by 24–48 hours	Both	Both
Discharge	Purulent	Watery	Watery
Pain	Gritty feeling	Gritty feeling	Itching
Distribution of redness	Generalised and diffuse	Generalised	Generalised but greatest in fornices
Associated symptoms	None commonly	Cough and cold symptoms	Rhinitis (may also have family history of atopy)

Notes:

1. Muco-purulent discharge is more suggestive of bacterial conjunctivitis especially if the eyes are glued together in the absence of itching.
2. Photophobia is usually associated with serious eye pathology, ex: keratitis and uveitis.
3. Redness of the eyes with itching and pain with Vomiting suggests glaucoma

A) Eye Drops for Allergic/Irritant Conjunctivitis:

1. **Irritation to the eye** usually occurs when exposed to an irritant or allergen (such as pollen, dust), or due a chemical substance that causes eye sensitization, **Symptoms of eye irritation include:** Redness and itching with tears and possible swelling with a tingling feeling in the eye.
2. **Allergic Conjunctivitis** occurs in people who suffer other types of allergies, such as seasonal allergies or asthma or allergic skin, so it may appear during certain times of the year such as the spring and usually have severe redness and burning with tears.
3. So, for these two conditions there is a variety of treatment options:
   1. Anti-histamine eye drops. **2. Mast cell stabilizer eye drops.**
   3. Corticosteroid eye drops. **4. NSAIDs eye drops.**
   5. Decongestant or (Decongestant + Anti-histamine) eye drops.

1. Anti-histamine Eye Drops:

Ophthalmic anti-histamines can be used for allergic conjunctivitis that is often associated with allergic rhinitis, usually used 2 – 3 times daily.

Scientific name	Dosage form	Trade name	concentration
***Olopatadine** **	Eye Drop	Pataday® , Patanot® , Olopat®	0.1% & 0.2%
Azelastine	Eye Drop	Optivar®, Allergodil®	0.05%
***Ketotifen** **	Eye Drop	Zaditor®, Alaway®, Cleroptic®	0.025%
Cetirizine	Eye Drop	Zerviate®	0.24%
Alcaftadine	Eye Drop	Lastacaft®	0.25%
Emedastine	Eye Drop	Emadine®	0.05%
Bepotastine	Eye Drop	Bepreve®	1.5%
Epinastine *	Eye Drop	Elestat®	0.05%
Levocabastine	Eye Drop	Livostin®	0.05%

*** Olopatadine, Ketotifen** and **Epinastine** also have a Mast cell stabilizing effect.

2. Mast cell stabilizer eye drops:

1. Mast cell stabilizers inhibits type-I immediate hypersensitivity reaction; also, may inhibit mast cell release of inflammatory mediators.
2. All Mast cell stabilizers are used 4 times per day, Except **Nedocromil** which is used twice daily, Treatment course is usually ranges from 4 weeks to 6 weeks.

Scientific name	Dosage form	Trade name	concentration
Na^+ Cromoglycate (or) Cromolyn Na^+	Eye drop	Crolom® , Opticrom® , Allergotin®	4% (10 ml) , 2% (10 ml)
Lodoxamide	Eye drop	Alomide®	0.1%
Nedocromil	Eye drop	Alocril®	2%
Pemirolast	Eye drop	Alamast®	0.1% (1 mg/ml)

3. Corticosteroids eye drops:

1. Used to prevent permanent damage to the eye, which may occur with certain eye problems (as **Iritis, Keratitis** and **Conjunctivitis**), they also provide relief from redness, irritation, itching and allergic reactions affecting the eye.
2. They should be **used with caution** for patients with the **Glaucoma** & **Cataract,** and they are preferably **not to be used more than about 7 – 10 days.**
3. Topical corticosteroids are applied frequently for the first 24–48 hours; once inflammation is controlled, the frequency of application is reduced.

Scientific name	Dosage form	Trade name	concentration
Betamethasone	Eye drop	Methadin®	0.1 % (10 ml)
Dexamethasone	Eye Drop	Maxidex®	0.1%
	Eye Oint.		0.05%
Hydrocortisone	Eye Drop	Hyrocort®, Opticort®	1%
	Eye Oint.		1 %
Fluorometholone	Eye Drop	FML® , Flucon® , FML Forte®	0.1% , 0.25% (Forte)
Fluorometholone + Na^+ Cromoglycate	Eye Drop	Fluca®	(0.1% + 2 %)
Prednisolone	Eye Drop	Pred Mild® , Pred Forte®	0.12% , 1% (Forte)
Loteprednol	Eye Drop	Alrex® , Lotemax®	0.2% , 0.5%
	Eye Gel	Lotemax®	0.5%
Rimexolone	Eye Drop	Vexol®	1%
Difluprednate	Eye Drop	Durezol®	0.05%

4. NSAIDs eye drops:

1. They are used **to suppress the optical mast cell responses** to allergens including (but not limited to) aerosolized dust particles and other allergens, **also used as ophthalmic analgesics or in allergic conjunctivitis to reduce the eye inflammation,** they should be avoided in patient with aspirin allergy.

Scientific name	Dosage form	Trade name	concentration
Diclofenac Na^+	Eye drop	Diclogesic® , Voltaphtha®	0.1 %
Indomethacin	Eye drop	Indocollyre®	0.1 %
Flurbiprofen	Eye drop	Ocufen®, Fluroptic®	0.03 %
Bromfenac	Eye drop	Bromday® , Prolensa®	0.07 % , 0.09 %
Nepafenac	Eye drop	Nevanac® , ILevro®	0.1 % , 0.3 %
Ketorolac	Eye drop	Acular® , Acular LS®	0.5 % , 0.4 % (LS)

5. Decongestant or (Decongestant + Anti-histamine) eye drops:

1. These should be used for only a short time, to avoid a condition called **(conjunctivitis medicamentosa)** that cause frequent redness and congestion of the eye, **Used cautiously in patients with Glaucoma**, (Relative contraindication in Glaucoma).
2. They work by producing a **temporary constriction of the conjunctival blood vessels**, thereby reducing eye redness.
3. Decongestants eye drops are beneficial when there is a swelling in the eye due to the inflammation and vasodilation.

Scientific name	D. form	Trade name	concentration
Decongestants			
Naphazoline *	Eye drop	Naphcon® , Antistine®	0.025% , 0.1%
Phenylephrine	Eye drop	Apifrin®, Mydfrin®	2.5%
Oxymetazoline	Eye drop	OcuClear® , Nasordin®	0.05%
Tetrahydrozoline	Eye drop	Tetryzoline® , Tyzine®	0.05% , 0.01%
Decongestant + Anti-histamine			
Naphazoline + Pheniramine	Eye drop	Naphcon A® , Visine A®	0.025% + 0.3%
Naphazoline + Antazoline	Eye drop	Antistine-Privine® , Apihist® , Ophtazoline®	0.025% + 0.5%
Naphazoline + Chlorpheniramine	Eye drop	Nozeylin® , Prisoline®	(0.5 mg + 0.5 mg)/ml
Decongestant + Ocular Wash			
Naphazoline + Sulfophenate	Eye drop	Oftalmil®	(0.16 gm + 0.2 gm)/10 ml
Naphazoline + Glycerin	Eye drop	Clear Eyes®	0.03% + 0.5%
Tetrahydrozoline + Zinc Sulfate **	Eye drop	Visine AC®	0.05% + 0.25%

*** (Naphazoline** and **Naphthazoline) is the same drug.**

**** Zinc sulfate** act as astringent to relief burning and itching.

B) Drops for other types of Conjunctivitis:

These include:

1. **Antibacterial eye preparations** for Bacterial Conjunctivitis
2. **Combination drops containing (Antibacterial + Corticosteroid)** for mixed type of Conjunctivitis.
3. **Antiviral eye preparation** for Viral Conjunctivitis
4. **Antifungal eye preparation** for fungal keratitis

Bacterial eye infections are generally treated topically with eye drops and eye ointments [3], Frequency of application depends on the severity of the infection.

- **a.** Drops are applied **as frequent as 1 drop every 2 hours**, continue for 48 hours after healing.
- **b.** Eye ointment, apply either at night (if eye drops used during the day) or 3–4 times daily (if eye ointment used alone).

Common anti-infective's available as an eye preparation include:

1. **Quinolones**: ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin.
2. **Aminoglycosides**: gentamicin, neomycin, and tobramycin
3. **Macrolides**: Azithromycin, Erythromycin.
4. **Others**: Chloramphenicol, Tetracycline, Polymyxin B, Fusidic acid.
5. **Anti-Virals** (Mainly Acyclovir), and **Anti-Fungals.**

A) Ophthalmic Quinolones:

Scientific name	Dosage form	Trade name	concentration
Ciprofloxacin	Eye drop/Oint.	Ciprodar® , Ciloxan®	0.3% (both)
Ofloxacin	Eye drop	Ocuflox®	0.3%
Norfloxacin	Eye drop	Chibroxin® , Apiflox®	0.3%
Lomefloxacin	Eye drop	Okacin®	0.3%
Levofloxacin	Eye drop	Iquix® , Quixin® , Vefloxin®	0.5% , 1.5%
Moxifloxacin	Eye drop	Vigamox® , Moxeza®	0.5%
	Eye Oint.	Moxicip®	0.5%
Besifloxacin	Eye drop	Basivance®	0.6% (5 ml)
Gatifloxacin	Eye drop	Zymar® , Tequin® , Zymaxid®	0.3% , 0.5%

B) Ophthalmic Aminoglycosides:

Scientific name	Dosage form	Trade name	concentration
Gentamicin	Eye drop/Oint.	Gentak® , Gendin®	0.3%
Tobramycin	Eye drop/Oint.	Tobrex®	0.3%
Natamycin *	Eye drop	Natacyn® , Pimaricin®	5%
Neomycin	**Comes in Combinations Only**		

*** Natamycin** also has an anti-fungal activity. (2)

C) Ophthalmic Macrolides:

Scientific name	Dosage form	Trade name	concentration
Azithromycin	Eye drop	Azasite® , Azyter®	1% , 1.5% (2.5 ml)
	Eye Oint.	Optithrocin®	1%
Erythromycin	Eye Oint.	ILotycin® , Erythrocin®	0.5%

D) Other Ophthalmic Antibacterial preparations:

Scientific name	Dosage form	Trade name	concentration
Chloramphenicol	Eye Oint.	Samaphenicol®	1%
	Eye drop		0.5%
Tetracycline	Eye Oint.	Samacycline®	1%
Fusidic acid	Eye Oint.	Fucithalmic®	1% (5 mg/Tube)
Polymyxin B	**Comes in Combinations Only**		
Bacitracin	Eye Oint.	Beocin®	500 Unit/gm (3.5 gm)
Sulfisoxazole	Eye drop	Gantrisin®	4%
Sulfacetamide	Eye drop	Cetamide® , Ocusulf®	10% , 20% , 30%
	Eye Oint.		10%

Note1: Combination products of antibacterial eye drops

Scientific name(s)	D. form	Trade name	concentration
Polymyxin B + Bacitracin	Eye Oint.	Polycin®	(10,000 Unit + 500 Unit)/gm
Neomycin + Polymyxin B + Bacitracin	Eye Oint.	Neo-Polycin®	(400 Unit + 3.5 gm + 10,000 Unit)/gm
Neomycin + Polymyxin B + Gramicidin	Eye Oint. , Eye Drop	Neo-Sporin®	3.5 gm (Oint.) , 10 ml (drop)
Polymyxin B + Trimethoprim	Eye Drop	Polytrim®	(10,000 Unit + 1 mg)/ml

Note2: antibacterial ophthalmic preparations combined with corticosteroid [2]

Scientific name(s)	Dosage form	Trade name	concentration
Betamethasone + Neomycin	Eye drop	Methadin-N®, Ophamesone-N®	0.1% + 0.5%
Dexamethasone + Neomycin	Eye drop	Neo-dexon®	0.1% + 0.5%
Tobramycin + Dexamethasone	Eye drop, Eye Oint.	Tobradex®	(0.3% + 0.05%), (0.3% + 0.1%)
Tobramycin + Loteprednol	Eye drop	Zylet®	0.3% + 0.5%
Chloramphenicol + Dexamethasone	Eye drop	Dexachlor®	(4 mg + 1 mg)/ml
Dexamethasone + Neomycin + Polymyxin B	Eye drop, Eye Oint.	Maxitrol® , Dexasporin®, PND®, Dexatrol®	(0.1%+3.5gm+10,000 Unit)/ml (0.1%+3.5gm+10,000 Unit)/gm
Framycetin + Gramicidin + Dexamethasone	Eye drop, Ear Drop	Sofradex®	5 mg + 0.05 mg + 0.5 mg
Framycetin + Dexamethasone	Eye drop	Frakidex®	630,000 IU + 100 mg (per 100 ml)
Gentamycin + Prednisolone	Eye drop, Eye Oint.	Pred G®	(0.3% + 1%) drop, (0.3% + 0.6%) Oint.
Sulfacetamide + Prednisolone	Eye drop, Eye Oint.	Cetapred®, Blephamide®	10% + 0.2%

Note3: Special Eye drop Combinations

Trade Name	D. form	Scientific name(s)	concentration
Tafazol®	Eye drop	Sulfacetamide + Phenolsulphonate + Naphazoline + Lidocaine	(30 mg + 5 mg + 0.05 mg + 7.5 mg) Per ml
Vasosulf®	Eye drop	Sulfacetamide + Phenylephrine	15%
Clogenta®	Eye drop	Gentamycin + Diclofenac Na^+	(3 mg + 1 mg)/ml
Loxtra®	Eye drop	Ofloxacin + Prednisolone + Tetrahydrozoline	(3 mg + 2 mg + 0.4 mg)/ml
Ocumethyl®	Eye drop	Naphazoline + Diphenhydramine + Zinc Sulfate	(10 mg + 10 mg + 10 mg) (per 10 ml)

E) Ophthalmic Antivirals: (For Viral Conjunctivitis)

Commonly used antivirals are **(Acyclovir or Ganciclovir) for herpes simplex infections.**
Frequency of administration may reach 5-6 times a day, duration range 14-20 days

Scientific name	Dosage form	Trade name	concentration
Acyclovir	Eye Oint.	Zovirax®, Veramed®	1%
Idoxuridine *	Eye drop	Idoxol®, Dendrid®	0.1%
	Eye Oint.	Dendrid®	0.5%
Ganciclovir *	Eye Gel	Zirgan®, Vitrasert®	0.15% (5 gm)
	Ocular Implant *		4.5 mg
Vidarabine	Eye drop	Vira-A®	3%
Trifluridine	Eye drop	Viroptic®	1%

*** Idoxuridine is used only topically due to cardio toxicity.** [2], it's not available in USA.
**** Ganciclovir** Ocular Implant is inserted as intra-vitreal every 5 to 8 months. [2]

F) Ophthalmic Antifungals:

1. Used in the treatment of **fungal keratitis** (although I.V. Antifungals as Amphotericin B is the 1st line therapy for such cases), Available Ophthalmic antifungals include: **Fluconazole, Natamycin** and **Boric acid.**
2. **Boric acid** has **mild antibiotic properties** against fungal or bacterial infection, **it is also used as an eye wash** to cleanse or irrigate the eyes. It provides soothing relief from eye irritation, and helps remove pollutants from the eye such as smog, chlorine, or other chemicals.

Scientific name	Dosage form	Trade name	concentration
Fluconazole	Eye drop	Fluzamed®	3 mg/ml (5 ml)
Itraconazole	Eye drop	Entozole®	1% (5 ml)
Natamycin *	Eye drop	Natacyn® , Pimaricin®	5%
Micafungin	Eye drop	MCFG®	0.1%
Boric acid	Eye drop	Collyrium Fresh®	----------

*** Natamycin** also has an antibacterial activity.

Third: Lubricating Eye Drops (Tear's Deficiency)

1. **Artificial tear preparations** act by stabilizing the tear film (by increasing the viscosity of tear thus decrease evaporation), Examples are: **Hypromellose (hydroxypropyl methylcellulose), Carmellose, polyvinyl alcohol** and **Carbomers**.
2. Some of these products may be available **as pack that contain single dose eye drops** (28 or 30 single dose eye drops); that contain small volume usually 0.4 mL and **each drop is intended for single use only**.
3. Some of these products may be available as **preservative free** eye drops; if a patient is likely to be **using artificial tears for a long time**, a preservative-free preparation should be considered because the prolonged exposure of the eye to the preservative (mostly it is **Benzalkonium Chloride**) can produce damage to the cornea.
4. **Artificial tears are used for the treatment of dry eye in the following cases:**
    - **a.** Dry eye caused by conditions such as the temporary use of the computer for long periods of time or because of the sun, wind, eye fatigue or for whatever reason.
    - **b.** Dry eye caused due to aging, as well as post-menopausal women.
    - **c.** Dry eye resulting from the use of certain medications such as antihistamines and birth control pills, as well as chemical treatments for cancer patients.
    - **d.** Dry eye caused by some diseases that affect the eye's ability of secreting tears (Sjögren's syndrome, rheumatoid arthritis, and collagen vascular diseases).
    - **e.** Dry eye caused by a defect in the eyelid, which makes the eyelid does not close completely, as happens in cases of nerve VII damage.
    - **f.** Dry eye resulting from the use of or contact lenses after LASIK operations.
5. The function of these drops is adding some elements of the natural tears that already exist in the eye, that give some comfort.
6. **Decongestant eye drops must be avoided in such cases,** it may remove redness shortly, but in the long term of use it will cause dryness of the eye.

Eye Lubricants are divided into three types:

A) Drops with preservatives:

1. Often come in multi-dose bottles and contain preservatives that inhibit the growth of bacteria and used 3-4 times per day, Examples include: (Genteal, Optive, Refresh Tears, Isotears, Hylo-Comod, Hameron)

2. Most eye drops contain preservatives that inhibit bacterial growth and keep them safer, **but some people are sensitive or even allergic to these preservatives,** so keep in mind that eye drops containing preservatives actually can cause irritation, redness and more dryness, rather than easing these symptoms.
3. **Classification of Preservatives:**
   a. **Detergent Preservatives:** cause bacterial cell death by way of interrupting the lipid component of cell membranes. The contents of the microbial cell are extruded from the cell due to membrane instability, ex: **Benzalkonium Chloride (BAK) and cetrimonium, Chlorobutanol, Edetate Disodium, Polyquaternium-1, Polyhexamethylene.**
   b. **Oxidizing Preservatives:** alter the lipid membrane of microbes in a different fashion to detergent preservatives, by penetrating the membrane and altering the DNA, protein and lipid components of bacterial cells, ex: **sodium perborate, stabilized oxychloro complex.**
   c. **Ionic-buffered Preservatives:** a combination of boric acid, zinc, sorbitol and propylene glycol, they induce less cytotoxicity to the ocular surface compared with conventional preservatives, **Ex: SofZia.**

Trade Name	D. form	Scientific name(s)	concentration
Genteal®	Eye Drop	Hypromellose	0.3%
Artelac®	Eye Drop	Hypromellose	1.6 mg/0.5 ml
Slezin®	Eye Drop	Hypromellose + Dextran	(3 mg + 1 mg)/ml (15 ml)
Septoclear Tears®, Tears Natural®	Eye Drop	Hypromellose + Dextran 70 (Benzalkonium CL as presrev.)	0.3% + 0.1%
Tears Natural II®	Eye Drop	Hypromellose + Dextran 70 (Polyquaternium as presrev.)	0.3% + 0.1%
Optive®	Eye Drop	Carmellose + Glycerol	10 ml
Refresh Tears®	Eye Drop	Carboxymethylcellulose Na^+	0.5%
Refresh Optive®	Eye Drop	Carboxymethylcellulose Na^+ + Glycerin + Polysorbate 80	0.5% + 1% + 0.5%
Liquifilm Tears®	Eye Drop	Polyvinyl alcohol	1.4%
Natural Tears®	Eye Drop	Polyvinyl alcohol + Povidone	0.5% + 0.6% (15 ml)
Isotears®	Eye Drop	Methylcellulose	0.3 %
Hylo-Comod®, Hameron®, ***HeyFresh®***	Eye Drop	Sodium Hyaluronate	1 mg/1 ml (10 ml)

*** Hypromellose = Hydroxypropyl methylcellulose**, they are the same.
*** Carmellose = Carboxymethylcellulose**, they are the same.

B) Drops free of Preservatives:

1. These drops are best used when there is a moderate or severe Dryness and usually **each dose comes in a separate package for single use only**, such as: TheraTears, Refresh Plus, Catinorm and Systane.

Trade Name	Dosage form	Scientific name(s)	concentration
TheraTears®	Eye drop	Carmellose sodium	2.5 mg/ml (0.25%)
Refresh Plus®	Eye drop	Carboxymethylcellulose Na^+	0.5%
Artelac® Advanced	Eye drop	Hyaluronic acid	0.2%
Refresh Optive® Advanced	Eye drop	Carboxymethylcellulose Na^+ + Glycerin + Polysorbate 80	0.5% + 1% + 0.5%
Catinorm®	Eye drop	Glycerol + Tyloxapol + Poloxmar 188	10 ml
Systane®	Eye drop	Polyethylene Glycol 400 + Propylene Glycol	0.4% + 0.3% (15 ml, 30 ml)

C) In Form of Gel:

1. **It is the best option for chronic use,** used only before going to sleep (because it causes Blurred vision), their effect is characterized by long term and give comfort for a longer period; they include: **Viscotears Gel, Refresh Celluvisc, Refresh Liquigel, Genteal Gel,** and **Liposic Gel.**

Trade Name	Dosage form	Scientific name(s)	concentration
Genteal Gel®	Eye Gel	Hypromellose	0.2%
Viscotears Gel® , Liquivisc® , ***Liposic®***	Eye Gel	Carbomer	2.0 mg/g
Refresh Celluvisc®	Eye Gel	Carboxymethylcellulose Na^+	1% (Preservative Free)
Refresh Liquigel®	Eye Gel	Carboxymethylcellulose Na+	1%
Systane Gel®	Eye Gel	Polyethylene Glycol 400 + Propylene Glycol	0.4% + 0.3% (Preservative Free)

Note: Some Eye lubricants also contain a decongestant as:

Scientific name	D. form	Trade name	concentration
Clear Eyes® Triple Action	Eye drop	Polyvinyl alcohol + Povidone + Tetrahydrozoline	0.5% + 0.6% + 0.05%
Clear Eyes® Maximum Eye Relief	Eye drop	Glycerin + Naphazoline + Zinc sulfate	0.25% + 0.012% + 0.25%
Clear Eyes® Complete Symptom Relief	Eye drop	Hypromellose + Naphazoline + Polysorbate 80 + Zinc Sulfate	0.2% + 0.025% + 0.5% + 0.25%

Fourth: Other Types of Ophthalmic Drops:

A) Drops that Extend the Iris (Mydriatics/Cycloplegics):

1. These are used during eye examination to let the doctor to see the details of the interior of the eye (cause Mydriasis), also used for children when prescribing glasses for them. **Ex: Atropine.**
2. **These are Anti-Cholinergics,** they block the action of acetylcholine resulting in relaxation of the cholinergic innervated sphincter muscle of the iris, also cholinergic stimulation of the accommodative ciliary muscle of the lens is also blocked, leading to the dilation of the pupil (Mydriasis) and paralysis of accommodation (Cycloplegia).
3. The use of these drops **causes blurred vision for a period ranging between 3 - 8 hours**, especially for near vision, so it is advisable to avoid driving a car meanwhile.

Scientific name	Dosage form	Trade name	concentration
Atropine	Eye drop	Isopto Atropine®	0.5% , 1%
	Eye Oint		1%
Tropicamide	Eye drop	Mydriacyl®, Midax®, Mydrapid®	0.5% , 1% (15 ml)
Cyclopentolate	Eye drop	Cyclogyl®	0.5% , 1% (15 ml)
Homatropine	Eye drop	Isopto Homatropine®	2% , 5%
Scopolamine	Eye drop	Isopto Hyoscine®	0.25%

Note: Some Mydriatics comes in combination product, which has been shown to induce Mydriasis greater than of each drug alone.

Scientific name (s)	D. form	Trade name	concentration
Cyclopentolate + Phenylephrine *	Eye drop	Cyclomydril®	0.2% + 1%
Scopolamine + Phenylephrine	Eye drop	Murocoll-2®	0.3% + 10%
Tropicamide + Hydroxyamphetamine	Eye drop	Paremyd®	0.25% + 1%

* **Phenylephrine** acts directly on alpha-adrenergic receptors in eye producing contraction of dilator muscle of pupil & constriction of arterioles in conjunctiva.

B) Anesthetic Eye Drops:

1. Ophthalmic Anesthetics are used in the initial assessment of minor eye trauma, the removal of superficial foreign bodies; measurement of intraocular pressure using **applanation tonometry** and in ocular surgery, a recent application in the correction of strabismus is being explored.
2. **These agents should not be used for long-term management of ocular pain: they are toxic to the corneal epithelium;** they also abolish the corneal reflex so increasing the risk of corneal damage.

Scientific name	Dosage form	Trade name	concentration
Lidocaine	Eye drop	Akten®	35 mg/ml
	Eye Gel		3.5%
Proparacaine	Eye drop	Alcaine® , Ophthaine®	0.25% , 0.5%
Tetracaine	Eye drop	Pontocaine® , TetraVisc®	0.5%
Benoxinate *	Eye drop	Novesine® , Burokain®	0.4%
Oxybuprocaine *	Eye drop	Colircusi®	0.4%

* Comes in a single dose unit containing 0.5 ml, each carton contains 20 single unit. (2)

* **Benoxinate = Oxybuprocaine**, they are the same drug.

Combinations products of Ophthalmic Anesthetics:

Scientific name(s)	D. form	Trade name	concentration
Oxybuprocaine + Tetracaine	Eye drop	Colircusi Double®	(4 mg + 1 mg)/1 ml
Oxybuprocaine + Chlorhexidine	Eye drop	Désomédine®	(4 mg + 0.6 mg)/1 ml
Benoxinate + Fluorescein *	Eye drop	Fluress® , Fluorox®	(0.4% + 0.25%)
Proparacaine + Fluorescein	Eye drop	Fluorocaine®	(0.5% + 0.25%)

* **Fluorescein** when gets in contact with aqueous humor it increases intensity of green fluorescence (helps to see the details of the interior eye).

C) Anti-Cataract Eye Drops:

1. A cataract is a clouding of the lens in the eye that blurs vision, changes the way you see colors (they seem faded) and generally reduces visual acuity; **Cataracts usually are age-related, and may occur due Diabetes and other metabolic disorders, and due accumulated free-radical damage** to the protein molecules that form the lens of the eye; once cataracts form, they tend to grow, clouding larger and larger areas of the lens.
2. Cataracts are **the most common cause of blindness**, and are **conventionally treated with surgery**; Visual loss occurs because opacification of the lens obstructs light from passing and being focused on to the retina at the back of the eye; **Also,** the use of the **oral antioxidants can be useful in cases of accumulated free-radical damage.**

Scientific name	D. form	Trade name	concentration
Azapentacene	Eye drop	Cataxol® , Lutrax®	0.15 mg/ml (15 ml)
Pirenoxine	Eye drop	Catalin®, Clarvisan®	0.8 mg /15 ml
N – Acetyl Carnosine	Eye drop	Can-C®	1%

Combination drops for Cataracts

Scientific name	D. form	Trade name	concentration
N – Acetyl Carnosine + Carboxymethylcellulose + Boric Acid + Glycerin	Eye drop	Oxymoist®	10 mg + 3 mg + 3 mg + 10 mg
K^+ Iodide + Na^+ Iodide	Eye drop	Vitreolent®	0.3% + 0.3% (10 ml)
K^+ Iodide + Ca^+ Chloride + Na^+ Chloride	Eye drop	Catagon® , Catarest®	(3.3% + 1% + 0.83%)/(5 ml)

D) Other Drops Types:

Scientific name	Dosage form	Trade name	concentration
***Taurine** **	Eye drop	Bestoxol®	0.4 gm /8 ml
Cysteamine **	Eye drop	Cystaran®	0.44%
Cyclosporine **	Eye drop	Restasis®	0.05%

Notes:

1. **Taurine** is an organic amino acid which has **anti-inflammatory** and **analgesic properties**, Taurine Eye Drops is used to **treat cataracts** caused by taurine metabolic disorders also can be used for the treatment of herpes conjunctivitis, viral conjunctivitis, adjuvant therapy, and acute conjunctivitis, **also can be used for Glaucoma (open-angle).**
2. **Cysteamine** is indicated for Corneal Cysteine Crystal accumulation.
3. **Cyclosporine** (immunosuppressant) drop is designed to increase tear production in patients with dry eyes, (it appears to work by decreasing swelling in the eyes; thus, increasing tear flow).
   - It's licensed for severe keratitis in patients with dry eye disease.

Fifth: Intra-vitreal Eye Injections:

1. Intra-vitreal is a route of administration of a drug directly into the eye; it has become a popular method of treatment of many retinal diseases, commonly including AMD, Diabetic Retinopathy, and Retinal Vein Occlusions.
2. This technique is very helpful and has the advantage of the direct effect and the fast onset, **BENEFITS of Intra-vitreal Injections** depend on the ocular pathology being treated, but mainly include improvement of vision or prevention of worsening of the vision (in the case of AMD or DR). In the case of an infection, the benefit is direct delivery of the antibiotic/antifungal into the eye close to the nidus of the infection.
3. **But it's also associated with many Risks,** including: Pain, Bleeding, retinal tear/detachment, Cataract (from inadvertently hitting the lens), Loss of vision, Increased IOP, with damage to optic nerve.
4. This procedure is performed in your doctor's office and requires only a local anesthetic. Before the medication is injected, the eye is numbed with anesthetic eye drops to help minimize discomfort; the eye is then cleaned with an antiseptic solution; the medication is then injected directly into the eye.
5. Intra-vitreal injections may **be administered as frequently as once a month**, depending on the condition being treated, in order to maintain eye health and optimize the vision.
6. **Common available Intra-vitreal Medications:**
   a. **Bevacizumab (Avastin®)** 1.25 mg/0.05 ml (0.675 mg/0.03 ml if considering using for treatment of Zone I+ ROP in an infant)
   b. **Ranibizumab (Lucentis®)** 0.5 mg/0.05 ml
   c. **Ganciclovir** Intra-vitreal 2.5 mg/0.05 ml (twice weekly for CMV Retinitis)
   d. **Foscarnet** Intra-vitreal 2.4 mg/0.1ml
   e. **Vancomycin** 1 mg/0.1ml
   f. **Ceftazidime** 2.25 mg/0.1ml
   g. **Amikacin** 0.4 mg/0.1ml
   h. **Amphotericin B** 0.1 ml of 5-10 mcg/ml
   i. **Dexamethasone** 0.4 mg/0.1 ml
   j. **Triamcinolone** 0.1cc of 4mg/ml **(Triesence®** is alcohol-free preparation that is FDA approved for intraocular use**)**

Sixth: Other drugs for retinal disorders:

Available pharmacological option(s) for different retinal disorders are listed below:

Retinal disorder	Available pharmacological option(s)
Age-related macular degeneration	Aflibercept, Pegaptanib, Ranibizumab and Brolucizumab (vascular endothelial growth factor inhibitors)
Macular edema	Fluocinolone acetonide, Aflibercept, Dexamethasone, and Ranibizumab,
Optic neuropathy	Idebenone (nootropic and antioxidant)
Vitreomacular traction	Ocriplasmin (recombinant proteolytic enzymes)

Scientific name	Dosage form	Trade name	concentration
Aflibercept	Intra-vitreal inj.	Eylea®	2 mg/0.05 ml (40 mg/ml)
Pegaptanib	Intra-vitreal inj.	Macugen®	0.3 mg/90 mcl
Ranibizumab	Intra-vitreal inj.	Lucentis® , Accentrix®	0.3 mg , 0.5 mg
Brolucizumab	Intra-vitreal inj.	Beovu®	6 mg/0.05 ml
Ocriplasmin	Intra-vitreal inj.	Jetrea®	0.5 mg/0.2 ml
Verteporfin	Vial	Visudyne®	15 mg

References

1- Rosemary R. Berardi. Handbook of Nonprescription Drugs: 18th Edition
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th ed.
4- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Ed.
5- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition. Ph. Press
6- Community Pharmacy: Symptoms, Diagnosis and Treatment, By Paul Rutter 4th Ed.
7- Comprehensive Ophthalmology, 4th Edition, by A.K. Khurana.

EAR, NOSE, AND THROAT

Chapter Thirteen: Ear, Nose, and Throat

13.1- Drugs acting on the Ear (Otics)

1. Guidelines for administering Ear drop (teach the patient)
2. Treatment of Otitis Externa
3. Treatment of Otitis Media
4. Removal of Ear Wax (Cerumen)
5. Complications of the Otitis Media
   - Vertigo
   - Ménière's disease:
   - Tinnitus

13.2 - Drugs acting on the Nose

- How to use Nasal Products: (teach the patient)

1. Drugs used in Nasal Allergy
   - **A.** Nasal Corticosteroids
   - **B.** Nasal Mast-cell stabilizers and Anticholinergics
   - **C.** Nasal Antihistamine
2. Sinusitis
   - **A.** Topical Nasal Decongestants
   - **B.** Oral Decongestants

13.3 - Drugs acting on the Oropharynx (Mouth & Throat)

First: Mouth Ulcers

- Topical corticosteroids (For Mouth Ulcers)

Second: Oral Thrush

- Topical antifungals
- Other Products for Oral Thrush

Third: Third: Dry Mouth (Xerostomia)

Fourth: Mouth Products

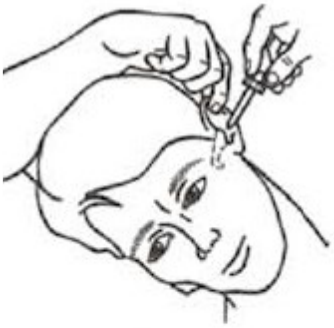
- **A.** Mouthwashes and Gargles
- **B.** Mouth sprays
- **C.** Lozenges
- **D.** Tooth Pastes

Chapter Thirteen: Ear, Nose, and Throat

13.1-Drugs acting on the ear (Otics)

13.1.1 Guidelines for administering Ear drop (teach the patient)

1-Wash your hands with soap and warm water; then dry them thoroughly.
2-Carefully wash and dry the outside of the ear, taking care not to get water in the ear canal.
3-Warm eardrops to body temperature by holding the container in the palm of your hand for a few minutes. Do not warm the container in hot water. Hot eardrops can cause ear pain, nausea, and dizziness.
4-If the label indicates, shake the container.
5-Tilt your head (or have the patient tilt his or her head) to the side, as shown in drawing A. Or lie down with the affected ear up, as shown in drawing B. Use gentle restraint, if necessary, for an infant or a young child.



A

B

6-Open the container carefully. Position the dropper tip near, but not inside, the ear canal opening. Do not allow the dropper to touch the ear, because it could become contaminated or injure the ear. Eardrop bottles must be kept clean.
7-Pull your ear (or the patient's ear) backward and upward to open the ear canal (see drawing A). If the patient is a child younger than 3 years old, pull the ear backward and downward (see drawing B).
8-Place the proper dose or number of drops into the ear canal. Replace the cap on the container.
9-Gently press the small, flat skin flap (tragus) over the ear canal opening to force out air bubbles and push the drops down the ear canal.
10-Stay (or keep the patient) in the same position for the length of time indicated in the product instructions. If the patient is a child who cannot stay still, the primary care provider may tell you to place a clean piece of cotton gently into the child's ear to prevent the medication from draining out. Use a piece large enough to remove easily, and do not leave it in the ear longer than an hour.
11-Repeat the procedure for the other ear, if needed.
12-Gently wipe excess medication off the outside of the ear, using caution to avoid getting moisture in the ear canal.

13.1.2 - Treatment of Otitis Externa

1. **Otitis Externa is a general term used to describe inflammation of the skin of the external auditory canal** that may be due to infection with bacteria, viruses, or fungi or secondary to skin disorders such as eczema.
2. Otitis Externa may be acute or chronic; the treatment of both acute and chronic otitis Externa includes thorough cleansing and the **use of appropriate antibacterial ear drops**, **with or without a corticosteroid**, even though some have doubted the value of topical Antibacterials (Topical corticosteroids are used to treat inflammation and eczema in otitis Externa; if infection is present, the corticosteroid is used in combination with a suitable anti-infective).
3. **Ear drops containing aminoglycosides** (Gentamicin, Neomycin, Framycetin, or Polymyxin) **should not be used when the ear drum is perforated** (the risk of ototoxicity).
4. Generally ophthalmic preparations containing antibiotics and/or corticosteroids can be used in the ears.
    - See chapter 12, for ophthalmic antibiotics.
    - See chapter 12, for ophthalmic Corticosteroids and NSAIDs.
    - See chapter 12, for combinations of antibiotics + Corticosteroids.

5. These drops are **designed for Otic use:**

Scientific name	Dosage form	Trade name	concentration
Acetic Acid *	Otic Drop	VoSol®	2%
Ciprofloxacin	Otic Drop	Cetraxal®	0.2% (0.25 ml single use)
Ofloxacin	Otic Drop	Floxin®	0.3%
Finafloxacin	Otic Drop	Xtoro	0.3%

* **Acetic Acid** has an antibacterial/antifungal activity.

6. Otic Combination Products:

Scientific name(s)	D. form	Trade name	concentration
***Phenazone + Chlorbutol** **	Otic Drop	Otocalm®	5% + 1%
***Phenazone + Lidocaine** **	Otic Drop	Otipax®	0.64 gm + 0.16 gm
Ciprofloxacin + Dexamethasone	Otic Drop	Ciprodex®	0.3% + 0.1%
Ciprofloxacin + Hydrocortisone	Otic Drop	Cipro HC®	0.2% + 1%
Ciprofloxacin + Fluocinonide	Otic Drop	Otovel®	0.3% + 0.025%
Acetic Acid + HC	Otic Drop	VoSol Plus®	2% + 1%
Clotrimazole * + Lignocaine	Otic Drop	Candid®	1% + 2% (per 10 ml)
Hydrocortisone + Neomycin + Polymyxin B	Otic Drop	Otosporin® , Cortisporin®	(1% + 0.35% + 10,000 Unit) Per 1 ml
Hydrocortisone + Neomycin + Colistin + Thonzonium	Otic Drop	Coly-Mycin S®	(3.3 mg + 10 mg + 3 mg + 0.5 mg) Per 1 ml
Polymyxin B + Neomycin + Hydrocortisone + Aminacrine + Benzocaine	Otic Drop	Flavaco®	0.1% + 0.25% + 0.02% + 0.1% + 2%

*** Phenazone (Tropex®)** is an analgesic, a NSAID drug and an antipyretic.
* **Chlorbutol (**or **Chlorobutanol)** has mild antibacterial and antifungal properties.
* **Clotrimazole** is a topical antifungal, **Lignocaine** is a topical anesthetic.

13.1.3 - Treatment of Otitis Media

1. Otitis media is a general term used to **describe inflammation of the middle ear** that usually results from dysfunction of the Eustachian tube after a viral infection of the nasopharynx. **It is one of the most frequent childhood illnesses seen in general practice**.

2. Acute otitis media is the commonest cause of severe ear pain in small children.

3. Its common practice to prescribe **a systemic antibacterial with an analgesic for otitis media**, although the need for routine antibacterial treatment is questionable.

4. The American Academy of Pediatrics has produced guidelines for the diagnosis and management of uncomplicated acute otitis media (**AOM)** in children from 2 months to 12 years of age; **they suggest that these children should be given symptomatic treatment and observed for 48 to 72 hours; if the illness worsens during the observation period or there is no improvement then systemic Antibacterials should be considered**.

5. Pain management is important, and appropriate analgesics should be offered, if antibacterial treatment is given → **high dose amoxicillin (80 to 90 mg/kg daily)** is recommended for most children, Alternative choices include **cephalosporins** or **macrolide** antibiotics, if there is no improvement after three days, switching antibiotics should be considered.

13.1.4 - Removal of Ear Wax (Cerumen)

A) Non-pharmacologic Therapy:

1. The only recommended non-pharmacologic method of removing cerumen is to use **a wet, wrung-out washcloth draped over a finger.**
2. The common **use of cotton-tipped swabs** to remove earwax is **ineffective and potentially dangerous**, increasing the risk of **Otitis Externa** and leading to **perforation** of the **eardrum.**

B) Pharmacologic Therapy (Cerumenolytics):

These agents used to soften ear wax examples are:

1. **Sodium bicarbonate** (freshly prepared): This product should be instilled **two to three times a day for up to 3 days**.
2. **Docusate (dioctyl sodium sulpho-succinate) (Dewax®):** The manufacturers of Dewax® recommend that adults and children **use enough ear drops to (Fill) the affected ear on not more than two consecutive nights (don't use more than 2 days).**
3. **Carbamide peroxide:** when it makes contact with the tissue, oxygen is released, producing a foaming action. This foaming action softens impacted cerumen, (used as 5 – 10 drops every 12 or 8 hours), **don't use more than 4 days.**
4. **Olive oil (sweet oil) is used to soften earwax and alleviate itching.**
5. **Hydrogen peroxide** may be diluted 1:1 with warm water and instilled in the ear to aid in cerumen softening and removal.

Scientific name	Dosage form	Trade name	concentration
Dioctyl Sodium Sulpho-Succinate	Otic Drop	Dewax®	5 mg/ml
Carbamide Peroxide	Otic Drop	Debrox®, Oticlean®, Murine®	6.5% , 10%
Triethanolamine	Otic Drop	Cerumenex®	10%
Arachis Oil + Chlorobutanol + Dichlorobenzene	Otic drop	Cerumol®	Herbal Combination

13.1.5 – Complications of the Otitis Media

A) Vertigo:

Vertigo is a **spinning sensation in the head often accompanied by nausea and vomiting**, it is usually caused by a disease affecting the organ of balance in the inner ear; It is a loss of equilibrium in which one might describe a room as spinning, the vestibular compartment of the inner ear is responsible for maintaining balance and Equilibrium, and the autonomic system may become involved if the vertigo is severe, producing dizziness, pallor, sweating, and nausea.

B) Ménière's disease:

a disorder in which **excess fluid builds up in the inner ear**, causing vertigo, noises in the ear, and gradual deafness; **In severe cases of Ménière disease**; the doctors sometimes tend to do some kind of **destructive surgery by injecting an aminoglycoside to the inner ear**, to benefit from its side effect (vestibular ototoxicity) in controlling the Tinnitus.

- It is usually treated with **Cinnarizine**, **Betahistine**, **Prochlorperazine**, or an **anti-anxiety drug**. A diuretic may also be given to reduce the excess fluid in the ear.

C) Tinnitus:

It's may be described by patients as a ringing, buzzing, hissing, whistling, or humming noise Lasting from seconds to minutes. Tinnitus has been linked to a variety of causes, including Ménière disease, head injuries, otitis media, syphilis, temporomandibular-joint (TMJ) dysfunction, and certain medications (NSAIDs, loop diuretics, and chemotherapeutic agents).

Note: Betahistine and **Cinnarizine** are used in the treatment of Vertigo and Tinnitus.
(See Chapter 4, section 6, for more details)

Scientific name	Dosage form	Trade name	concentration
Betahistine	Tab	Betaserc®	8 mg , 16 mg
Cinnarizine	Tab	Stugeron®	25 mg
	Cap		75 mg

13.2 - Drugs acting on the Nose

1. **Allergic rhinitis**, also known as hay fever, is a type of inflammation in the nose which occurs when the immune system overreacts to allergens in the air; signs and symptoms include a runny or stuffy nose, sneezing, red, itchy, and watery eyes, and swelling around the eyes.
2. **Treatment options** include:
    1. Intra nasal corticosteroids (1st line therapy), see below.
    2. Oral antihistamine (1st line therapy), see chapter 1.
    3. Oral Leukotriene receptor antagonist, see chapter 1.
    4. Intra nasal antihistamine, see below.
    5. Decongestants, see below; and for more combination products see chapter 1
    6. Intra nasal mast cell stabilizer, see below.
    7. Intra nasal muscarinic/anticholinergic, see below.

- **Nasal sprays are preferable for adults and children aged over 6 years** because spray has a faster onset of action and cover a large surface area.
- **Nasal drops are preferable for children aged below 6 years** because their nostrils are not sufficiently wide to allow effective use of sprays.

How to use Nasal Products: (teach the patient)

Drops	Spray (Atomizer)	Inhalers	Metered-Dose Pump (Spray)
• Blow nose • Squeeze rubber bulb on dropper and withdraw medication from bottle • Recline on bed and hang head over side (preferred) *or* tilt head back while standing or sitting • Place drops into each nostril and gently tilt head from side to side to distribute drug • Keep head tilted back for several minutes after instilling drops • Rinse dropper with hot water	• Blow nose • Remove cap from spray container • For best results, do not shake squeeze bottle • Administer one spray with head in upright position • Sniff deeply while squeezing bottle • Wait 3–5 mins, then blow nose • Administer another spray if necessary • Rinse spray tip with hot water, taking care not to allow water to enter bottle • Replace cap	• Blow nose • Warm inhaler in hand to increase volatility of medication • Remove protective cap • Inhale medicated vapor in one nostril while closing off other nostril; repeat in other nostril • Wipe inhaler clean after each use • Replace cap immediately • *Note*: Inhaler loses its potency after 2–3 months even though aroma may linger	• Blow nose • Remove protective cap • Prime metered pump by depressing several times (for first use), pointing away from face • Hold bottle with thumb at base and nozzle between first and second fingers • Insert pump gently into nose with head upright • Depress pump completely, and sniff deeply • Wait 3–5 mins, then blow nose • Administer another spray if necessary • Rinse spray tip with hot water, taking care not to allow water to enter bottle • Replace cap

13.2.1 - Drugs used in Nasal Allergy:

A) Intra Nasal Corticosteroids

1. Nasal preparations containing corticosteroids have a useful role in the **prophylaxis and treatment of allergic rhinitis** [3], **Regular us**e is essential for full benefit and **it takes several days** before full effect is reached; Considered as 1st line therapy; they reduce sneezing, itching, rhinorrhea and congestion; They are **more effective than intra nasal/oral antihistamines** in the treatment of persistent or sever rhinitis.
2. Triamcinolone, Mometasone, Fluticasone Furoate can be used form age of 2 years and above.
3. Beclomethasone, Budesonide, Ciclesonide can be used from age of 6 years and above.

Scientific name	Dosage form	Trade name	concentration
Betamethasone	Nasal drop	Methadin®	0.1 % (10 ml)
Beclomethasone	Nasal spray	Beconazse®	42 mcg/spray
Budesonide	Nasal spray	Rhinocort Aqua®, Cortinase®	32 mcg , 64 mcg (per Actuation)
Mometasone	Nasal spray	Nasonex® , Momate®	50 mcg/spray
Triamcinolone	Nasal spray	Nasacort®	55 mcg/spray
Ciclesonide	Nasal spray	Omnaris®	50 mcg (per Actuation)
Flunisolide	Nasal spray	Aerospan nasal®	25 mcg (per Actuation)
Fluticasone	Nasal spray	Flonase® , Flixonase®	50 mcg/spray
Combination products			
Fluticasone + Azelastine *	Nasal spray	Dymista®	(50 mcg + 137 mcg)/spray
Mometasone + Azelastine	Nasal spray	Momate AZ®	(50 mcg + 140 mcg)/spray

* **Azelastine is an anti-histamine.**

B) Mast-cell stabilizers and Anticholinergics

1. Such as **Nedocromil**, and **sodium Cromoglicate**, they are an **alternative to corticosteroids in the prophylactic treatment of allergic rhinitis**; (**but may be less effective**).
2. All Mast cell stabilizers are used 4 times per day, **Except Nedocromil** which is used twice daily, Treatment course is usually ranges from 4 weeks to 6 weeks.
3. It's useful for patients with specific known allergy who plan on getting in contact with that allergen. (intended prophylaxis use).
4. **Ipratropium** bromide (anticholinergic) is available as intranasal spray for Rhinorrhea associated with allergic and non-allergic rhinitis.

These are ophthalmic products, but can be used nasally.

Scientific name	Dosage form	Trade name	concentration
Na^+ Cromoglycate (or) Cromolyn Na^+	Eye drop	Crolom®, Opticrom®, Allergotin®	4% (10 ml), 2% (10 ml)
Lodoxamide	Eye drop	Alomide®	0.1%
Nedocromil	Eye drop	Alocril®	2%
Pemirolast	Eye drop	Alamast®	0.1% (1 mg/ml)
Ipratropium	Nasal spray	Atrovent Nasal®	0.03% , 0.06%

C) Intra nasal Antihistamine

1. Topical antihistamines are considered less effective than topical corticosteroids but probably more effective than Cromoglicate.
2. Approved for use from age of 5 years and above.
3. **Azelastine** is useful for controlling breakthrough symptoms in allergic rhinitis.

Scientific name	Dosage form	Trade name	concentration
Azelastine	Nasal Spray	Astelin®, Allergodil® , Astepro®, Rhinolast®	0.1%
Olopatadine	Nasal Spray	Patanase®	6%

13.2.2 - Sinusitis

1. **Symptoms** → Headache, face pain around sinus area, yellowish discharge, sinus congestion, Cough & Loss of smell, Additional symptoms may include Fever, Bad breath, Fatigue.
2. **Acute sinusitis** may be diagnosed when a person has two or more symptoms and/or by the Presence of thick, green, or yellow nasal discharge .
3. **Viral Nasopharyngitis** (common cold) commonly spreads to involve the Para-nasal sinuses but this usually subsides within 2-3 days without treatment; However, secondary bacterial infection of sinuses may occur and results in persistence of purulent nasal discharge, high fever or persistent cough; **Management includes** :
   1. **Antibiotic therapy:** An oral broad-spectrum antibiotic for 10-14 days is indicated for control and eradication of bacterial infection. Choices are
      a. **Broad spectrum Penicillins** as ampicillin or amoxicillin (50-100 mg/kg/day); The newer drugs as sultamicillin (ampicillin + sulbactam) or Co-Amoxiclave (amoxicillin + clavulanic acid) are more effective than either drug alone.
      b. **Second generation Cephalosporins** as cefuroxime (40 mg/kg/day) are effective.
      c. **Macrolides** as clarithromycin or azithromycin can be also used.
   2. **Nasal decongestants:** Oral nasal decongestants can be used in the first 4-5 days of therapy to reduce sinus congestion.
   3. **Analgesic and antipyretics:** Paracetamol or other antipyretics may be needed in the first few days to control fever and pain.

A) Topical Nasal Decongestants

1. Intra-nasal Sympathomimetics such as **phenylephrine, Naphazoline, Oxymetazoline,** and **Xylometazoline** may be useful for **short-term treatment to relieve severe nasal congestion**, (Symptoms of nasal congestion associated with rhinitis and the common cold can be relieved by the short-term use (usually not longer than 7 days) of decongestant nasal drops and sprays).
2. **Not to use these products for longer than 7 days because** of **rebound congestion** (with congestion returning after stopping the drug often worse than before).
3. Some of these products may present **in 2 concentrations** (one for children and for adults).
4. Nasal drop containing **normal saline is preferred for infants** (may relieve nasal congestion by helping to liquefy mucous secretions).
5. **Xylometazoline** is also available as a **topical cream 1%**, indicated for the topical treatment of persistent **facial erythema associated with rosacea in adults.**
   - **Xylometazoline can be abused** by addicts to obtain the **psychoactive effects** of inhaled Xylometazoline; which include excitation and feeling of strength.

Scientific name	Dosage form	Trade name	concentration
Xylometazoline	Nasal Drop / Nasal Spray	Otrivin Adult®, Triaminic®, Xylo-mepha®	0.1%
	Nasal Drop	Otrivin Child®	0.05%
Oxymetazoline	Nasal Drop	Afrin® , Dristan® , Nasordine®	0.05%
Phenylephrine	Nasal Spray/Drop	NeoSynephrine®	0.25% , 0.5%
Naphazoline	Nasal Spray/Drop	Privine®	0.05%
Tetrahydrozoline	Nasal Drop	Visine® , Burnil®	0.05% , 0.1%
Propylhexedrine	Nasal inhaler	Benzedrex®	250 mg

Notes:

1. All topical Sympathomimetics **are not recommended to use in children below 6 years, Except for Xylometazoline 0.05% which can be used in children above 2 years old, younger children (below 2 years) are to use NaCl nasal drops for treatment of decongestion.**
2. Adverse effects of topical decongestants are: burning, stinging, sneezing, and dryness.

B) Oral Decongestants

1. Systemic decongestants are sympathomimetic agents that act on adrenergic receptors in the nasal mucosa to produce vasoconstriction, shrink swollen mucosa, and improve ventilation.
2. Usually comes in combinations of sympathomimetic like **pseudoephedrine** and **phenylephrine** (they reduce nasal congestion) and antihistamine (like **Triprolidine**) (they reduce rhinorrhea and sneezing).
3. Systemic decongestants should be used with caution in hypertension, hyperthyroidism, and ischemic heart diseases.

Trade name	D.form	Scientific name(s)	Concentration
Actifed®	Tab	Triprolidine + Pseudoephedrine	2.5 mg + 60 mg
Actifed®, Samafed®	Syrup	Triprolidine + Pseudoephedrine	(1.25 mg + 30 mg)/5ml
Semprex D®	Cap	Acrivastine + Pseudoephedrine	8 mg + 60 mg
Snip®	Tab	Paracetamol + Pseudoephedrine	325 mg + 15 mg
Salzone®	Cap	Paracetamol + Phenylephrine	500 mg + 6.1 mg
Clarinase®	Tab	Loratadine + Pseudoephedrine	5 mg + 120 mg
Xinase®, Clearest®	Tab	Cetirizine + Pseudoephedrine	5 mg + 120 mg
Coldin®	Tab	Paracetamol + Promethazine Phenylephrine	450 mg + 5 mg 5 mg

**** For more info, see chapter 1, section 3.**

13.3 - Drugs acting on the Oropharynx (Mouth & Throat)

First: Mouth Ulcers:

1. **Aphthous ulcers**, more commonly known as **mouth ulcers**, is a collective term used to describe various different clinical presentations of **superficial painful oral lesions** that occur in recurrent episodes, **it's not due infection** but several other causes have linked to it including: stress, trauma, food sensitivities, nutritional deficiencies (Iron, Zinc and Vitamin B_{12}), but none have so far been proven.
   - Sometimes **Aphthous ulcers occurs in smoking patient when the quite smoking**; the use of Nicotine replacement therapy for people who have developed oral ulceration after stopping smoking is recommended in such cases; although, starting smoking again does not usually lessen the condition.
2. **Treatment options include**
   a. Topical products containing **anesthetics** or **analgesics**
   b. **Topical corticosteroids**
   c. **Amlexanox**; an anti-inflammatory and anti-allergic immunomodulator used to treat recurrent Aphthous ulcers, and (in Japan) used for several inflammatory conditions; This drug has been discontinued in the U.S.
   d. **Benzydamine**; a topical anti-inflammatory and anesthetic, indicated for acute pharyngitis and Aphthous ulcers.
   e. **herbal remedies** as alternative treatments, including aloe vera, myrtus communis, Rosa damascena, potassium alum, zinc sulfate.

Topical corticosteroids (For Mouth Ulcers)

1. **Triamcinolone** in orabase (oral gel) (**Kenalog in orabase®**) is used for mouth ulcer, it is applied 2-4 times **daily after food** (after food, as food is likely to rub the paste off).
2. **Hydrocortisone** Lozenges (pellets): used 4 times daily.
3. **Betamethasone** Mouth wash: comes as a tablet (0.5 mg) that dissolves in water (in 15 ml) then wash with it the mouth for 5 minutes, used 4 times a day. (**Do not swallow it).**

Scientific name	Dosage form	Trade name	concentration
Triamcinolone	Oral gel/Paste	Kenalog®, Danticort®	1 mg/gm (10 gm tube)
Lidocaine + Aminoacridine	Gel	Medijel®	(2 mg + 0.15 mg)/gm
Rhubarb + Salicylic Acid	oromucosal Solu.	Pyralvex®	(50 mg + 10 mg)/ml
Hydrocortisone	Pellets	Corlan®	2.5 mg
Betamethasone	Tab	Betnesol®	0.5 mg
Amlexanox	Oral Paste	Aphthasol®	5%

Second: Oral Thrush

1. Oropharyngeal candidiasis (oral thrush) is an **opportunistic mucosal infection** and is unusual in healthy adults; The very young (neonates) and the very old are most likely to suffer from it.
2. The classical presentation of oral thrush is of **creamy-white soft elevated patches** that **can be wiped off revealing underlying erythematous mucosa**, Pain, soreness, altered taste and a burning tongue can be present. Lesions can occur anywhere in the oral cavity but usually affect the tongue, palate, lips and cheeks.

Topical antifungals

1. Topical antifungals for **thrush** include **Nystatin** (as an oral drop (as a Susp.) and **Miconazole** (as an oral gel).
   - **Nystatin dose: Adult** and **child 100,000 units** (1ml of the drop) **4 times daily after food (hold in mouth),** usually for 7 days (continued for 48 hr. after lesions have resolved); **Nystatin** is used safely for any child age (it's non-absorbable by the guts).
   - **Miconazole** is applied twice daily for 5 days. **(Used in patient older than 4 months Only)**, treatment should be continued for at least 7 days after lesions have healed or symptoms have cleared, to be administered after meals, retain near oral lesions.

Scientific name	Dosage form	Trade name	concentration
Nystatin	Oral Drop	Mycostatin®	100,000 units
Miconazole	Oral paste	Daktarin®, Miconaz®	20 mg
Clotrimazole	Lozenges	Mycelex Troche®	10 mg

Other products for Oral Thrush

Scientific name	Dosage form	Trade name	concentration
Metronidazole	Oral Gel	Metrogel® , Elyzol®	25% (250 mg/gm)
Gentian Violet*	Topical Solu.	Gentian®	1%

*** Gentian Violet** is a dye that kills bacteria and fungi; It can be an effective treatment for thrush, it's **applied topically ONLY** using a cotton swab to apply a very small amount, **it should not be given to new-borns, because it can cause open sores (ulcers) in the mouth.**

Third: Dry Mouth (Xerostomia)

1. Dry mouth may be caused by drugs with antimuscarinic (anticholinergic) side effects, by diuretics, by irradiation of the head and neck region or by damage to or disease of the salivary glands, as in Sjögren's syndrome (an autoimmune disease; in which the immune system attacks the glands that make tears and saliva); Patients with a persistently dry mouth may develop a burning or scalded sensation and have poor oral hygiene; they may develop increased dental caries, periodontal disease, and oral infections (particularly candidiasis).
2. Dry mouth may be relieved in many patients by simple measures such as frequent sips of cool drinks or sucking pieces of ice or sugar-free fruit pastilles; Sugar-free chewing gum stimulates salivation in patients with residual salivary function.
3. Artificial saliva can provide useful relief of dry mouth, also Salivary stimulants (**Cevimeline** and **Pilocarpine**, are indicated for xerostomia in patients with Sjögren's syndrome.
   - ➢ They are effective only in patients who have some residual salivary gland function, and therefore should be withdrawn if there is no response

Scientific name	Dosage form	Trade name	concentration
Cevimeline	Cap	Evoxac®	30 mg
Pilocarpine	Tab	Salagen®	5 mg

Fourth: Mouth Products

A) Mouthwashes and Gargles:

1. Mouthwashes are employed for the **improvement of oral hygiene**; For example, **Chlorhexidine, Hexetidine** are both an effective antiseptic which has the advantage of inhibiting plaque formation on the teeth.
   - **a.** They are also useful in minor mouth infections including thrush.
   - **b.** Used as an aid in the prevention and treatment of gingivitis.
   - **c.** Used in the management of sore throat and recurrent Aphthous Ulcers.
2. Notes regarding **Chlorhexidine** containing Mouthwashes:
   - **a.** Dose: rinse mouth **with 10 mL for about 1 minute twice daily**.
   - **b.** It may cause **reversible brown staining of teeth**.
   - **c.** **Chlorhexidine gluconate may be incompatible with some ingredients in toothpaste**; so, leave an interval of at least 30 minutes between using mouthwash and toothpaste.

Scientific name	Dosage form	Trade name	concentration
Chlorhexidine	Mouthwash	***Corsodyl®, Zak®, BioFresh K®***	0.12%
Hexetidine	Mouthwash	***Oraldene®***	0.1%
Cetrimide + Lidocaine	Mouthwash	***Citrolin®***	(25 mg + 3 mg)/100 ml
Cetrimide + Lidocaine + Chlorhexidine + Sodium Fluoride	Mouthwash	***Citrolin F ®***	(25 mg + 3 mg + 20 mg + 50 mg)/100 ml
Chlorhexidine + Sodium Fluoride	Mouthwash	***Parodontax®***	0.06% + 0.055%
Sodium Fluoride + Cetylpyridinium Cl + Zinc Cl	Mouthwash	***Sensodine Fresh®***	0.055% + 0.05% + 0.1%
Permethol + Vit. B_5	Mouthwash	***BioFresh P®***	0.1% + 0.5%
Chlorhexidine + Menthol + Thymol + Eucalyptol + Clove Oil	Mouthwash	***Listermix Plus®***	0.1% + 0.042% + 0.064% + 0.092% + 0.06%
Menthol + Thymol + Methyl salicylate + Eucalyptol	Mouthwash	***Listerine®***	0.042% + 0.064% + 0.06% + 0.092%

* **Cetrimide, Cetylpyridinium** are antiseptics.

B) Mouth sprays:

These usually contain antiseptics and anesthetics or an anti-inflammatory, maybe used to relief pain after teeth removal or pain due gingivitis.

Scientific name	D. form	Trade name	concentration
Cetrimide + Lidocaine	Spray	***Lido spray®***	5% , 10%
Cetrimide + Lidocaine + Chlorhexidine	Spray	***Lido Plus®***	(1 gm + 8 gm + 0.2 gm) Per 100 ml
Dequalinium Chloride + Lidocaine	Spray	Bucco-spray®, Buccosan®	----------
Dequalinium Chloride + Dibucaine	Spray	Decatylen Neo®	----------
Dequalinium Chloride + Enoxolone + Lidocaine + Hydrocortisone + Tyrothricin	Spray	***Anginovag®***	100 mg + 60 mg + 100 mg + 60 mg + 400 mg

Notes:

1. **Dequalinium Chloride** is an **antiseptic and disinfectant**. It is a **topical bacteriostatic**, used in wound dressings and mouth infections and may also have antifungal action. It may cause skin ulceration with high concentrations.
2. **Lidocaine and Dibucaine** are topical anesthetics.
3. **Enoxolone** is also called glycyrrhetinic acid (Mild antibacterial + anti-inflammatory).
4. **Tyrothricin** is local antibiotic effective against gram-positive bacteria.

C) Lozenges:

1. They are medicated tablet intended to be dissolved slowly in the mouth to temporarily stop coughs and lubricate and soothe irritated tissues of the throat (usually due to a sore throat). [1-3]
2. Lozenges may contain **benzocaine**, **Lidocaine** (an anesthetic), or **eucalyptus oil**, Non-menthol throat lozenges generally use **zinc gluconate, glycine or pectin** as an oral demulcent. Several brands of lozenges contain **dextromethorphan** (antitussive) and **Ambroxol** (mucolytic).
3. Some contain **menthol, peppermint oil** and/or **spearmint** as their active ingredient(s), Honey lozenges are also available, some contains **Flurbiprofen,** and some contain **Vit. C.**
4. **The recommended dosage is one lozenge every 2–3 hours for adults.**

Here are some selected lozenges available in our Market (Not All of them)

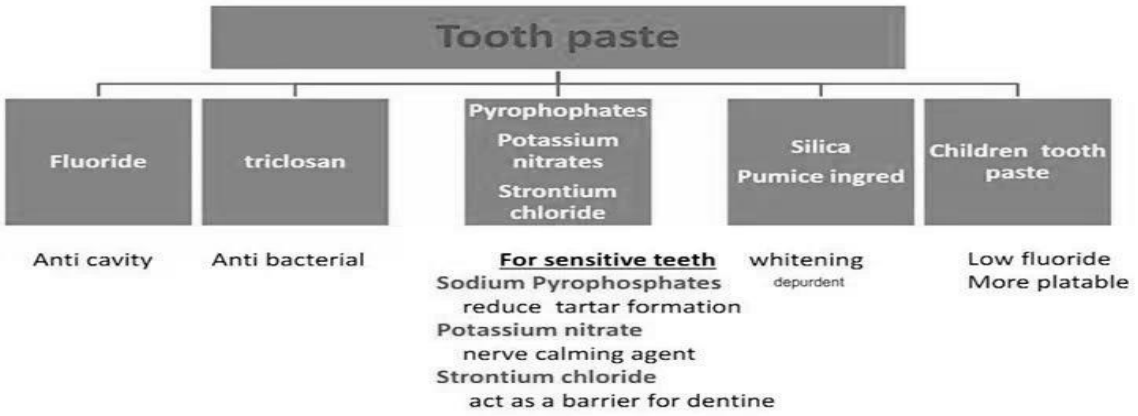
Trade Name	Dosage form	Scientific name(s)	concentration
Orofar®	lozenges	Benzoxonium + Lidocaine	1 mg + 1 mg
ZeCuf®	lozenges	Herbal Blend	----------
Strepsils®	lozenges	Dichlorobenzyl alcohol + Amylmetacresol	1.2 mg + 0.6 mg
Pectol®	lozenges	Eucalyptus oil + Vit. C	----------
Trocal®	lozenges	Dextromethorphan	7.5 mg
Boxol®	lozenges	Ambroxol	20 mg
Strefen®	lozenges	Flurbiprofen	8.75 mg

D) Tooth Pastes:

1. There is a variety of tooth paste products in the market, so check them by yourself …. They include: **Sensodine, Crest, Colgate, Parodontax** … etc.
2. Availability of adequate **Fluoride confers significant resistance to dental caries**; It is now considered that the topical action of fluoride (tooth paste, mouthwash) on enamel and plaque is more important than the systemic effect (tablet, oral drop).

Note1:

Generally, tooth pastes contains the following; each ingredient with its benefit:



Note2:

Fluoride is also available as oral tablets, and indicated for the Prophylaxis of dental caries.

Trade Name	Dosage form	Scientific name	concentration
Zymafluor®	Tab	Sodium Fluoride	0.25 mg , 0.5 mg , 1 mg
Zymafluor D®	Tab	Sodium Fluoride + Vit. D_3	(0.25 mg + 500 IU), (0.25 mg + 1000 IU)

Note3: Magic Mouth Wash

Its one of the old Rx, prescribed by the old dentists or prepared locally in the pharmacy, or in the hospital wards for the patients with mouth infections, or immunocompromised patients; there are several forms of this Rx; choose what's suits your need:

- 80 ml viscous lidocaine 2% + 80 ml diphenhydramine 12.5 mg/ml elixir + 80 ml Nystatin 100,000 IU Susp. + 80 ml Prednisolone 15 mg/5 ml + 80 ml Distilled water.
- 80 ml viscous lidocaine 2% + 80 ml Maloox Susp. + 80 ml diphenhydramine 12.5 mg/ml elixir.
- 100 ml dexamethasone 0.5 mg/5 ml + 60 ml Nystatin 100,000 IU Susp. + 100 ml diphenhydramine 12.5 mg/ml elixir + 3 capsule of 500 mg Tetracycline.

All used every 6 hours as needed, it can be swallowed if there is an esophageal involvement.

References

1- Rosemary R Berardi. Handbook of Nonprescription Drugs, 18th Edition
2- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition. Ph. Press.
3- Lexi-comp, Drug information handbook, 2022 Ed.
4- Community Pharmacy: Symptoms, Diagnosis and Treatment, By Paul Rutter 4th Ed.
5- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition.

DERMATOLOGY

Chapter Fourteen: Dermatology

Part one: Introduction

14.1- Dermatologic Drug Delivery Systems

14.2- Common Skin Diseases, by Body Location

14.3- Anti-infective skin preparations

- **A. Antibacterial preparations**
  - Combination products of some topical anti-Bacterials
  - Combination products of Anti-Bacterials + Corticosteroids
- **B. Antifungal preparations**
  - Combination Products: (Anti-Fungal + Corticosteroid)
  - Combination Products: (Anti-Fungal + Anti-Bacterial + Corticosteroid)
- **C. Antiviral preparations**

14.4- Parasiticidal preparations

- **A.** Scabies (body lice)
- **B.** Head lice
- **C.** Pubic lice

14.5- Topical Corticosteroids

14.6 - Preparations for minor cuts and abrasions

14.7- Skin Cleansers, and antiseptics

14.8- Emollients and Barrier prep.

14.9- Topical Antihistamines and antipruritics

14.10- Topical Anesthetics

14.11 - Shampoos for Dandruff

14.12 - Preparations for Psoriasis

- **A.** Topical Therapies
- **B.** Combination Topical Products
- **C.** Oral/Systemic Therapies
- **D.** Biological Agents

14.13 - Preparations for Eczema

14.14- Acne and Rosacea

- **A.** Acne
- **B.** Rosacea
  - Topical Products
  - Oral Products

14.15- Preparations for Warts and Calluses

14.16- Sunscreen preparations

14.17- Hair Loss

- **A.** Androgenetic Alopecia
- **B.** Alopecia Areata

14.18- Products for treating Hirsutism

14.19 – Vitiligo

14.20 – Skin Aging and wrinkles

14.21 – Antiperspirants

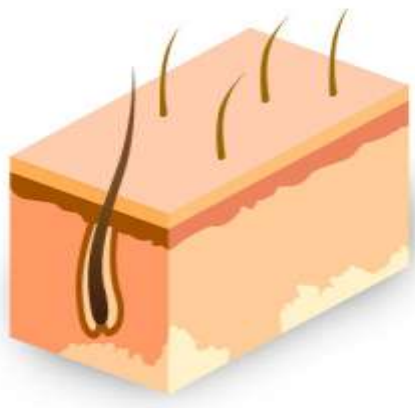
14.22 – Skin Bleachers/Skin whitening (Depigmenting Agents)

14.23 – Dark spots under the Eyes

14.24 – Topical Products for Scars

14.25 – Wound Care Products

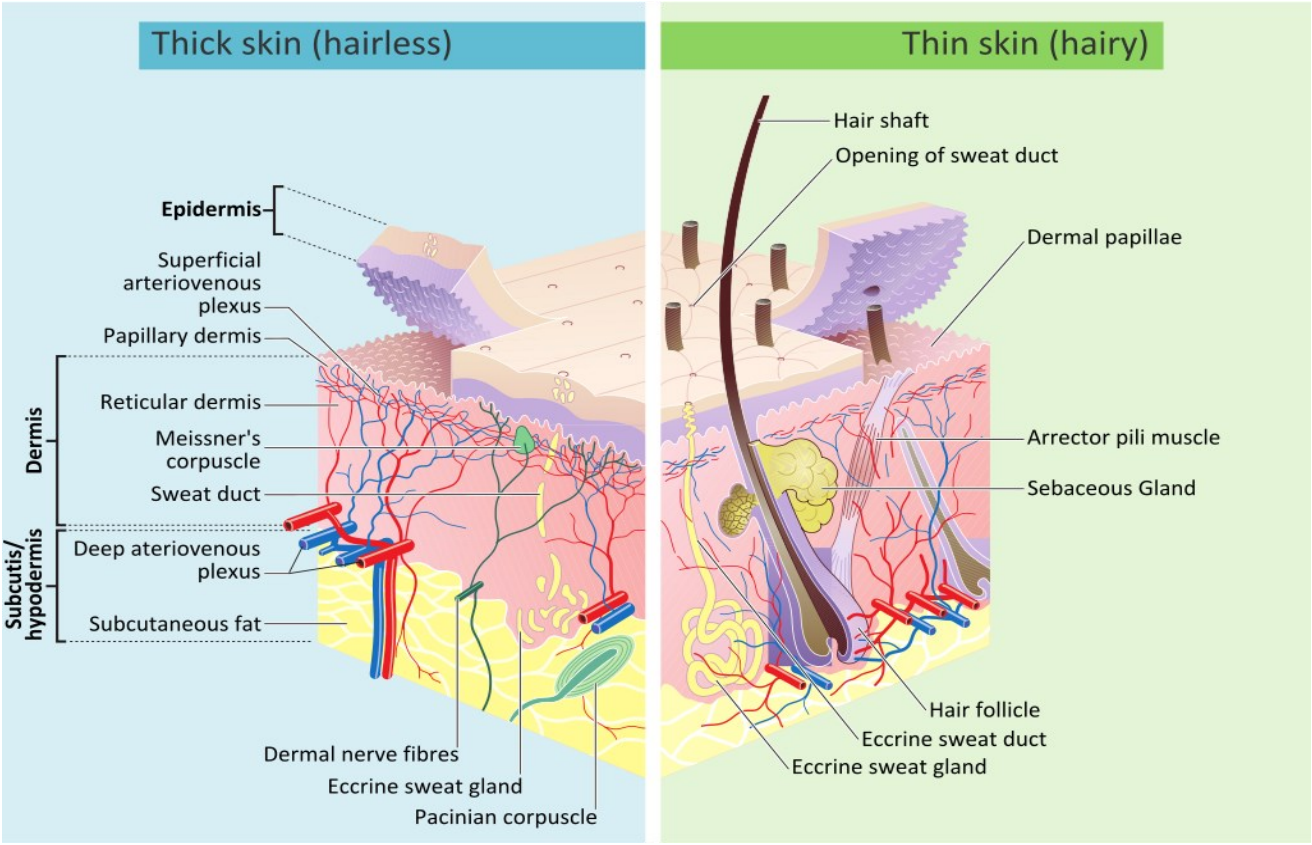
14.25 – Burns and Burn care products



Chapter Fourteen: Dermatology

Introduction:

1. The skin waterproofs, cushions, and protects the rest of the body and is, in fact, its largest organ; it provides a barrier against innumerable infections and infestations, it helps the body to retain its vital fluids, helps in the synthesis of vitamin D; and it plays a major role in temperature control, and it houses the sensory nerves of touch.
2. The skin consists of two main layers: a thin, tough top layer, the **Epidermis**, and below it a thicker layer, the **Dermis**. The epidermis also has two layers: the skin surface, or stratum corneum (horny layer) consisting of dead cells, and below, a layer of active cells.
3. The cells in the active layer divide and eventually die, maintaining the horny layer, living cells produce **Keratin**, which toughens the epidermis and is the basic substance of hair and nails.
4. Some living cells in the epidermis produce **Melanin**, a pigment released in increased amounts following exposure to sunlight.
5. The dermis contains different types of nerve ending for sensing pain, pressure, and temperature; sweat glands to cool the body; sebaceous glands to lubricate and waterproof the skin; and white blood cells that help to keep the skin clear of infection.



6. Human skin shows high skin color variety from the darkest brown to the lightest pinkish-white, (Human skin shows higher variation in color than any other single mammalian species and is the result of natural selection), skin pigmentation in humans evolved to primarily regulate the amount of ultraviolet radiation (UVR) penetrating the skin, controlling its biochemical effects.
7. The actual skin color of different humans is affected by many substances, although the single most important substance determining human skin color is the pigment **Melanin**; it is produced within the skin in cells called melanocytes and it is the main determinant of the skin color of darker-skinned humans; The skin color of people with light skin is determined mainly by the bluish-white connective tissue under the dermis and by the hemoglobin circulating in the veins of the dermis (The red color underlying the skin becomes more visible, especially in the face, when, as consequence of physical exercise or the stimulation of the nervous system (anger, fear), arterioles dilate).

8. There is a correlation between the geographic distribution of UV radiation (UVR) and the distribution of indigenous skin pigmentation around the world; Areas that highlight higher amounts of UVR reflect darker-skinned populations, generally located nearer towards the equator, Areas that are far from the tropics and closer to the poles have lower concentration of UVR, which is reflected in lighter-skinned populations.
9. In the same population it has been observed that adult human females are considerably lighter in skin pigmentation than males; Females need more calcium during pregnancy and lactation, and vitamin D which is synthesized from sunlight helps in absorbing calcium; and for this reason, it is thought that females may have evolved to have lighter skin in order to help their bodies absorb more calcium.

14.1 – Dermatological Drug Delivery Systems:

A range of dermatologic formulations is available: solutions, suspensions or shake lotions, powders, lotions, emulsions, gels, creams, ointments, and aerosols.

Each dermatologic delivery vehicle has specific characteristics and uses based on the type, and location of the lesion.

Appropriate Dermatologic Vehicle Selection Across the Range of Dermatologic Lesions

Range of Lesions	Range of Vehicles
Acute inflammation: Oozing, weeping, vesication, edema, pruritus	Aqueous vehicles and water, and then powder solutions, lotions, sprays, and aerosols
↓	↓
Subacute inflammation: Crusting, less oozing, pruritus	Creams, gels
↓	↓
Chronic inflammation: Lichenification, dryness, erythema, pruritus, scaling	Ointments

1. **Powders** are used mainly in **intertriginous areas** (e.g., groin, under the breasts, or in skin folds) to decrease friction, which can cause mechanical irritation.
   They also are useful in the treatment of Tinea pedis (athlete's foot), Tinea cruris (jock itch), and diaper dermatitis (diaper rash).
2. **Lotions** are suspensions or solutions of powder in a water vehicle (semi-liquid preparations); They are especially advantageous in the treatment of conditions characterized by significant inflammation and tenderness. In these situations, creams or ointments may cause pain on application; **Also, lotions are useful for hairy areas of the body and scalp**.
3. **Gels** are jelly-like in consistency and are often water-based, they are used increasingly for a wide variety of topical skin treatments because they are easy to apply, usually non-greasy, and more rapidly absorbed than ointments, they are most useful when applied to **hairy areas or other areas such as the face or scalp,** where it is considered cosmetically unacceptable to have the residue remain on the skin.
4. **Creams are the most commonly used** vehicle in dermatology, these have an **emollient effect,** they are usually composed of an oil-in-water emulsion and are used in the treatment of dry skin disorders; the most common mistake made by patients when applying creams is that **they use too much or do not rub them in fully;** Generally, if the cream can be seen on the skin after application, the patient has made one or both of these application mistakes.
5. **Ointments** are usually greasy and are suitable for treating wet (weeping) eczema and very dry chronic lesions (they are most useful on **chronic lesions)**, relieving dryness, brittleness, and protecting fissures owing to their occlusive properties; They **should not be used on acutely inflamed lesions**. Ointments should not be applied to intertriginous or hairy areas because they tend to trap heat and promote maceration. Ointments are greasy and may be cosmetically unacceptable.
6. **Collodions** are painted on the skin and allowed to dry to leave a flexible film over the site of application (dry out to form a protective film).

14.2 - Common Skin Diseases, by Body Location

Common Skin Diseases by Body Location

Location	Skin Diseases
Scalp	Seborrheic dermatitis, dandruff
Face	Acne, rosacea, seborrheic dermatitis, perioral dermatitis, impetigo, herpes simplex, atopic dermatitis
Ears	Seborrheic dermatitis
Chest or abdomen	Tinea versicolor, tinea corporis, pityriasis rosea, acne, herpes zoster
Back	Tinea versicolor, tinea corporis, pityriasis rosea
Genital area	Tinea cruris, scabies, pediculosis, condyloma acuminate (venereal warts)
Extremities	Atopic dermatitis (cubital and popliteal fossa)
Hands	Tinea manuum, scabies, primary irritant contact dermatitis, warts
Feet	Tinea pedis, contact dermatitis, onychomycosis
Generalized or localized	Primary irritant or contact dermatitis, photodermatitis

14.3 - Anti-infective skin preparations

- The skin is the body's first line of defence against infection. Yet the skin can also become infected itself, especially if the outer layer (epidermis) is damaged by a burn, cut, scrape, insect bite, or an inflammatory skin condition – for example, eczema or dermatitis.
- Several different types of organism may infect the skin: bacteria, viruses, fungi, and yeasts.

A) Antibacterial preparations

1. Topical Antibacterials and antiseptics may be useful for superficial skin infections, but Antibacterials should only be used short term because of the risks of inducing bacterial resistance and contact allergy.
   - Any topical antibiotic product can irritate the skin or cause an allergic reaction.
   - Irritation is sometimes provoked by another ingredient of the preparation rather than the active drug, such as a preservative contained in the product.
2. An antibiotic or antibacterial skin cream may also be used to prevent infection when the doctor considers this to be a particular risk (for example, in the case of **severe burns**).
3. Other skin disorders in which topical antibiotics may be prescribed include **Impetigo**, **Cellulitis Infected Eczema, Bedsores,** and **Nappy Rash.**
4. To minimize the development of resistant organisms it is **advisable to limit the choice of Antibacterials applied topically to those not used systemically**.
5. **Silver sulfadiazine** is used in the treatment of **infected burns**.
6. **Metronidazole** is used topically for the treatment of **Rosacea** and to reduce the odor associated with anaerobic infections.
7. Acute **Impetigo** (caused by *Staphylococcus aureus*) on small areas of the skin may be treated by short-term topical application of **Fusidic acid**.
   - **Mupirocin** should be used only to treat methicillin-resistant Staphylococcus aureus.
   - **If the impetigo is extensive or longstanding**, an oral antibacterial such as **flucloxacillin** (or **clarithromycin** in penicillin allergy) should be used.
8. **Cellulitis** is a rapidly spreading deeply seated inflammation of the skin and subcutaneous tissue, requires systemic antibacterial treatment

Scientific name	Dosage form	Trade name	concentration
Gentamycin	Cream	Gendin®, Garamycin®	0.3%
	Oint.		0.1%
Tetracycline	Oint.	Samacycline®	3 %
Erythromycin	Gel/Oint.	Erythrodar® , Erythrocin®	2 %
	Gel	Spotex®	4%
Clindamycin	Gel/Lotion	Cleocin T® , Clindacyn T®	1%
Bacitracin	Oint./Powder	Beocin® , Baciquent®	500 Unit/gm
Fusidic acid	Cream/Oint.	Fucidin®, Fucine®, Fucibact®	2%
Silver Sulfadiazine	Cream	Silvadene®, Floumizine®	1%
Nadifloxacin	Cream	Nadixa®, Magnis®	1%
Metronidazole	Gel	Rozex®	0.75%
Ozenoxacin	Cream	Xepi®	1%
Mafenide	Cream, Topical Solu.	Sulfamylon®	----------
Mupirocin	Cream/Oint.	Bactroban®, Avoban®	2%
Retapamulin	Oint.	Altabax®	1% (5 gm , 10 gm Tubes)
Nitrofurazone	Cream	Furacin®	2 mg/gm
Fusafungine	Oro/Nasal Spray	Locabiotal® , Bioparox®	1% (500 mcg)

Notes:

1. **Erythromycin** and **Clindamycin** are usually used topically in the treatment of Acne.
2. **Bacitracin:** (bacteriostatic), used only for the prevention of superficial skin infections caused by the susceptible bacteria. (Not substantially absorbed from intact or denuded skin, wounds, or mucous membranes).
3. **Fusidic acid:** (bacteriostatic), the only indication for their use is in infections caused by penicillin-resistant staphylococci; It's also used in the treatment of burns.
    a. Occasionally used as a treatment for acne.
    b. Comes in combination with **hydrocortisone** or **betamethasone**.
4. **Nadifloxacin** is a **topical fluoroquinolone** antibiotic for the treatment of acne vulgaris; It is also used to treat bacterial skin infections, it also showed potent antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA).
5. **Ozenoxacin** is a topical fluoroquinolone antibiotic licensed for the treatment of Impetigo.
6. **Silver Sulfadiazine** and **Mafenide** are usually used for infective burns.
7. **Mupirocin:** used for furuncle, impetigo, open wounds, do not apply to eyes; do not apply topical to mucous membranes
8. **Retapamulin:** for treatment of bacterial skin infections such as impetigo.
9. **Nitrofurazone** is indicated as an adjunctive therapy for second- and third-degree burns.
10. **Fusafungine:** for the treatment of nasal and throat infection; It also possesses anti-inflammatory properties.

Note1: Combination products of some topical anti-Bacterials:

Scientific name(s)	D. Form	Trade name	concentration
Polymyxin B + Bacitracin	Cream/Oint	Polysporin®	(10,000 unit + 500 unit) per gm
Neomycin + Polymyxin B + Bacitracin	Cream, Oint.	TAO®	(3.5 mg + 5,000 unit + 400 unit) Per 1 gm
Neomycin + Polymyxin B + Bacitracin + Pramoxine	Oint.	TriBiozene®	(3.5 mg + 10,000 unit + 500 unit + 10 mg) per 1 gm

Note2: Combination products of Anti-Bacterial + Corticosteroids:

Scientific name(s)	D. form	Trade name	concentration
Fusidic acid + Betamethasone	Cream	Fucibet® , Fucibact B®	2% + 0.1% (15 gm tube)
Fusidic acid + Hydrocortisone	Cream	Fucidin H®	2% + 1% (15 gm tube)
Gentamicin + Betamethasone	Oint.	Betnosam – G®	0.1% + 0.1%
Neomycin + Betamethasone	Oint.	Betnosam – N®	0.5% + 0.1%
Neomycin + Fluocinolone	Cr/Oint	Synalar N®	0.5% + 0.025%
Neomycin + Polymyxin B + Hydrocortisone	Cream	Cortisporin®	3.5 mg + 10,000 Unit + 5 mg
Bacitracin + Neomycin + Polymyxin B + Hydrocortisone	Oint.	Cortimyxin®	400 Unit + 3.5 mg + 5,000 Unit + 1 mg
Clioquinol + Hydrocortisone	Cr/Oint.	Corque® , Viocort®	3% + 1%
Clioquinol + Betamethasone	Cream	Beta-Vioform®	3% + 0.1%
Iodoquinol + Hydrocortisone	Cream	Dermazene®,Vytone®	(10 mg + 10 mg)/gm

*** Iodoquinol and Clioquinol** has both antifungal and antibacterial properties. (5)

** **Iodoquinol** is also an anti-parasitic drug; it's given orally as an amebicide (anti-protozoal). (5)

B) Antifungal preparations

1. Most localized fungal infections are treated with topical preparations.
2. To prevent relapse, local antifungal treatment **should be continued for 1–2 weeks after the disappearance of all signs of infection**.
3. **Combination products of an antifungals and corticosteroids** are available to treat fungal infection associated with inflammation.
4. **Duration of therapy is dependent on the site of the infection** and may extend to a number of months (2 to 8 weeks for infections of the hair and skin, up to 6 months for infections of the fingernails, and 12 months or more for infections of the toenails).
5. **Pityriasis versicolor,** or called **tinea versicolor** (Patches of skin that may be darker or lighter than your normal skin color, or may be red, brown or pink, they tend to develop gradually and may join up to form larger patches over time); can be treated with ketoconazole shampoo (apply once daily for maximum 5 days, leave preparation on for 3–5 minutes before rinsing).

Scientific name	Dosage form	Trade name	concentration
Butenafine	Cream	Lotrimin®, Mentax®	1%
Ciclopirox	Cream, Lotion, Gel	Loprox®, Penlac®	0.77%
	Shampoo		1%
	Nail Lacquer		8%
Clotrimazole	Cream, Lotion	Gynomizole® , Mycelex®	1%
Econazole	Cream	Ecostatin®, Spectazole®	1%
Efinaconazole	Cream, Nail Lacq.	Topazole®	10%
Ketoconazole	Cream, Gel, Foam	Nizoral® , Ketonaz®	2%
	Shampoo		1% , 2%
Luliconazole	Cream	Luzu® , Lulican®	1%
Miconazole	Cream	Desenex®, Fungoid®, Daktarin®	2%
Naftifine	Cream, Gel	Naftin®	1% , 2%
Nystatin	Cream, Oint	Pediaderm®, Mycostatin®	100,000 Units/gm
Oxiconazole	Cream, Lotion	Oxistat®	1%

Sertaconazole	Cream	Ertaczo®, Dermofix®, Onabet®	2%
Eberconazole	Cream	Ebernet®	1%
Sulconazole	Cream, Lotion	Exelderm®	1%
Terbinafine	Cream, Lotion	Lamisil®, Lamifin®, Terbisil®	1%
Tolnaftate	Cream, Powder	Tinactin®, Aftate®	1%

Note1: Combination Products: (Anti-Fungal + Corticosteroid)

Scientific name(s)	D. form	Trade name	concentration
Miconazole + Hydrocortisone	Cream/Oint.	Daktacort®, Monicort®	(20 mg +10 mg) /1 gm
Miconazole + Betamethasone	Cream	Micosone®	2% + 0.1%
Miconazole + Mometasone	Cream	Elica-M®, Avocom-M®	2% + 0.1%
Miconazole + Fluprednidene	Cream	Domycotin®	2% + 0.1%
Isoconazole + Diflucortolone	Cream	Travazole®, Oly Plus® Azonit-D®	10 mg + 1 mg
Clotrimazole + Hydrocortisone	Cream	Canesten HC®	1% + 1%
Clotrimazole + Betamethasone	Cream	Fougera®, Lotrisone® Opizole-B®	1% + 0.05%
Nystatin + Triamcinolone	Cream/Oint.	Mycolog II®	100,000 Unit + 0.1%
Ketoconazole + Hydrocortisone	Gel	Ketocon Plus®	2% + 1%

Note2: Combination Products: (Anti-Fungal + Anti-Bacterial + Corticosteroid)

Scientific name	D. form	Trade name	concentration
Gentamycin + Clotrimazole + Betamethasone	Cream	***Tetraderm®***	(0.1 gm + 1 gm + 0.05 gm) Per 100 gm
Gentamycin + Miconazole + Mometasone	Cream	***Momenta®***	(0.1% + 2% + 0.1%) Per 1 gm
Gentamicin + Tolnaftate + Clioquinol + Betamethasone	Cream	***Quadriderm®, Mixderm®, Quard®***	1 mg + 10 mg + 10 mg + 0.5 mg
Gramicidin + Neomycin + + Nystatin + Triamcinolone	Cream, Oint.	***Nystagram®, Nystacort® (SDI)***	(0.025% + 0.25% + 100,000 IU + 0.1%)/gm
Neomycin + Nystatin + Hydrocortisone	Cream	Dioderm®, Nystacort N®	1% + 0.5% + 1%
Neomycin + Nystatin + Clobetasol	Cream, Oint.	Dermovate NN®	1% + 0.5% + 0.05%
Oxytetracycline + Nystatin + Clobetasone	Cream	Trimovate®	3.0% + 0.5% + 0.05%
Chlorhexidine + Nystatin + Hydrocortisone	Cream, Oint.	Nystaform HC	(1.15% + 100,000 IU + 1%)/gm
Chlorhexidine + Nystatin + Dexamethasone	Cream, Oint.	Nystacort® (UM)	(1.15% + 100,000 IU + 0.1%)/gm

*** Clioquinol = iodochlorohydroxyquin,** they are the same drug; which has both antifungal and antibacterial properties.

C) Antiviral preparations

1. These include: **Acyclovir, Penciclovir** and **Docosanol.**
2. **About Acyclovir:**
   a. Acyclovir cream can be used for the treatment of initial and recurrent labial herpes simplex infections **(cold sores)**; also used for **initial Genital Herpes.**
   b. Acyclovir is **best applied at the earliest possible stage**, usually when prodromal changes of sensation are felt in the lip and before vesicles appear.
   c. **Systemic acyclovir treatment** may be necessary in **herpes zoster (shingles)**.
3. **Penciclovir** and **Docosanol** are mainly used for **recurrent labial herpes.**
   - Penciclovir needs to be applied more frequently than acyclovir cream.
4. Systemic anti-viral treatment is necessary for buccal or vaginal infections and for herpes zoster.

Scientific name	Dosage form	Trade name	concentration
Acyclovir	Cream/Oint.	Zovirax® , Veramed®	5%
Penciclovir	Cream	Denavir®	1%
Docosanol	Cream	Abreva®	10%
Combination product			
Acyclovir + Hydrocortisone	Cream	Xerese®, Lipsovir®	5% + 1%

14. 4 - Parasiticidal preparations

1. Mites and lice are the most common parasites that live on the skin; One common mite causes the skin disease scabies. The mite burrows into the skin and lays eggs, causing intense itching. Scratching the affected area results in bleeding and scab formation, as well as increasing the risk of infection.
2. **There are three types of lice**, each of which infests a different part of the human body: the head louse, the body (or clothes) louse, and the crab louse, which often infests the pubic areas but is also sometimes found on other hairy areas such as the eyebrows.
3. All of these lice cause itching and lay eggs (nits) that look like white grains attached to hairs.
4. Both mites and lice are passed on by direct contact with an infected person (during sexual intercourse in the case of pubic lice) or, particularly in the case of body lice, by contact with infected bedding or clothing.

A) Scabies (body lice)

1. A contagious skin infection caused by the mite (**Sarcoptes scabiei)**, the mite is usually not directly visible; it burrows under the host's skin, causing intense allergic itching.
2. **Treatment options include:** Permethrin, Ivermectin, Lindane, Benzyl Benzoate, Crotamiton, Malathion, Isopropyl Myristate, Spinosad and Sulfur preparations (usually 10%).
3. **All members of the affected household should be treated** simultaneously; Treatment should be applied to the whole body including the scalp, neck, face, and ears, particular attention should be paid to the webs of the fingers and toes and lotion brushed under the ends of nails.
4. The **itch** and **eczema** of scabies persists for some weeks after the infestation has been eliminated and treatment for pruritus and eczema may be required.
   - Application of **Crotamiton** (a topical Scabicidal and general antipruritic) is used to control itching after treatment of scabies.
   - A **topical corticosteroid** may help to reduce itch and inflammation **after scabies has been treated successfully**; however, persistent symptoms suggest that scabies eradication was not successful; Oral administration of a **sedating antihistamine** at night may also be useful.
   - Some Dermatologist actually **add a corticosteroid during the treatment**.

Notes:

1. **Permethrin 5% cream is the drug of choice** due to ease of administration and high cure rate.
2. **Ivermectin** oral tablet has been **used in combination with Permethrin**, for the treatment of hyperkeratotic (crusted) scabies that does not respond to topical treatment alone; although dermatologists use it for any type of scabies, for a better accelerated result.
3. The use of **Benzyl benzoate** emulsion is decline nowadays because the cure rate is about 50%, and up to 25% of patient's experience side-effects such burning, irritation and itching on application, in addition **its application is less convenient than Permethrin cream.**
4. **Sulfur Oint.** is prepared in the pharmacies by mixing 10 mg of sulfur with Vaseline.

Scientific name	D. form	Application
Permethrin	**5% - 2.5% Cream and Lotion**	The treatment is applied to the entire body, from neck down-words (including web spaces of fingers and toes, the genitalia, and under the nails), but not the neck, face and scalp in adults; However, in children age under 2 years and the elderly (aged 70 and over) the advice now is to include the scalp, neck, face (avoiding the eyes and mouth) and ear in the application unless the product packaging contraindicates this**,** they should be treated again with cream. Repeat application after 7 days. (3)
Ivermectin	**6 mg, 12 mg Tablet**	Taken as two doses, 200µg/kg/dose, one week apart
Benzyl benzoate	**5% - 10% Emulsion**	Application: Apply over the whole body except the head and neck and left to dry on skin, repeat (without bathing or washing of the first application) on the following day. The second application is washed off 24 hours later. (3) A third application may be required in some cases. (3)

Scabicidals			
Scientific name	Dosage form	Trade name	concentration
Permethrin	Cream/Lotion	Nix®, Scalix®, Scabicore®	2.5% , 5%
Benzyl benzoate	Emulsion	Scabanca®	5% , 10%
Ivermectin	Lotion	Sklice®	0.5%
	Tab	Scav®, Gmectin®	6 mg , 12 mg
Lindane	Lotion, Shampoo	Lindane®	1%
Malathion	Lotion	Ovide®	0.5%
Crotamiton *	Cream/Lotion	Eurax®, Crotaphil®	10%
Isopropyl Myristate **	Lotion, Shampoo	Resultz®	120 mL
Spinosad **	Topical Susp.	Natroba®	0.9%

Notes:

1. **Malathion** is intended for use on persons 6 years of age and older; it can be irritating to the skin. **Malathion lotion is flammable**; do not smoke or use electrical heat sources.
2. **Crotamiton** is also an anti-pyretic, it's related to antihistamine in chemical structure.
3. **Isopropyl Myristate** dissolves the waxy shell of mite and lice, causing water loss from their body, once they lose this protective layer, they dehydrate, become immobile and die.
4. **Spinosad** causes neuronal excitation in insects (interferes with GABA neurotransmission), followed by hyper-excitation, paralysis, and then death (what a lame way to die?)

B) Head lice

1. Head lice are wingless insects spending their entire life on the human scalp and feeding exclusively on human blood, although any part of the scalp may be colonized, lice favor the nape of the neck and the area behind the ears, where the eggs are usually laid.
2. Head lice infestation **(pediculosis)** should be treated **using lotion or liquid formulations** (Shampoos are diluted too much in use to be effective).
3. **A contact time of 8–12 hours** or **overnight treatment** is recommended for lotions and liquids.
4. In general, a course of treatment for head lice **should be 2 applications of product 7 days apart to kill lice emerging from any eggs that survive the first application;** all affected household members should be treated simultaneously.
5. A new formula contains **Dimeticone;** which **kills the lice by a physical process** rather than by any chemical effect. It is thought to work by blocking the tubes used by the lice to breathe and by blocking the way the lice pass out water, which kills them.
   - It **causes complete eradication of lice and nits after a single use**; and all the lice and nits will be dead in 10 minutes; although **treatment should be repeated after 7 days** to make sure of complete eradication; **Resistance is unlikely to develop** because it uses a physical mode of action to eradicate head lice and nits.

Scientific name	Dosage form	Trade name	concentration
Dimeticone	Lotion, Spray	Dimeticone®	10% , 20%
	Solu.	Nadia® , DeLice®	92%
Phenothrin	Shampoo	Parasidose® , Full Marks®	0.5%
Isopropyl Myristate	Lotion, Shampoo	Resultz®	120 mL
Lindane	Lotion, Shampoo	Lindane®	1%
Malathion	Lotion	Ovide® , Prioderm®	0.5%
	Shampoo	Derbac-M®	1%
Permethrin	Shampoo	Nix® , Pyrifoam®, **Sali®**	1%
Combination products			
Permethrin + Malathion	Spray	**Para Plus®**	1% + 0.5%
Pyrethrins + Piperonyl Butoxide	Shampoo	**Lycid®**	(0.165 gm + 1.65 gm) Per 100 ml
Piperonyl Butoxide + Pyrethrum Extract	Shampoo	**Lice Killer®**	(4% + 0.33%)
Dimeticone + Vitamin E + Diisopropyl	Spray	**Butolice®**	80% m/v
Na Laureth Sulfate + Kocamad P-Bettine + Permethrin	Shampoo	**Stop Lice®**	----------

C) Pubic lice

1. **Crabs** is another name for pubic lice, they're tiny insects that can take up residence on the pubic hair; Like head lice and body lice, they feed on human blood.
2. Common symptoms of pubic lice include: **itching around the genitals or anus**, small pink or red bumps around the genitals or anus, low-grade fever; The patient might also be able to see the lice or their tiny white eggs around the roots of pubic hair .
3. If left untreated, pubic lice can spread to other people through skin-to-skin contact or shared clothing, bedding, or towels; also Scratched bites can also become infected. It's best to treat pubic lice infestations immediately.
4. Treatment as with head or Body lice; **Permethrin** and **Ivermectin**, (see above).

14.5 - Topical Corticosteroids

1. Topical corticosteroids are used for the **treatment of inflammatory conditions of the skin** (other than those arising from an infection), like **Eczema, Dermatitis,** And **Insect Stings**.
   - Also, may be prescribed for the treatment of psoriasis.
   - They do not affect the underlying cause of skin irritation, and the condition is therefore likely to recur unless the substance (allergen or irritant) that has provoked the irritation is removed, or the underlying condition is treated.
   - Topical corticosteroids are of **not recommended in the treatment of urticaria** and **they may worsen ulcerated or secondarily infected lesions**.
2. Irritation of the skin, caused by exposure to allergens or irritant factors, provokes white blood cells to release substances that dilate the blood vessels, making the skin hot, red, and swollen.
   - Applied to the skin surface, corticosteroids are absorbed into the underlying tissue; There, they **inhibit the action of the substances that cause inflammation**, allowing the blood vessels to return to normal and reducing the swelling.
3. **Application of Corticosteroids:**
   a. They **should be applied no more than twice daily;** Increasing the application from twice daily to four times daily does not produce superior responses, and may lead to increased frequency of topical and systemic adverse effects.
   b. **One fingertip** unit (approximately 500 mg) is sufficient to cover an area that is **twice that of the flat adult palm**.
4. Preparations should be rubbed in thoroughly and, when possible, **applied while the skin is moist (after bathing).** Hydration of the skin increases percutaneous absorption and the resultant therapeutic effect of topical steroids [(1)].
5. **Children, especially infants, are particularly susceptible to side-effects;** thus, a mild corticosteroid such as hydrocortisone 1% ointment or cream is useful for treating nappy rash and for atopic eczema in childhood; a moderately potent or potent corticosteroid may be appropriate for severe atopic eczema on the limbs, for 1–2 weeks only, switching to a less potent preparation as the condition improves.
6. **Thinning of the skin**, **telangiectasia** (a visible permanent dilatation of small cutaneous blood vessels), localized **fine hair growth**, **hypopigmentation**, and **striae** (pink, red or purple lines or bands) can result from repeated application of topical corticosteroids.
   a. With chronic use, topical corticosteroids (especially the potent agents) show decreased efficacy, a phenomenon known as "tachyphylaxis".
   b. They mask the symptoms of infections such as Tinea (fungal) and scabies.
7. Prolonged use of a **topical corticosteroid on the face should be avoided**, some advocate using only **hydrocortisone 0.5% or 1% cream on the face**.
8. They come in **different potencies (Low, Medium, High,** and **Very High);** their Potencies are commonly classified according to the vasoconstrictor assay, based on the degree to which an agent causes cutaneous vasoconstriction on normal human subjects.
   - **Changing the salt form will also change the potency.**

Low Potency Topical Corticosteroids			
Scientific name	Dosage form	Trade name	concentration
Alclometasone	Cream, Oint.	Aclovate®	0.05%
Desonide	Cream, Oint. Gel	Desonate® , Verdeso®	0.05%
Hydrocortisone	Cream, Oint.	Dermacort®	1% , 2.5 %
Dexamethasone	Cream, Gel	Dexacare®	0.075% , 0.4%

Medium Potency Topical Corticosteroids			
Betamethasone (Valerate)	Cream, Oint. Lotion	Betnovate®, Betnosam®	0.05% , 1%
Fluocinolone	Cream, Oint.	Synalar®, Capex®, Sinoderm®	0.025% , 0.01% , 0.1%
Fluticasone	Cream, Oint.	Cutivate®	0.05%
Budesonide	Cream	Biosonide®	0.025%
Hydrocortisone (Butyrate)	Cream, Lotion	Locoid®, Aquax-H®	1%
Hydrocortisone (Valerate)	Cream, Oint.	Westcort® , Hydroval®	0.2%
Triamcinolone	Cream, Oint.	Aristocort®, Kenalog®, Triacet®	0.025% , 0.05% , 0.1%
	Oral Gel	Kenalog®	1 mg/gm (10 gm tube)
	Topical Spray	Flutex®	0.147 gm/gm
High Potency Topical Corticosteroids			
Betamethasone (Dipropionate)	Cream, Oint. Lotion	Diprosone® , Alphatrex®	0.05%
Desoximetasone	Cream, Oint. Gel	Topicort®	0.05% , 0.25%
	Topical Spray	Topicort Fast®	0.25%
Fluocinonide	Cream, Oint. Gel	Lidemol® , Lidex®	0.05% , 1%
Halcinonide	Cream, Oint.	Halog®	0.1%
Mometasone	Cream, Oint.	Elocom® , Elica®	0.1%
Very High Potency Topical Corticosteroids			
Clobetasol	Cream, Oint.	Temovate®, Dermovate® Promax® , Clobex® , Dermodin®	0.05%
	Topical Spray		0.05%
	Topical Solu.		0.5 mg/ml
	Shampoo		0.05%
Halobetasol	Cream, Oint.	Utravate®	0.05%
Diflorasone	Oint.	Psorcon® , Apexicon®	0.05%

Other Topical Corticosteroids (less frequently prescribed)

Scientific name	Dosage form	Trade name	concentration
Amcinonide	Cream, Oint.	Cyclocort®	0.1%
Clocortolone	Cream	Cloderm®	0.1%
Flurandrenolide	Cream, Lotion	Cordran®	0.025% , 0.05%
Prednicarbate *	Cream, Oint.	Peitel® , Dermatop®	0.25% , 0.1%
Crisaborole	Oint.	Eucrisa®	2%

*** Prednicarbate** has a favorable benefit-risk ratio, with an inflammatory action similar to that of a medium potency corticosteroid, but with a low potential to cause skin atrophy.

****** Topical Corticosteroids Comes in many Combinations with topical antibiotics, antifungals, Emollients, etc. (See above).

14.6 - Preparations for minor cuts and abrasions

- They are applied as necessary but should not be used on large wounds or for prolonged periods because of the possibility of hypersensitivity, **these are generally used for cuts, grazes, insect bites, minor wounds, spots, minor burns ONLY, napkin rash, abrasions and scalds.**

Scientific name	D. form	Trade name	concentration
Cetrimide	Cream	Savlon First Aid®	0.5%
	Spray	Wound Wash®	0.5%
Chlorhexidine	Cream/Solu.	Betasept® , Chlorostat®	0.1% , 4% (solution)
Cetrimide + Chlorhexidine	Cream	Savlon® , ***Celavex®***	0.5% + 0.1%
	Liquid	Savlon Liquid®	3% + 0.3%
Cetrimide + Dimeticone	Cream	Boots Nappy Rash®	0.5% + 10%
Cetrimide + Benzalkonium	Cream	Drapolene®	0.2% + 0.01%
Cetrimide + Urea + Dimeticone + Chlorocresol	Cream	Cymex®	0.5% + 1% + 9% + 0.1%
Cetrimide + Lidocaine + Chlorobutanol + Alcloxa	Cram	***Dermidex®***	0.5% + 1.2% + 1% + 0.25%
Cetrimide + Lidocaine + Zinc Sulphate	Cream	Lypsyl® , Savlon® Bites & Stings	0.5% + 2% + 1%
Proflavine	Cream/Lotion	***Proflavine®***	0.1%
Magnesium Sulfate	Paste	----------	45 gm

- **Cetrimide, Chlorhexidine, Proflavine** are disinfectants having bactericidal activity.
- **Dimethicone** is water repellent and will protect the skin against water soluble irritants.
- **Urea** has keratolytic properties.
- **Magnesium sulfate** pastes are used to treat carbuncles and boils.

14.7 - Skin Cleansers, and antiseptics

1. **Wound cleansing** is required to remove any dirt or foreign bodies and to **remove exudate** and slough (pus and necrotic tissue); This helps to prevent infection and aids healing, commonly used cleansing solutions are: **sodium chloride 0.9%, hypochlorite, hydrogen peroxide, Povidone-iodine,** and **Chlorhexidine**.
2. **Alcohol Solution (95%) Indications:** skin preparation before injection, Cautions: flammable; avoid broken skin.
3. **Wound dressings** and packing preparations help to protect the wound and provide the correct environment for wound healing. Some also help by absorbing exudates; (**sofra-tulle**®).

Scientific name	D.form	Trade name	concentration
Sodium Chloride 0.9%	Solu.	(Various Trade names)	0.9%
Hypochlorite	Solu.	(Various Trade names)	0.5%
Hydrogen Peroxide	Solu./Cream	Crystacide®	3% , 6%
Povidone-Iodine	Solu./patch	Betadine®	5% , 10%
K^+ Permanganate	Tab for Solu.	Permitabs®	400 mg (0.1%)
Chlorhexidine	Solu.	(Various Trade names)	1% , 2.5% , 4%

Notes:

1. Antiseptics such as **chlorhexidine** or **Povidone-iodine** are used on intact skin before surgical procedures; their antiseptic effect is enhanced by an alcoholic solvent.
2. Antiseptic solutions containing **Cetrimide** can be used if a detergent effect is also required.
3. **Hydrogen peroxide**, an oxidizing agent, can be used in solutions of up to 6% for skin disinfection, such as cleansing and deodorizing wounds and ulcers; hydrogen peroxide is also available as a cream for superficial bacterial skin infections.
4. **Potassium permanganate** solution 1 in 10,000, a mild antiseptic with astringent properties, can be used for exudative eczematous areas; treatment should be stopped when the skin becomes dry, it can stain skin and nails especially with prolonged use.

14.8 - Emollients and Barrier preparations

1. **Emollients** (like Soft Paraffin) **soothe**, **smooth and hydrate the skin** and are indicated for all dry or scaling disorders (like napkin rash, eczema).
2. Barrier preparations (Zinc oxide, castor oil) often **contain water-repellent substances** and are used to **protect the skin against hydration and irritations** (as in nappy rash), also used on the skin around stomas, bedsores, and pressure areas in the elderly where the skin is intact.
3. **Notes concerning Napkin Rash**:
   a. The first line of treatment is to ensure that **nappies are changed frequently**. The rash may clear when left exposed to the air and a barrier preparation can be helpful.
   b. If the rash is associated with a **fungal** infection, an **antifungal cream such as Clotrimazole cream is useful.**
   c. **A mild corticosteroid such as hydrocortisone 1%** is useful in moderate to severe inflammation. The barrier preparation is applied after the corticosteroid preparation.
   d. Preparations containing **hydrocortisone should be applied for no more than a week.**
   e. **Using Higher Potency Corticosteroids are not recommended for such age.**

Scientific name	D. form	Trade name	concentration
Zinc Oxide	Oint.	----------	15%
Zinc Oxide + Castor Oil	Cream	----------	7.5% + 50%
Zinc Oxide + Castor Oil + Simethicone + Vit. E	Cream	Proskin®	Blend of 30 gm
Dexpanthenol	Cream/Oint. , Body Lotion	Bepanthine®	0.05 gm/1 gm
Dexpanthenol + Chlorhexidine	Cream	Bepanthine Plus®	(50 mg + 5 mg)/30 gm

14.9- Topical Antihistamines and antipruritics

1. They can be used as an emollient, and may be of value where the pruritus is associated with dry skin, Preparations containing **Crotamiton are sometimes used but are of uncertain value**, Preparations containing **calamine are often ineffective**.
2. **Calamine** preparations are of **little value for the treatment of insect stings or bites**.

Scientific name	Dosage form	Trade name	concentration
Crotamiton	Cream/Lotion	Eurax®	10%
Crotamiton + Hydrocortisone	Cream	Crotaphil-H®	100 mg
Calamine	Lotion	Calamine®	10%
Calamine + Glycerin + Camphor	Cream	Dermocal®	8% + 10% + 0.1%
Calamine + Zinc Oxide	Lotion	Calamyl®	(8 gm + 8 gm)/100 ml
Calamine + Zinc Oxide + Diphenhydramine	Lotion	Calamyl-D®	(8 gm + 8 gm + 1 gm) Per 100 ml
Diphenhydramine	Gel	Banophen®	1% , 2%
Diphenhydramine + Zinc Acetate	Cream, Spray	Banophen® Plus	2% + 0.1%
Diphenhydramine + Menthol	Spray	Dermamycin®	2% + 1%
Diphenhydramine + Allantoin	Cream	Allerga®	2% + 0.5%
Pramoxine	Cream/Lotion Spray/Gel	Tronolane® , Prax® Eczemin®	1%
Pramoxine + Zinc Acetate	Lotion	Caladryl®	1% + 0.1%
Pramoxine + Calamine	Cream/Lotion	Avenoo®	(1% + 8%) lotion , (1% + 3%) Cream
Pramoxine + Menthol	Cream	Gold Bond®	1% + 1%

14.10 – Topical Anesthetics

- Topical **local anesthetics** are only **marginally effective** and occasionally **cause sensitization**.
- Can be used **for insect stings and insect bites, but a short course of a topical corticosteroid is more appropriate**; Short-term treatment with an oral sedating antihistamine may help in insect stings where sedation is desirable.

Scientific name	Dosage form	Trade name	concentration
Lidocaine	Cream , Gel	Xylocaine®	4% , 5%
Benzocaine	Gel	Benzocaine®	10% , 20%
Dibucaine	Oint.	Nupercainal®	10%
Lidocaine + Hydrocortisone	Gel , Patch	AnaMantle®	2% + 2.5%
Lidocaine + Tetracaine	Cream , Patch	Pliaglis® , Synera®	7% + 7%
Lidocaine + Prilocaine	Cream , Dental Gel	Emla® , Oraqix®	2.5% + 2.5%

14.11 - Shampoos for Dandruff

1. **Dandruff** is an irritating, but harmless, condition that involves an acceleration in the normal shedding of skin cells from the scalp; Extensive dandruff is considered to be a mild form of a type of dermatitis known as **seborrheic dermatitis**, which is caused by an overgrowth of a yeast organism that lives in the scalp.
2. In severe cases, a rash and reddish-yellow scaly pimple appear along the hairline and on face.
3. Shampoos containing **Selenium Sulphide** may have beneficial effects.
4. **Ketoconazole** shampoo should be considered for more persistent or severe dandruff or for seborrheic dermatitis of the scalp.
5. A cream/ointment/Solution containing **coal tar** and **salicylic acid** is reserved for resistant Dandruff; it is also very helpful in **psoriasis that affects the scalp**.
   - **Coal tar** and **salicylic acid** preparations reduce the overproduction of new skin cells and break down scales which are then washed off while shampooing.

Scientific name	**Dosage form**	**Application**
Ketoconazole	**Shampoo**	Treatment of **seborrheic dermatitis** and **dandruff** apply twice weekly for 2–4 weeks (prophylaxis apply once every 1–2 weeks). Treatment of **pityriasis versicolor** apply once daily for max. 5 days (prophylaxis apply once daily for up to 3 days before sun exposure.
Selenium Sulphide	**Shampoo**	**Seborrheic dermatitis** and **dandruff**, apply twice weekly for 2 weeks then once weekly for 2 weeks and then as necessary.

Scientific name	Dosage form	Trade name	concentration
Ketoconazole	Shampoo	Nizoral® , Ketonaz®	1% , 2%
Selenium Sulphide	Shampoo	Selsun®	2.5% (120 ml)
	Shampoo	Selsun Blue®	1%
Pyrithione zinc	Shampoo	Head and Shoulders®	1%

Combination Products for Dandruff			
Trade name	Dosage form	Scientific name(s)	concentration
Irox Sebarox®	Shampoo	Climbazole + Ciclopirox * + Salicylic acid + Vit. B_5	120 ml
GAM Pyrithione®	Shampoo	Pyrithione zinc + Salicylic acid	2% (275 ml)
GAM Pirox®	Shampoo	Octopirox + D-Panthenol	1% (275 ml)
Ketazole Pluse®	Shampoo	Ketoconazole + Salicylic acid	130 ml
Scalpex® , Ketros®	Shampoo	Ketoconazole + Pyrithione zinc	2% + 1% (60 ml)
Fungicide®	Lotion	Ketoconazole + Pyrithione zinc	2% + 1% (90 ml)
Silkin®	Shampoo	Ketoconazole + Pyrithione zinc + Aloe Vera	100 ml

*** Ciclopirox = Cyclopyrox,** they are the same drug.

14.12 - Preparations for Psoriasis

1. The skin is constantly being renewed; as fast as dead cells in the outer layer (epidermis) are shed, they are replaced by cells from the base of the epidermis; **Psoriasis occurs when production of new cells increases while shedding of old cells remains normal**; As a result, the live skin cells accumulate and produce patches of inflamed, thickened skin covered by silvery scales.
2. Thus, **Psoriasis** is a chronic inflammatory skin disorder characterized by **enhanced epidermal proliferation** leading to erythema, **scaling**, and thickening of the skin.
3. There are several types of psoriasis including guttate, flexural, pustular, and erythrodermic, **but chronic plaque psoriasis (psoriasis vulgaris) is the most common form**. In chronic plaque psoriasis the area's most commonly affected are the extensor sides of the knees, elbows, and hands, and the scalp and sacrum.
4. **In Psoriasis, there is no cure,** treatments are designed to induce a remission or suppress disease to a tolerable level.
5. **Drug therapies for psoriasis are** summarized in table 4.
6. A recent study published on JAMA dermatology, showed that people with Psoriasis have an increased risk of developing cancer and dying of it. (6)
7. **Topical drugs** are the treatment of first choice for chronic plaque psoriasis.; Psoriasis refractory to topical therapy may respond to **systemic drugs**.
8. A cream/ointment containing **coal tar** and **salicylic acid** (Keratolytic) is very helpful in psoriasis that affects the scalp or the skin, they remove the layers of dead skin cells.

Table 4. Therapies Used in the Treatment of Psoriasis

Topical Therapies
Emollients, keratolytics (salicylic acid, urea), omega fatty acids, corticosteroids, vitamin D analogues (calcitriol, calcipotriene, tacalcitol), tazarotene, anthralin, coal tar

Systemic Therapies
Methotrexate, cyclosporine, acitretin, fluorouracil, oral vitamin D, phototherapy, photochemotherapy

Biological Agents
Anti-TNFs (infliximab, adalimumab, etanercept), T-cell–targeted therapies (alefacept,), monoclonal antibody (ustekinumab)

TNF: tumor necrosis factor.

9. **Calcipotriene** and **Tacalcitol** are analogues of vitamin D, that **affect cell division** and differentiation; (by inhibiting keratinocyte proliferation and enhancing their differentiation).
10. Topical **Tacrolimus** and **Pimecrolimus** have a role in the treatment of psoriasis (they act by blocking synthesis of several inflammatory cytokines); they are indicated also for atopic eczema.
11. **Acitretin** is a metabolite of etretinate, a retinoid (vitamin A derivative).
    - Acitretin reduce production of keratin, the hard protein that forms in the outer layer of skin.
    - Acitretin is **teratogenic**; In women with a potential for child-bearing, the possibility of pregnancy must be excluded before treatment and effective contraception must be used during treatment and for **at least 3 years** afterwards.
    - Monitor serum-triglyceride, cholesterol, and liver function before and during treatment.
    - Taken with or just after meal, Patient should protect the skin from sunlight; even on a bright but cloudy day.

A) Topical Therapies:

Scientific name	Dosage form	Trade name	concentration
Calcipotriene *	Cream/Oint.	Dovonex® , Daivonex® , Sorilux®	0.005% (50 mcg)
Tacalcitol	Oint./Lotion	Curatoderm® , Bonalfa®	0.0004% (4 mcg)
Calcitriol	Oint.	Vectical®	0.0003% (3 mcg)
Tazarotene	Gel , Cream	Zorac®, Fabior® , Avage®	0.05% , 1%
Methoxsalen	Lotion	Uvadex®	1%
Crisaborole	Oint.	Eucrisa	2%
Anthralin *	Oint. , Paste	Dithrocream® , Micanol®	0.1% , 0.5% , 1%
Fluorouracil **	Cream	Fluoroplex® , Efudex®	0.5% , 1% , 5%
Tacrolimus **	Oint.	Protopic®, Tacrus® , Talimus®	0.03% , 0.1%
Pimecrolimus **	Cream	Elidel® , Pacroma®	1%

* **Calcipotriene = Calcipotriol,** they are the same drug. * **Anthralin = Dithranol**, they are the same drug.
** **Tacrolimus, Pimecrolimus** and **Fluorouracil** are immunosuppressants.

B) Combination Topical Products:

Scientific name	D. form	Trade name	concentration
Calcipotriene + Betamethasone	Oint, Gel, Foam	Dovobet® , Daivobet®	50 mcg + 0.5 mg
Salicylic Acid + Betamethasone	Oint./Lotion	Diprosalic®	30 mg + 0.5 mg
Salicylic Acid + Mometasone	Oint.	Elica-sal®	5% + 0.1%
Salicylic Acid + Dexamethasone	Oint.	Salidex®	30 mg + 1.2 mg
Dithranol + Coal Tar + Salicylic acid	Oint.	Psorin®	0.11% + 1% + 1.6%
Salicylic Acid + Zinc Oxide	Paste	Lassar's Paste®	2% + 24%
Fluocinolone + Tar Extract	Oint.	Cinolone Tar®	0.25 mg + 50 mg
Halobetasol + Tazarotene	Lotion	Duobrii®	0.01% + 0.045%

C) Oral/Systemic Therapies:

Scientific name	Dosage form	Trade name	concentration
Acitretin	Cap	Soriatane® , Neotigason®	10 mg , 25 mg
Methoxsalen	Cap , Tab	Uvadex® , Neo-Medanine®	10 mg
	Inj. Solu.		20 mcg/ml (10 ml Vial)
Azathioprine	Tab	Imuran®	50 mg , 75 mg , 100 mg
	Inj. Powder		100 mg/Vial
Cyclosporine	Cap	Sandimmune® , Gengraf®	50 mg , 100 mg
Apremilast	Tab	Otezla® , Aprezo®	10 mg , 20 mg , 30 mg
Fluorouracil	Inj. Solu.	Adrucil®	50 mg/ml

C) Biological Agents:

1. **Biological agents** are manufactured proteins that interrupt the immune process involved in psoriasis, unlike generalized immunosuppressive drug therapies such as **methotrexate**, **biological agents** target specific aspects of the immune system contributing to psoriasis, These medications are generally well-tolerated and limited long-term outcome data have demonstrated them to be safe for long-term use in moderate to severe plaque psoriasis, However, due to their immunosuppressive actions, they have been associated with a small increase in the risk for infection, Guidelines regard **biologics as third-line treatment for plaque psoriasis** following inadequate response to topical treatment, phototherapy, and non-biologic systemic treatments.
   - Individuals with psoriasis may develop neutralizing antibodies against monoclonal antibodies, specifically, neutralization occurs when the antidrug antibody binds to the binding site instead of TNF-α; Thus, it no longer decreases inflammation, and psoriasis may even worsen.

Biological Agents for Psoriasis			
Scientific name	Dosage form	Trade name	concentration
Infliximab	Inj. Powder	Remicade®	100 mg/vial
Adalimumab	Prefilled Inj.	Humira®	40 mg/0.8 ml
Golimumab	Prefilled Inj.	Simponi®	50 mg/0.5 ml
Etanercept	Inj. Solu.	Enbrel®	50 mg/ml
Alefacept	Inj. powder	Amevive®	7.5 mg , 15 mg (per vial)
Efalizumab	Prefilled Inj.	Raptiva	30 mg
Ustekinumab	Inj. Solu.	Stelara®	45 mg/0.5 ml
Secukinumab	Prefilled Inj.	Cosentyx®	150 mg
Brodalumab	Prefilled Inj.	Siliq®	210 mg/1.5 ml
Dupilumab	Prefilled Inj.	Dupixent®	300 mg/2 ml
Guselkumab	Prefilled Inj.	Tremfya®	100 mg/ml
Ixekizumab	Prefilled Inj.	Taltz®	80 mg/ml

Notes:

1. **Infliximab, Adalimumab, Golimumab** and **Etanercept** are also used in the treatment of severe cases of Crohn's Disease and Ulcerative Colitis, Ankylosing Spondylitis, Rheumatoid arthritis.
2. **Alefacept** and **Efalizumab** are the only two drugs that target T cells.
   - They are monoclonal antibodies that specifically targets the CD11a subunit of LFA-1, it also blocks the adhesion molecules on the endothelial cells that lines the blood vessels, which attract T cells.
   - **Efalizumab** was voluntarily withdrawn from the European market in February 2009 and from the US market in June 2009 by the manufacturer due to the medication's association with cases of progressive multifocal leukoencephalopathy.
3. **Brodalumab** binds to the interleukin-17 receptor and so prevents interleukin 17 (IL-17) from activating the receptor. In 2017 it received US FDA approval to treat moderate to severe plaque psoriasis in people who have not improved with other treatments.
4. **For other Biological Agents see chapter 10, Immunologics.**

14.13 - Preparations for Eczema

1. Eczema is a skin condition causing a dry, itchy rash that may be inflamed and blistered.
2. Eczema can be triggered by allergy but often occurs for no known reason. In the long term, it can thicken the skin as a result of persistent scratching; The most common type is **Atopic Eczema**, in which there is often a family history of eczema, asthma, or allergic rhinitis.
3. **Atopic Eczema** commonly appears on the hands, due to detergents, and the feet, due to warm, moist conditions in enclosed footwear.
4. **Contact dermatitis**, (another common form of eczema), is caused by chemicals, detergents, or soaps; it may appear only after repeated exposure to the substance, but strong acids or alkalis can cause a reaction within minutes; It can also result from irritation of the kin by traces of detergent on clothes and bedding.
5. **Allergic contact dermatitis** can appear days or even years after initial contact has been made with triggers such as nickel, rubber, elastic, or drugs (antibiotics, antihistamines, antiseptics, or local anesthetics); Sunlight can also trigger contact dermatitis following use of aftershave or perfume.
6. **Nummular Eczema** causes circular dry, scaly, itchy patches to develop anywhere on the body, and bacteria are often found in these areas, **all types of Eczema can become infected.**
   - Thus, some dermatologists combine routinely a topical antibiotic (Fusidic acid) with topical corticosteroids in the treatment of infected Eczema or Nummular Eczema.

7. **Treatment options for Eczema:**
   - **Emollients** soften and moisten the skin; **Coal tar** may be used for chronic atopic eczema.
   - **Oral antihistamines** may be prescribed for a particularly itchy rash (**topical antihistamines** make the skin more sensitive and should not be used).
   - **Topical corticosteroids** may be needed to help control a flare up.
   - severe cases that are resistant to other treatments may need to be treated with the **immunosuppressant drugs** as (ciclosporin).
   - **Oral corticosteroids** may be used to treat contact dermatitis.
   - Nummular eczema usually requires corticosteroid treatment; If it is resistant**, antibiotics may be prescribed because infection is likely.**
   - **Topical phosphodiesterase inhibitors;** (**Crisaborole**); FDA approved for atopic dermatitis.

14.14 - Acne and Rosacea

1. Acne, known medically as **Acne Vulgaris**, is a common condition caused by excess production of the skin's natural oil (sebum), leading to blockage of hair follicles, it mainly affect adolescents but it may occur at any age, due to certain drugs, exposure to industrial chemicals, oily cosmetics, or hot, humid conditions.
2. Acne primarily affects the face, neck, back, and chest, the primary symptoms are blackheads, papules (inflamed spots), and pustules (raised pus-filled spots with a white center).
   - Mild acne may produce only blackheads and an occasional papule or pustule.
   - Moderate cases are characterized by larger numbers of pustules and papules.
   - In severe cases of acne, painful, inflamed cysts also develop; These can cause permanent pitting and scarring.

A) Acne

Drug treatment nan be classified according to the severity (into mild, moderate and sever):

1. **Mild acne** is treated topically, in particular with benzoyl peroxide, Retinoids, and Antibacterials.
2. **Moderate acne** is best treated with oral rather than topical Antibacterials, of which Tetracyclines (Tetracycline, Doxycycline) appear to be the drugs of first choice; Alternatives to the Tetracyclines include erythromycin, and co-trimoxazole.
3. **Severe acne** is usually treated with **oral Isotretinoin**.

Specific notes for the topical preparations for acne:

a. Topical preparations, such as **benzoyl peroxide, salicylic acid,** and **tretinoin**, have a keratolytic effect**; Benzoyl peroxide** also has an antibacterial effect.

b. It is usual to **start with a lower strength** and to increase the concentration of benzoyl peroxide gradually (to minimize skin irritation).

c. **Benzoyl peroxide can bleach clothing and bedding;** If it is applied at night, white sheets and pillowcases are best used and patients can be advised to wear an old T-shirt or shirt to minimize damage to good clothes.

d. **Topical Antibacterials** are probably best reserved for patients who wish to avoid oral Antibacterials or who cannot tolerate them; Topical preparations of **Erythromycin** and **Clindamycin** are effective for inflammatory acne.

e. **Topical Tretinoin** (isomer of Isotretinoin), and **Adapalene** (a retinoid-like drug), are useful for treating mild to moderate acne; Patients should be warned that some redness and **skin peeling** can occur initially but settles with time; thus, Topical retinoids **should be applied at night**, a half hour after cleansing the area effected with acne.

f. **Topical Retinoids are contraindicated in pregnancy**; women of child-bearing age must use effective contraception.

g. **Dapsone** 5%, 7.5% gel is approved by the (FDA) for the treatment of acne vulgaris in adults and children older than 12 years, Although **Dapsone has antibacterial and anti-inflammatory activity**, the mechanism of action in the treatment of acne is unknown.

B) Rosacea

1. **Rosacea** is a skin condition that is sometimes confused with acne; It is a common chronic inflammatory disorder of the **facial pilosebaceous** units, coupled with an increased reactivity of capillaries leading to **flushing and telangiectasia.**
2. **Rosacea** has characteristic features of reddening (flushing), papules (a raised solid lesion, usually less than 0.5 cm in diameter) and pustules (an accumulation of pus in the skin, in rosacea there are **no comedones (as in acne)**; age of onset of rosacea is 30 to 50 years.
   - Severe rosacea can result in the thickening of facial skin, especially around the nose. The nose can become bulbous and enlarged (rhinophyma); This is a very rare complication, and tends to affect males much more than females.
   - Ocular rosacea: There is a burning, gritty sensation in the eyes, making them bloodshot; The inside of the eyelid may become inflamed (blepharitis) and appear scaly, causing conjunctivitis; Some people may not tolerate contact lenses and sties may develop, In very rare cases, vision can become blurred.
3. **Oral Antibacterials** (**Doxycycline**, **Tetracycline**) have been widely used, but clarithromycin, erythromycin, and metronidazole are suitable alternatives.
4. **Topical therapies**, particularly **Metronidazole** and **Azelaic acid**, provide effective alternatives to oral drugs; Other topical therapies that may be useful include **Retinoids**.
5. Topical **Brimonidine** is licensed for the treatment of facial erythema in rosacea
6. **Ivermectin** cream 1%; is FDA approved for the treatment of inflammatory lesions of **Rosacea**.
7. **Oxymetazoline** is an alpha1A adrenoceptor agonist; which acts as a vasoconstrictor, it is specifically indicated for the topical treatment of persistent facial erythema associated with Rosacea in adults.

First: Topical Products for Acne:

Scientific name	Dosage form	Trade name	concentration
Benzoyl peroxide	Gel, Lotion, Cream	Brevoxyl®, Benoxide®	2.5% , 5% , 10%
Azelaic acid	Cream, Gel	Skinoren®, Azelex®, Finacea®	20% , 15%
Topical Retinoids			
Tretinoin	Cream, Gel Lotion , Soap	Retin A®, Retinoid® Acretin®	0.025% , 0.05% , 0.1%
Tazarotene	Gel , Cream	Zorac®, Fabior® , Avage®	0.05% , 1%
	Lotion	Arazlo®	0.045%
Iso-Tretinoin	Gel	Isotrex®	0.05%
Adapalene	Cream, Gel	Differin® , Surecure®	0.1%
Trifarotene	Cream	Aklief®	0.005%
Topical Antimicrobials			
Clindamycin	Lotion/Gel	Dalacin T®	1%
Erythromycin	Gel/Oint.	Erythrodar® , Erythrocin®	2%
	Gel	Spotex®	4%
Other Products for Rosacea/Acne			
Metronidazole	Gel	Rozex®	0.75%
Dapsone	Gel	Aczone®	5 %, 7.5% (30, 60 gm tube)
Ivermectin	Cream	Soolantra®	1%
Brimonidine	Gel	Mirvaso®	0.33%
Oxymetazoline	Cream	Rhofade®	1%

Combination Topical Products for Acne			
Benzoyl peroxide + Clindamycin	Gel	Duac®	5% + 1%
Benzoyl peroxide + Erythromycin	Gel	Benzamycin®	5% + 3%
Benzoyl peroxide + Adapalene	Gel	Epiduo®	2.5% + 0.1%
Isotretinoin + Erythromycin	Gel	Isotrexin®	0.05% + 2%
Erythromycin + Zinc Acetate **	Lotion	Zineryt®	(40 mg + 12 mg) per ml
Tretinoin + Erythromycin	Solu. , Gel	Aknemycin® Plus (solu.), Retinomycin®, Eramax®	(0.025% + 4%)
Tretinoin + Clindamycin	Gel	Veltin® , Ziana®	0.025% + 1.2%
Tretinoin + Salicylic acid + Allantoin + D-Panthenol	Cream	Lino Riten A®	0.1% + 1% + 0.5% + 1%

** **Zinc** will increase the wound healing and increase the absorption of **Erythromycin**.

Second: Oral Products for Acne:

A) Oral Retinoid for acne:

1. **Isotretinoin** reduces sebum secretion, soothes inflammation, and helps to unblock hair follicles; It is used for the systemic **treatment of severe acne**.
   - Treatment with **Isotretinoin often causes dry and scaly skin, particularly on the lips**, also the skin may become itchy and **some hair loss may occur.**
   - its **Teratogenic** and must not be given to women of child-bearing age unless they practice effective contraception or at least one month before treatment, during treatment, and for at least one month after stopping.
   - Isotretinoin sometimes increases blood lipid levels.
   - It is **given for at least 15-20 weeks**; repeat courses are not normally required.
   - Dosed as 0.5-1 mg/kg/day orally divided by two (twice daily).
   - Dosed as 2 mg/kg/day if disease is very severe or is primarily manifested on the trunk.

Scientific name	D. form	Trade name	concentration
Isotretinoin	Cap	Roaccutane®, Retane®, Decutan®	5 mg , 10 mg , 20 mg
	Cap	Isocor®	10 mg , 20 mg
Alitretinoin	Cap	Toctino®	10 mg , 30 mg
Acitretin	Cap	Soriatane® , Neotigason®	10 mg , 25 mg

B) Oral Hormonal treatment for Acne:

1. **Products usually contains an anti-androgen**; it is no more effective than an oral broad spectrum antibacterial but is useful in women who also wish to receive oral contraception.
2. Improvement of acne with hormone therapy probably occurs because of decreased sebum secretion which is under androgen control; Some women with moderately severe hirsutism may also benefit because hair growth is also androgen-dependent.
3. **Contra-indications include** pregnancy and a predisposition to thrombosis.

Scientific name	Dosage form	Trade name	concentration
Cyproterone	Tab	Androcur®	50 mg
Cyproterone + Ethinyl Estradiol	Tab	Diane® * , Clairette®	2 mg + 0.035 mg
Drospirenone + EE	Tab	Yasmine® , Zahraa®	3 mg + 0.03 mg

*** Diane®** was withdrawn from the markets in 2012 in Canada, France due the high risk (4 times more risk) of venous thromboembolism (blood clots in veins) than other alternatives.

14.15 - Preparations for Warts and Calluses

1. **Warts** (verrucas) are caused by **a human papillomavirus (HPV)**, which most frequently affects the hands, feet (plantar warts), and the anogenital region; treatment usually **relies on local tissue destruction**.
2. Preparations of **salicylic acid (keratolytic)** are suitable for the removal of warts on hands and feet; it is also suitable for the removal of corns and calluses.
3. Other treatment options include: **Formaldehyde, Glutaraldehyde** or **Silver nitrate.**
4. **Paints and liquids contain salicylic acid**, often in a collodion-based vehicle**. Collodions contain a nitrocellulose derivative**, dissolved in a volatile solvent such as ether, acetone or alcohol. On application, the solvent evaporates, leaving on the skin an adherent, flexible, water-repellent film containing the medicament. **This has the advantage of maintaining the salicylic acid at the site of application.**
5. **Note**: **do not let adjacent area of normal skin come in contact with drug (apply some Vaseline around the area)**. If they do, wash off the solution immediately with soap and water.
   - Or simply **use the Gel Dosage form** (instead of Solu.), it delivers the salicylic acid and lactic acid through a continuous release, allowing deeper penetration, and longer action whilst simultaneously protecting the surrounding normal skin
6. The treatment is helped by **prior soaking of the affected hand or foot in warm water for 5–10 min** to soften and hydrate the skin, increasing the action of the salicylic acid.
7. **Lactic acid** is included in some preparations with the aim of enhancing availability of the salicylic acid which may enhance the effects of salicylic acid; However, it appears that combination therapy **has no additional benefit over salicylic acid alone.**
8. **Salicylic acid plasters:** Corn and callus plasters contain high conc. (usually 40%), **they should be changed every 1–2 days** for about a week, after which the callosity should lift away easily.

Scientific name	D. form	Trade name	concentration
Salicylic acid + Lactic acid	Solu.	Duofilm®	16.7% + 16.7%
	Gel	Cornex®	16.7% + 16.7%
Salicylic acid + Lactic acid	Solu.	Cuplex®	11% + 4%
Salicylic acid + Lactic acid	Gel	Salatac®	12% + 4%
Salicylic acid + Lactic acid + Polidocanol*	Solu.	Collomak®	2 gm + 0.5 gm + 0.2 gm
Formaldehyde	Gel	Veracur®	0.75%
Glutaraldehyde	Solu.	Glutarol®	10%
Urea + Salicylic acid	Cream	GAM US®	20% + 2%
Silver Nitrate	Pen, Stick	Avoca®**	75% , 95%

* **Polidocanol** is a local anesthetic and antipruritic.

** **Avoca®** is used for removing warts including verruca and excess tissue, it works by destroying tissue on the surface layers of warts and verruca.

9. The treatment of **Anogenital Warts** should be accompanied by screening for other sexually transmitted infections.
   a. Soft non-keratinized external anogenital warts are usually treated with topical application of Podophyllin **(Podophyllotoxin);** while Keratinized lesions may be better treated with Cryo-therapy or other forms of physical ablation.
   b. Genital Warts are treated with **Imiquimod** 5% cream (Aldara®), 3 time per week for up to 16 weeks, or by **Podophyllotoxin** 0.5% solution or gel (Wartec®), twice daily for 3 days, then 4 days of no therapy and repeating this cycle for up 4 times if necessary .
10. **Imiquimod** acts by **enhancing the immune system to produce interferons** to fight the virus causing the wart; it is licensed for the treatment of external anogenital warts; it may be used for both keratinized and non-keratinized lesions. It is also licensed for the treatment of superficial basal cell carcinoma and actinic keratosis.

Scientific name	Dosage form	Trade name	concentration
Podophyllotoxin	Solu.	Condyline®	0.5%
	Genital Solu.	Condylox®	0.5% (3.5 ml)
	Cream	Warticon®, Wartec®	0.15%
Podophyllum resin + Benzoin + Aloe Vera	Paint	Podowart®	(20% + 10% + 2%)/10 ml
Podophyllum resin + Benzoin + Aloe Vera + Salicylic acid	Paint	Podowart S®	(20% + 10% + 2% + 5%) Per 10 ml
Imiquimod	Cream	Aldara® , Zyclara®	5% , 3.75%

14.16 - Sunscreen preparations

1. People vary in their sensitivity to sunlight. Fair-skinned people generally have the least tolerance and tend to burn easily when exposed to the sun, while those with darker skin, especially brown or black skin, can withstand exposure to the sun for longer periods.
2. The light from the **UVA spectrum is responsible for skin tanning** and **UVB light causes sunburn**; Sunburn is an inflammatory response to excessive exposure to ultraviolet which result in vasodilatation and increase capillary permeability.
3. The rays of the sun are the most direct and damaging **between 10 am and 3 pm,** therefore the customer should avoid sun exposure during this time of day as much as possible.
4. Sunscreen preparations contain **substances that protect the skin against UVA and UVB radiation,** which usually contains 3 types of materials:
   - **Physical sunscreens**: acts as a physical barrier to reflect and scatter about 99% of the light, these include: **Titanium dioxide, Red Petrolatum** and **Zinc oxide**.
   - **Chemical sunscreens**: these protect the skin by absorbing the light particles; when the light is absorbed, a chemical reaction occurs which leads to destroying these light particles, this chemical reaction generates free radicals (which may cause a secondary free radical damage if used for a long period); these include: **PABA** (para amino benzoic acid), **Cinoxate, Octocrylene, Ethyl Salicylate, Homo salicylate, Oxybenzone, Dioxybenzone, Avobenzone** and **Sulisobenzone**.
   - **Antioxidants**: these are usually included to prevent or reduced the damage from the free radicals that is generated during the chemical sunscreen process; these include: Vitamin E, green tea extract etc.

   So, **a prefect sunscreen usually contains these 3 types of ingredients** to ensure the maximum protection; commercially available sunscreens usually contain these materials.
5. The **sun protection factor (SPF)** gives a rough estimate of the efficiency of the product to block UVB: For example, if a person normally show a signs of burning in 30 minutes without protection, then a product with a SPF of 6 would extend the period of time until burning begins to 3 hours (it extends the time taken to burn by 6 times), and so on with SPF of 15, 30, …. (However, in practice, users do not apply sufficient sunscreen product and the protection is lower than that found in experimental studies). [3]
6. **SPF higher amount doesn't affect that much** and can be misleading; as follows:
   SPF 15 = protects 93% of UVB, **SPF 30** = protects 97% of UVB
   SPF 50 = protects 98% of UVB, **SPF 100** = protects 99% of UVB
7. **Application**:
   - Sunscreen must be **applied to all exposed areas of the body** including the nose ad lips (avoid contact with eye); Sunscreen should be **reapplied every 2-3 hours**; and for most sunscreen product, they should **be applied 15-30 min. before sun exposure.**

14.17 - Hair Loss

First: Androgenetic Alopecia

1. It's mainly a hair loss due to the **presence of high serum amounts of Dihydrotestosterone** (the potent form of testosterone); it's a condition that is very related to Genetics.
2. **Finasteride (1 mg tablet)** is licensed for the treatment of Androgenetic alopecia **in men**. **Continuous use for 3–6 months** is required before benefit is seen, and effects are reversed 6–12 months after treatment is discontinued.
   - It's a 5α-reductase inhibitor (inhibits the enzyme responsible for metabolizing Testosterone into Dihydrotestosterone; which is related to androgenic alopecia).
   - Finasteride could **produce feminization of a male fetus** if used in pregnant women; therefore, it recommended that women who are or may become pregnant should not handle crushed or broken Finasteride tablets.
   - Finasteride has been **detected in semen**, therefore use of a condom is recommended if the patient's sexual partner is, or may become pregnant.
3. **Alfatradiol** is a 5α-reductase inhibitor (like **Finasteride**) used **topically** for the treatment of androgenic alopecia (hair loss) **in men and women.**
4. **Minoxidil:**
   a. Topical application of **Minoxidil** may stimulate limited hair growth in a small proportion of adults, **but only for as long as it is used**.
   b. Minoxidil acts by **lengthening the duration of the anagen phase** of the hair follicle; it also **increases the blood supply** to the hair follicle (it acts as a potassium channel opener; thus, widening blood vessels; which allows more oxygen, nutrients supply to the follicles).
   c. **Minoxidil** is available as 2% and 5% products: however, women should use 2% products (since females respond better to minoxidil than males); **women should not use the 5% products,** since it can cause hirsutism at other sites, such as the face, chest, ear rim, and back.
      - **Dose**: Apply **1 mL twice daily** to dry hair and scalp.
5. The combination of both **oral Finasteride** and **topical Minoxidil** has a better result than if used each alone in the treatment of hair loss.
6. **For females**; the use of **oral antiandrogens** (**Cyproterone**) or **Spironolactone** (diuretic with mild antiandrogen activity) may be useful in cases of hair loss due androgenic alopecia.
7. There are several **herbal combinations for hair loss**, such as the **Cysteine B_6 Shampoo** and **tablets,** these prove efficacy by live examples.
8. Some anti-hair loss Shampoos contain **Caffeine**; which can help to promote hair growth in the initial phase of hair growth; it does that through inhibiting DHT (Dihydrotestosterone).
9. **Procyanidin B_2** is an innovative new molecule (which is extracted from Green Apples), which in some studies have shown **200% more effective than 1% Minoxidil**, it Increases both the total number of hair and the thickness of hair, and can be used in men and women.
   - It's considered as a topical 5α-reductase inhibitor (topical antiandrogen).

Scientific name	Dosage form	Trade name	concentration
Finasteride	Tab	Propecia® , Pro-hair®	1 mg
Alfatradiol	Scalp Solu.	Pantostin®	100 ml
Minoxidil	Spray, Shampoo	Regaine®, Rogaine®, Minoxidil®	2% , 5%
	Topical Solu.	Avogain® , Minostyl®	2% , 5%
	Topical Solu.	Minoxidil MAX®	6.5%
Minoxidil + Finasteride	Topical Solu.	Coverit Plus®	5% + 0.1%
Procyanidin B_2	Scalp Solu.	Mostal®	50 ml
Cysteine + B_6	Shampoo	Cystine B6 Shampoo®	200 ml
Cysteine + B_6 + Zinc + Arginine	Tab	Cystine B6 bailleul®	76% + 2% + 2% + 1%

Second: Alopecia Areata

1. It's a hair loss **due to an autoimmune disease**, in which the immune (the T-lymphocytes) attacks its own hair follicles, **causing round patches of hair loss.**
2. Alopecia Areata is genetically related to other autoimmune diseases as atopic dermatitis, Vitiligo and asthma; which can effect both males, females and children.
3. It most often affects the scalp; however it can also **affect any hair-bearing areas**, including **beard**, **eyebrows** and **eyelashes.**
4. Treatment options include: **intralesional corticosteroids injections, topical corticosteroids, topical/systemic immunosuppressants, Minoxidil** and **Anthralin.**
5. **Intralesional corticosteroids** are the 1st line of therapy for localized conditions of alopecia areata, and are superior to topical corticosteroids.
   - **Triamcinolone** is the most common corticosteriod used; less than 0.1 ml is injected per site, and injections are spread out to cover all the affected areas (usually 1 cm between each injection site); injections are given every 4-6 weeks.
6. **Minoxidil** is mainly used for androgenic alopecia, but its of a **little value in Alopecia Areata**, (response rate vary from 8%-44%); initial regrowth may be seen withen 12 weeks of treatment (5% solution applied twice daily).
7. **Anthralin** alters the skin's immune system (its mainly used for Psoriasis); used for Areata as short contant therapy, applied to the skin and left for 20-50 minutes before washing it out.
8. Some cases of Alopecia Areata (AA) responed to **PRP therapy** (platelet rich plasma).
9. Some studies shows a benefit of oral **Zinc Gluconate (30-50 mg/day)** in the treatment of AA.
10. In the cases of **hair loss in eye lashes**, **Latanoprost** and **Bimatoprost** are used (they are prostaglandin analogs, which are usually used to treat Glucoma); they are shown to increase the number, length and thickness of eyelashes.

Scientific name	Dosage form	Trade name	concentration
Anthralin *	Oint. , Paste	Dithrocream® , Micanol®	0.1% , 0.5% , 1%

*** Anthralin = Dithranol, they are the same drug.**

14.18 – Products for treating Hirsutism

1. Hirsutism (excessive hair growth) may result from hormonal disorders, or as a side-effect of drugs such as Minoxidil, corticosteroids, anabolic steroids, androgens, Danazol, and Progestogens.
2. **Eflornithine** (an antiprotozoal drug), inhibits the enzyme ornithine decarboxylase in hair follicles, (thus Blocks putrescine that is necessary for the growth of hair follicles); **Topical Eflornithine can be used as an adjunct to laser therapy for facial hirsutism in women;** it should be discontinued in the absence of improvement after treatment for 4 months.
   - The best solution for excessive hair is **laser therapy**; but unfortunately, laser therapy doesn't work for gray-white hair, (**Eflornithine** works both on all hair types including gray ones).
3. Other option for treating hirsutism include**: Metformin**, **Spironolactone** and **Cyproterone**.
   - **Metformin** is used for Hirsutism in women with polycystic ovary syndrome (PCOS); Systemic treatment is required for 6–12 months before benefit is seen.
   - **Spironolactone** (diuretic + mild antiandrogenic activity) and **Cyproterone** (antiandrogen) are useful when Hirsutism is due high androgen levels.

Scientific name	Dosage form	Trade name	concentration
Eflornithine	Cream	Vaniqa®	11.5%
	Cream	Florexa®	13.9%

14.19 – Vitiligo

1. Vitiligo is a long-term skin condition characterized by patches of the **skin losing their pigment** (due to **losing melanin**, the pigment that determines the color of skin, hair and eyes), The patches of skin affected become white and usually have sharp margins; The hair from the skin may also become white, often **the patches begin on areas of skin that are exposed to the sun** and It is more noticeable in people with dark skin (Its occurs mainly when the cells that produce melanin (melanocytes) die or no longer produce melanin).
2. The exact cause of vitiligo is unknown; but it is believed to be due to genetic susceptibility that is triggered by an environmental factor such that an **autoimmune disorder**, which results in the **destruction of skin pigment cells.**
3. There is **no known cure for vitiligo** (the treatment goal is to stop or slow the progression of pigment loss); For those with light skin, sunscreen and makeup are all that is typically recommended, other treatment options may include **corticosteroid** creams or **phototherapy** to darken the light patches; Alternatively, efforts to lighten the unaffected skin, such as with **hydroquinone** can be sometimes usefull.
4. Treatment options for Vitiligo include:
   a. **Immune mediators,** which include **Topical Corticosteroids** (can help to return the color to skin, Repigmenting), and **calcineurin inhibitors** (such as tacrolimus or pimecrolimus).
   b. **Topical Vitamin D analogs** (Calcipotriene, which can be combined with other therapies).
   c. **Photochemotherapy** (Psoralen + Ultraviolet A) or called PUVA.
   d. **Laser therapy** (Excimer laser, which can be used for small areas of vitiligo).
   e. **Depigmentation the darker skin** (using **Hydroquinone** or **Monobenzone**).

14.20- Skin Aging and wrinkles

1. As skin ages, it becomes thinner and more easily damaged; Intensifying this effect is the decreasing ability of skin to heal itself as a person ages, and among other things, skin aging is noted by a decrease in volume and elasticity.
2. There are many internal and external causes to skin aging (called **Intrinsic aging** and **extrinsic aging**); also, aging skin receives less blood flow and lower glandular activity, chronic topical corticosteroid using causes degradation of collagen, which accelerate skin aging.
   - Intrinsic aging is influenced by internal physiological factors alone, and extrinsic aging by many external factors (also called chronologic aging); extrinsic aging is most often referred to as photoaging; also **free radicals cause a direct damaging effect** on the dermal fibers.
3. A validated comprehensive grading scale has categorized the clinical findings of skin aging as laxity (sagging), rhytids (wrinkles), and the various facets of photoaging, including erythema (redness), and telangiectasia, dyspigmentation (brown discoloration), solar elastosis (yellowing), keratoses (abnormal growths) and poor texture.
4. **Intrinsic aging** is sometimes referred to as chronological aging and is an inherent degenerative process due to declining physiologic functions and capacities; aging process may include qualitative and quantitative changes and includes diminished or defective synthesis of collagen and elastin in the dermis.
5. **Extrinsic aging** of skin is a distinctive declination process caused by external factors, which include ultra-violet radiation, cigarette smoking, air pollution.
   - Radiation from sunlight has the most widespread documentation of its negative effects on the skin, because of this, extrinsic aging is often referred to as photoaging.
   - Photoaging may be defined as skin changes caused by chronic exposure to UV light. Photodamage, implies changes beyond those associated with aging alone, defined as cutaneous damage caused by chronic exposure to solar radiation and is associated with emergence of neoplastic lesions.

6. **Wrinkles** are a by-product of the aging process, As people age, skin cells divide more slowly, and the middle layer of the skin (dermis) begins to thin; the dermis is composed of a network of elastin and collagen fibers, which offer support and elasticity, as this **network loosens and unravels with time, depressions are created on the skin surface**; Aging skin is also less able to retain moisture, less efficient in secreting oil, and slower to heal, and all these factors contribute to the development of wrinkles.
   - Lines on the forehead, between the eyebrows (frown lines), and jutting from the corner of the eyes (crow's feet) are believed to develop because of small muscle contractions; Smiling, frowning, squinting and other habitual facial expressions cause these wrinkles to become more prominent, over time, these expressions coupled with gravity contribute to the formation of wrinkles.
   - Exposure to **UV light breaks down collagen fibers and leads to the production of abnormal elastin;** when ultraviolet light damages skin tissue, an enzyme called metalloproteinase is produced; this enzyme creates and reforms collagen, and during the process some healthy collagen fibers are damaged, resulting in solar elastosis (the disorganized formation of fibers); Wrinkles develop when the rebuilding process occurs over and over, less efficiently each time.
7. Wrinkles fall into two functional categories: fine surface lines (caused by ultraviolet light) and deep furrows (caused by muscle contractions from facial expressions due aging); Wrinkle treatments are in general much more effective for fine lines; Deeper creases may require techniques that are more aggressive.
8. **Treatments available for skin wrinkles** include topical medical treatments (such as vitamin A acid or its derivatives as Tretinoin, alpha hydroxy acids, antioxidants, and moisturizers) and more invasive procedures (such as glycolic acids peels, deep peels, dermabrasion, laser resurfacing, surgical procedures, injection of fillers, and Botox).
   - **Dermabrasion** or mechanical peeling (sanding layers away), and **chemical peels** (dissolving skin away) are two of the traditional methods used in skin resurfacing; common chemical peels include: **Alpha Hydroxy Acid (AHA), Beta Hydroxy Acid (BHA), Trichloroacetic Acid (TCA), Lipo Hydroxy Acid (LHA), Salicylic Acid** and **Phenol.**
   - **Tretinoin** decreases cohesiveness of follicular epithelial cells, it also stimulates mitotic activity and increased turnover of follicular epithelial cells; other Tretinoin derivatives include **Retinol**, **Retinyl Palmitate** and **Retinaldehyde (Retinal)**; which are found in most antiwrinkles creams.
   - Topical glycosaminoglycans supplements (**Topical Hyaluronic acid**) can help to provide temporary restoration of enzyme balance to slow or prevent matrix breakdown and consequent onset of wrinkle formation, Glycosaminoglycans (GAGs) are produced by the body to maintain structural integrity in tissues and to maintain fluid balance (**Hyaluronic acid promotes collagen synthesis, repair, and hydration**) it also serve as a natural moisturizer and lubricant between epidermal cells to inhibit the production of matrix metalloproteinases (MMPs).
   - **Argireline** (Acetyl Hexapeptide-3) relaxes facial muscles to prevent wrinkles and fine lines formation; **Topical Vitamin C** aids in the healing process, it also stimulates the synthesis of collagen; and also act as antioxidant; **Topical antioxidants**, as **Vitamin E** (Tocopherol), topical **Co-enzyme Q10,** helps to reduce the damage caused by free radicals.
   - **Dermal fillers** are injectable products frequently used to correct wrinkles, and other depressions in the skin, they are injected into the face to help fill in facial wrinkles and restoring a smoother appearance, The most common Filler products are **Hyaluronic Acid, Calcium Hydroxylapatite, Collagen, Polycaprolactone, Polymethylmethacrylate** and **Polyacetic Acid.**

- **Botulinum toxin** (Botox) is a neurotoxin protein produced by the bacterium Clostridium botulinum; Besides its cosmetic application, Botox is used in the treatment of other conditions including migraine headache and cervical dystonia (spasmodic torticollis) (a neuromuscular disorder involving the head and neck).
  - **Botulinum toxin** treats wrinkles by **immobilizing the muscles** which cause wrinkles (when injected in small doses into muscles; it blocks the chemical signals that cause muscle to contract – inhibits Acetylcholine), and when the muscles relax; **the skin flattens and appears smoother with less wrinkles.**
  - It is **not appropriate for the treatment of all wrinkles**; it is indicated for the treatment of glabellar lines or frown lines (between the eyebrows), lines across the forehead and for crow's feet (corners of the eyes) in adults.
- **Laser resurfacing** is FDA-cleared skin resurfacing procedure in which lasers are used to improve the condition of the skin; Two types of lasers are used to reduce the appearance of fine lines and wrinkles on the face; an **ablative laser** that removes thin layers of skin and a **nonablative laser** that stimulates collagen production; Nonablative lasers are less effective than ablative ones but they are less invasive and recovery time is short, after the procedure people experience temporary redness, itching and swelling.

Trade name	D. form	Scientific name(s)	concentration
Ardene C20®	Cream	Vitamin C + Glycolic Acid + Vitamin E + Grape seed oil + Retinyl Palmitate + others	20% + 6%
Duolys CE® (ACM)	Serum	Vitamin C concentrate	15 ml
H3 Retinol® (Gerovital)	Cream	Retinol + antioxidants	40 gm
Derma Anti-Wrinkles®	Cream	Retinyl Palmitate + Hyaluronic acid Biopeptide CL + Ronacare AP *	30 gm cream
Derma Instant Youth®	Cream	Argireline + Hyaluronic acid	30 gm cream

* Ronacare AP = Bis-Ethylhexyl Hydroxydimethoxy benzlmalonate, which is an antioxidant.

14.21- Antiperspirants

1. **Hyperhidrosis** (**excessive sweating**) can be generalized or focal, affecting the palms of the hands, soles of the feet, or axillae, People with hyperhidrosis **may sweat even when the temperature is cool or when they are at rest**, those with hyperhidrosis appear to have overactive sweat glands.
2. Excessive sweating may be controlled with strong **anti-perspirants**, they act by forming gel spheres in sweat glands that absorb sweat leading to negative feedback to decrease sweating.
   - Antiperspirants can cause skin irritation, and large doses of aluminum chlorohydrate can damage clothing.
   - **Deodorants** do not prevent sweating, but are helpful in reducing body odor.
3. **Anticholinergic drugs**, such as **Glycopyrrolate**, help to prevent the stimulation of sweat glands; Although effective for some patients, these drugs have not been studied as well as other treatments, their Side effects include dry mouth, dizziness, and problems with urination.
4. **Beta-blockers** or **benzodiazepines** may help reduce **stress-related sweating**.
5. **Botulinum toxin type A** (Botox) is FDA approved for the treatment of severe underarm sweating, a condition called primary axillary hyperhidrosis; their effect lasts for several months.
   - Small doses of purified botulinum toxin injected into the underarm temporarily block the nerves that stimulate sweating.; Side effects include injection-site pain and flu-like symptoms.
   - Botox can be used for the sweating of the palms; but it can cause mild, but temporary weakness and intense pain.

6. Drug therapy should be tried initially but is often ineffective in severe cases.
   - **Aluminum salts**, such as **aluminum chloride** or **aluminum chlorohydrate** in alcoholic solvents applied topically, may be successful in milder forms of focal hyperhidrosis.
   - Initially a patient may need to use Aluminum salts **three to seven times a week**; and after sweating becomes normal, the person may need to use it only once every one to three weeks.
   - In more severe cases specialists use **Glycopyrronium Bromide** as a (0.05%) solution in the iontophoretic treament of hyperhidrosis of plantar and palmar area.

Scientific name	Dosage form	Trade name	concentration
Aluminum Chloride Hexahydrate	Solu. , Spray	Anhydrol®, Driclor®	20%
Aluminum Chlorohydrate	Cream	Aquax-Deo®	75 gm Cream
Aluminum zirconium tetrachlorohydrix	Soap	Secret®	19%
Glycopyrronium Bromide	Powder	Robinul®	3 gm
Glycopyrronium tosylate *	Cloth , pouch	Qbrexza®	2.4%

* The drug solution is on a pre-moistened cloth for application to the skin; approved **for use only in underarms q24 hours** (not suitable for other areas).

14.22 – Skin Bleachers/Skin whitening (Depigmenting Agents)

1. **Hyperpigmentation** is the darkening of an area of skin caused by the increased melanin in that spot, it can be caused by sun damage, inflammation, and skin injuries including Acne.
2. There are two main types of hyperpegmintation, **Melasma** and **post-inflammatory hyperpigmentation (PIH).**
   - **Melasma** is more **common in females than males**, can be tiggered during sun exposure (worsen during summer), **its common in pregnant women** and those who are taking contraceptive or hormonal replacment therapy (HRT).
   - **post-inflammatory hyperpigmentation (PIH)** is a **temporary pigmentation** that follows skin injury (sun burn, dermatitis, skin infections, Acne).
3. Topical depigmenting agents inhibit melanogenesis (the pigmentation pathway by which cells produce melanin), they are applied on the skin, on the affected area to treat hyperpigmentation or to whiten the skin. [5], these include: Hydroquinone, Monobenzone, Tretinoin, Azelaic Acid, Cysteamine and Glutathione.
   - **Hydroquinone** inhibits tyrosinase (an enzyme involved in the production of melanin).
   - **Monobenzone** works by increasing elimination of melanin from skin cells.
   - **Tretinoin** increases keratinocytes turnover.
   - **Azelaic Acid** decrease the activity of melanocytes.
   - **Cysteamine** works by inhibiting melanin synthesis pathway.
   - **Glutathione** cause skin lightening by converting melanin to a lighter color and deactivating the enzyme tyrosinase, which helps produce the pigment.
4. Other products that cause skin lightening when used topically include: **Kojic Acid, Arbutin, Licorice extracts, Mequinol, Niacinamide (vit B_3), N-Acetyl Glucosamine, Aloe vera** and **Soy.**
5. Oral **Tranexamic acid** has shown to provide rapid and sustained lightening in melasma; by **decreasing melanogenesis** in epidermal melanocytes.
   - Although, some dermatologists use topical Tranexamic acid for whitening combinations.
6. **Other intervesions** for **skin whitening** include:
   - **Chemical peeling**, using (Alpha Hydroxy Acid (AHA), Beta Hydroxy Acid (BHA), Trichloroacetic Acid (TCA), Lipo Hydroxy Acid (LHA), Salicylic Acid and Phenol.
   - **Mechanical peeling**, using either microdermabrasion or dermabrasion.
   - **Laser therapy** by either pulsed CO2 or Q-switched alexandrite.

Scientific name	Dosage form	Trade name	concentration
Hydroquinone	Cream	Melquin® , Eldopaque®	2% , 4%
	Cream	Avoquin®	1.9%
	Soap	Eldoquin®	4%
Monobenzone	Cream	Benoquin®	20%
Azelaic acid	Cream, Gel	Skinoren®, Azelex®, Finacea® Azeclear®	20%, 15% (gel)
Cysteamine	Cream	Cyspera®	5%
Mequinol + Retinol	Topical Solu.	Solage®	(2% + 0.01%), (10% + 1%)
Hydroquinone + Tretinoin	Cream	Derma Lightening®	2% + 0.025%
Hydroquinone + Fluocinolone + Tretinoin	Cream	Tri-Luma®, Triderma®	4% + 0.01% + 0.05%
Hydroquinone + Mometasone + Tretinoin	Cream	Melacare® , Getlite® Makcare®	2% + 0.1% + 0.025%
Hydroquinone + Hydrocortisone + Tretinoin	Cream	Pigmanorm®	4% + 1% + 0.1%
Hydroquinone + Vit. C + Vit. E +Kojic acid + Milfoil Extract	Cream	Ardene Skin lightener®	30 gm combo
Hydroquinone + Vitamin C + Vitamin E + (sunscreen)	Cream	Avalon Whitening®	1.9%
Glutathione	Soap	G Soap® , Glutathione®	----------
	Vial	RM Glutathione®	100 mg/vial
	Cap	Glutawhite®	500 mg
	Spray	Ivory Caps®	30 ml

Other products for skin whitening/depigmenting

Trade name	Dosage form	Scientific name(s)	concentration
Aquax Whitening®	Cream	β-white	50 gm cream
Alpha Plus®	Cream	Arbutin + Glabridin	1% + 0.5%
Eva®	Serum	Vitamin C + Salicylic Acid + Hyaluronic acid + Niacinamide + Retinol + MSM	20% + 2% + 5% + 3.5% + 2% + 10%
Rexsol Pigment®	Serum	Hydroquinone + Lactic acid + Citric acid	60 ml Solu.
Rilastil D-Clar®	Serum	Butyl Resorcinol + Vitamin C + Alpha Hydroxy Acid	30 ml Solu.

Notes:

1. **β-White** is a complex combination of a Transforming growth factor-β1 (TGF-β1) agonist peptide encapsulated in a liposome vehicle, recently TGF-β1 was described for its role in melanogenesis, it has demonstrated an inhibitory activity on melanin synthesis.
2. **Glabridin**, a component of licorice, it is a tyrosinase inhibitor.
3. **Arbutin** (a glycoside; a glycosylated hydroquinone), is a naturally derived substance found in plants such as bearberry, cranberries, blueberries, wheat, and pears. Our bodies break down arbutin into glucose and hydroquinone; Since hydroquinone is released slowly by arbutin, it is less irritating to skin than directly applied synthetic hydroquinone.
4. **Kojic acid** works by blocking tyrosine from forming, which then prevents melanin production.
5. **Resorcinol** exerts a keratolytic activity; mainly used for acne.

14.23 – Dark spots under the Eyes

1. The area under the eyes is very thin, the venous circulation underneath the skin contributes to the dark color of the area, which is mainly due lack of enough sleeping or due to tiredness.
   - Also, Oversleeping, extreme fatigue, or just staying up a few hours past your normal bedtime can cause dark circles to form under your eyes.
2. The dark circles are also due to the accumulation of hemoglobin and its metabolism's by-products (bilirubin and iron) in the tissues underneath the eyes, both in the corium and in the epidermis.
3. **Causes of dark circles:**
   - **Hereditary factors:** The thinnest the skin, the more intense the blue tone; also, the bone structure may also form cavities in the face, causing the dark circles to look even more intense due to the shadows created.
   - **Allergies, asthma and eczema:** Histamine release is also causing dark coloration of the skin, rubbing of the skin due to itching intensifies the appearance of dark circles; also, it's more common for people with seasonal allergy, food allergy etc.
   - **Medication:** All drugs causing vasodilation are also intensifying the problem of dark circles.
   - **Iron deficiency anemia:** The iron deficiency can also intensify the appearance of dark circles due to lower quantity of oxygenated blood (which has intense red color).
   - **Tiredness:** It increases skin's paleness and allows the circulation of the blood to be more apparent underneath the skin.
   - **Hepatic disturbance:** Dark circles under the eye can also be a symptom of a systemic disease.
   - **Pregnancy and Menstruation:** These conditions can be associated with dark circles due to lower quantity of iron in the blood
   - **Ageing:** With age and the loss of collagen the skin becomes thinner and more transparent; in such a case dark circles are becoming more intense and they are often associated with bags or sacs under the eyes.
   - **Nutrition:** In rare cases lack of vitamins can cause dark circles. A healthier nutrition is helping reduce the appearance of the dark circles.
   - **Sun exposure:** intensifies the appearance of dark circles as the sun is causing the increase of melanin synthesis.
4. The treatment for your dark circles depends upon their severity and the underlying cause; Multiple interventions can be used to address the pigmentation around the eyes, but each treatment may not work for all types of dark circles; A number of cosmetic products may help **lighten skin discoloration while improving collagen synthesis**; (the two factors that can minimize the appearance of dark circles.)
   - **Retinoids** are among the most widely used topical agents that aim to enhance the structural quality and appearance of the skin.
   - Other skin-enhancing compounds that can be used to address under-eye hyperpigmentation include **Hydroquinone**, **Azelaic Acid**, **Kojic Acid**, **Arbutin**, **Vitamin C**, **Vitamin K**, **Haloxyl**.
     - These compounds can only help diminish the visibility of dark circles when applied in the right dosage; Overuse of such skin products can lead to irritation and other side effects.
5. Other interventions for dark areas include:
   - **Chemical peeling** may help lighten the dark circles caused by surface-level hyperpigmentation; Given that the skin covering the lower lids is extremely thin, only a mild exfoliant such as glycolic acid is used to prevent potential skin damage.
   - **Laser therapy:** Both invasive and noninvasive lasers have been used to improve under-eye darkening, the type of laser depends on the underlying issue with the skin:
     - **Q-switched laser** targets pigmentation, **radiofrequency** helps with collagen production and skin tightening, and **intense pulsed light (IPL)** can improve mild pigmentation secondary to sun damage.
     - **Ablative laser** resurfacing is a more powerful invasive laser that can improve skin pigmentation, stimulate collagen production, and soften fine lines, this laser has the ability to target multiple factors contributing to under-eye circles.

- **Hyaluronic acid gel soft tissue fillers:** If the dark circles are the result of irregularly shaped lower eyelids, hyaluronic acid (HA) fillers may be used to flesh out the under-eye hollows.
- **Blepharoplasty:** a surgery involves cutting into the lower eyelid area to scoop out the excess fat deposits, muscle, and skin that may be casting a shadow under your eyes.
  - Even though this surgery is one of the more invasive measures, it is also one of the most effective ways to correct the contour irregularities that contribute to baggy eyelids and dark circles.

Trade name	D. form	Scientific name(s)	concentration
Derma Under Eye®	Gel	Haloxyl + Hyaluronic acid	2% + 5% (30 gm gel)
Cetaphil Hydrating Eye®	Cream	Hyaluronic Acid + Licorice Extract + Vitamin Complex	14 gm cream
Rilastil Micro Eye Contour®	Cream	Retinol + Haloxyl + Hyaluronic Acid + Vitamin Complex	15 gm cream

*** Haloxyl** = a combination of (N-hydroxy succinimide, chrysin, palmitoyl tripeptide1, palmitoyl tripeptide7); which when applied topically solubilize the accumulated iron for easier elimination and stimulates the enzyme that is responsible for clearance of bilirubin.

14.24 - Topical Products for Scars

1. Topical applications include the use of products such as **silicone gels** or sheeting, creams or salves, **vitamins E and A** (retinoic acid), herbal remedies, and others, these are the most widely used approaches by patients because they are easy to use and are of low cost.
2. Depressed scars can be filled with temporary or permanent **filler materials.**
3. **Silicone gel or silicone sheeting** may be applied over healing wounds to promote scar improvement, The improvement in scarring is purportedly due to the water retention in tissues beneath the occlusive silicone dressings, Other petroleum-based ointments also provide this occlusive effect, promoting hydration and improving scar appearance.
4. **Topical applications including vitamin A** have been shown to improve the aesthetic properties of scars, Vitamin A as applied to the skin is 0.05% retinoic acid and is an effective resurfacing agent; Scars exposed to retinoic acid are typically less irritated, less elevated, and softer.
   The topical route of administration is preferred because the systemic toxicity of vitamin A is more easily avoided than with oral intake of the vitamin.
5. **Vitamin E** penetrates deeply into the dermis and has an antioxidant effect, If applied to a wound in the early stages of healing, the recovery of tensile strength may be adversely affected; Lastly, creams or salves containing herbal remedies have been shown to be largely ineffective in changing the attributes of scars, or at best, are of unproven efficacy.
6. **Intralesional injections** allow for greater penetration of the scar by the therapeutic agent and for delivery of greater concentrations locally than with topical or systemic administrations.
7. The **2 most common intralesional injections are corticosteroids and antimitotic agents.** Intralesional corticosteroid injection has been extensively studied and proven to reduce the size of hypertrophic scars and keloids. (1)
   a. **Steroids** exert several effects on healing scars, including reducing fibroblast populations, reducing the formation of new vasculature, and decreasing fibrosis.
   b. **Antimitotic agents** such as **5-fluorouracil** or **bleomycin** are used intralesionally to inhibit proliferation of scar tissue; These agents are contraindicated in pregnancy.

Trade name	D. form	Scientific name(s)	concentration
Contractubex®	Gel	Heparin Na + Allantoin + Extractum cepae (onion)	5000 IU + 1 gm + 3 gm
	Patch	Cepalin + Allantoin	----------
Mebo Scar®	Lotion	Sesame + Cactus + Beeswax extracts + Linoleic acid + Tyramine	----------
Acnethro®	Gel , Soap	Allantoin + Aloe Vera + Vit E	----------
NewGel+®	Gel , Patch	Silicon dioxide	30 gm gel
Scarmed®	Gel	Silicon dioxide	15 gm gel
Dermatix®, Vaniza®	Gel	Polysiloxane + Silicon dioxide	10 gm gel
Opexa®	Gel	Dimeticone + Ascorbyl Testraisopalmitate	10 gm gel
Dermatix Ultra®	Gel	Cyclopentasiloxane + Vit. C ester	----------
Mederma®	Cream/Gel	PEG-4, Allium Cepa, Bulb Extract, Xanthan Gum, Allantoin	----------

14.25 – Wound Care Products:

1. These products help in wound cleansing and moisturizing; some also help in the healing process.
2. There are simple techniques which are applied for wound care and cleaning, they include:
   a. **Negative pressure wound therapy (NPWT)**, this therapy is also called wound vacuum, or wound vac. therapy. A vacuum device uses suction to remove fluid and waste from the wound and pull the edges closer together. NPWT may also increase blood flow and new tissue growth in the wound. (1)
   b. **Hyperbaric oxygen therapy (HBO)** is used to get more oxygen into the body. The oxygen is given under pressure inside of a tube-like chamber called a hyperbaric or pressure chamber.
3. **Topically applied Simvastatin** may have significant therapeutic potential for enhanced wound healing in patients with impaired microcirculation such as that in diabetes; (by enhancing angiogenesis and lymphangiogenesis).
4. **Phenytoin Spray** enhance the formation of granulation tissue; promoting deposition of collagen and other connective tissue components, thus enhance wound healing.
5. Appling **Insulin Topically or by injecting it around the wound and burn** can increase and accelerate the wound healing.

Trade name	Dosage form	Scientific name(s)	concentration
Dermabond®	prefilled appl.	2-octyl cyanoacrylate *	----------
Regranex®	Gel	Becaplermin	0.01%
Prontosan®	Gel , Solution	Betaine + Polyhexanide	0.1% + 0.1%
Iodosorb®	Gel	Cadexomer iodine	0.9%
Santyl®	Oint.	Collagenase	250 units/gm
Hametan®	Cream	Hamamelis Virginiana extract	536 mg/30 gm tube
Madecassol®	Oint.	Centella Asiatica + Neomycin	(10 mg + 3.5 mg)/1 gm
Eletone® , Tropazone®	Cream	Petrolatum + Mineral oils	100 gm tube
Mebo®	Oint.	β-Sitosterol	0.25%
Magic Cream®	Cream	β-Sitosterol	0.25%
Solcoseryl®	Oint.	Protein-free hemodialysate	5%
Solcoseryl® Jelly	Gel	Protein-free hemodialysate	10%
Healsol®	Spray	Phenytoin	----------

Notes:

1. **Dermabond®** is indicated to hold closed easily approximated skin edges of wounds.
   a. Countraindicated in Wounds with active infection, gangrene.
2. **Becaplermin** is a Recombinant human PDGF-BB; stimulates chemotactic recruitment of wound-healing cells; promotes angiogenesis and induces fibroblast proliferation and differentiation to promote wound healing; also granulation tissue enhancer.
   a. this drug should be used with caution in patients with known malignancy.
   b. increase risk of mortality secondary to malignancy in patients treated with 3 or more tubes of becaplermin gel.
3. **Betaine** Acts as surfactant/detergent to aid with debridement, **Polyhexanide** is a Preservative, The combination of these 2 products provides a lower surface tension than water and improves biofilm removal in wounds, they are indicated for wound irrigation for acute/chronic wounds
4. **Cadexomer** Cleans wet ulcers & wounds; reduces microbial load including MRSA, absorbs exudate, helps in debridement, creates moist wound environment, & retards eschar formation
   a. Releases iodine that has antimicrobial function
5. **Collagenase** is a Collagen-degrading enzyme; digests collagen in necrotic tissue but not in healthy tissues.
6. **Petrolatum + Mineral oils** combination is indicated for superficial wounds, minor abrasions, dermal ulcers, donor sites, 1st and 2nd degree burns, including sunburns and radiation dermatitis.
7. **Mebo®** is indicated for acute/chronic wounds, 1st and 2nd type burns.
8. **Solcoseryl® Oint**. Is used for dry wounds and simple burns only, while the **Solcoseryl® Jel** is used for weeping wounds and burns.

14.25– Burns and Burn care products

1. A burn is a **type of injury to skin**, or other tissues, caused by heat, cold, electricity, chemicals, friction, or radiation; Burns that affect only the superficial skin layers are known as **superficial first-degree burns**, They appear red without blisters and pain typically lasts around three days.
2. When the injury extends into some of the underlying skin layer, it is a **partial-thickness or second-degree burn**, Blisters are frequently present and they are often very painful, Healing can require up to eight weeks and scarring may occur.
3. **A full-thickness or third-degree burn**, the injury extends to all layers of the skin, Often there is no pain and the burnt area is stiff, Healing typically does not occur on its own.
4. **A fourth-degree burn** additionally involves injury to deeper tissues, such as muscle, tendons, or bone, The burn is often black and frequently leads to loss of the burned part.
6. Treatment of burns depends on the type and extent of the injuries; Most minor burns can be treated by using over-the-counter products , They usually heal within a few weeks.
7. **Some Clinical Notes about burns:**
   a) Calculation of **Total Burned Body Surface Area (TBSA)** by using the **RULE OF NINE**:
      - Head & Neck = 9% , Each upper extremity (Arms) = 9%
      - Each lower extremity (Legs) = 18% , Anterior trunk= 18%
      - Posterior trunk = 18% , Genitalia (perineum) = 1%
   b) **Vascular changes** resulting from burn injuries: Circulatory disruption occurs at the burn site immediately after a burn injury; Blood flow decreases or cease due to occluded blood vessels and Damaged macrophages within the tissues release chemicals that cause constriction of vessel; Blood vessel thrombosis may occur causing necrosis.
   c) **Fluid shift** resulting from burn injuries: Occurs after initial vasoconstriction, then dilation; Blood vessels dilate and leak fluid into the interstitial space Known as third spacing or capillary leak syndrome Causes decreased blood volume and blood pressure; Occurs within the first 12 hours after the burn and can continue to up to 36 hours.

d) Fluid imbalances resulting from burn injuries: Occur as a result of fluid shift and cell damage; these include Hypovolemia, Metabolic acidosis, Hyperkalemia, Hyponatremia, Hemoconcentration (elevated blood osmolarity, hematocrit/hemoglobin) due to dehydration

e) Curling's ulcer: Acute ulcerative gastro duodenal disease Occur within 24 hours after burn Due to reduced GI blood flow and mucosal damage; Treat clients with H2 blockers, mucoprotectants, and early enteral nutrition

f) For serious burns, after appropriate first aid care and wound assessment, the treatment may involve **I.V. Fluids, pain medications and antibiotics, wound dressings, and surgery**; The goals of treatment are to control pain, remove dead tissue, prevent infection, reduce scarring, regain function and address emotional needs.

- **I.V. fluids** is calculated based on the **TBSA** using **Parkland formula** (burn >20% TBSA): **4 x Wt(kg) x %TBSA = mL/24 hours** ; Deliver 1/2 volume over 1st 8hrs then Deliver 2nd half over next 16 hours.

Medications used in Burns:

a. Antimicrobial ointments (such as **silver sulfadiazine, mafenide, silver nitrate, and povidone-iodine**) are used to reduce risk of infection.

b. Bacitracin may be used for first-degree burns; One study found that parrafin gauzes are valuable for superficial burns while silver-based dressings are preferable for deep burns.

- **Silver Sulfadiazine is used only for 2nd and 3rd degree burns**, and used with caution in patients with sulpha allergy.
- **Nitrofurazone** is indicated as an adjunctive therapy for second- and third-degree burns.

c. Antibiotics (Gentamicin) are used to treat infection; Antibiotics will also probably be used if the risk of developing infection is high (for example, when the body surface area of the burn is large).

d. Pain medications (such as **paracetamol** with **codeine**, **morphine**, or **meperidine**) are used for severe burns; **Anabolic steroids,** such as **oxandrolone**, may be used for severe burns to help decrease wound healing time.

Scientific name	Dosage form	Trade name	concentration
Bacitracin	Oint./Powder	Beocin® , Baciquent®	500 Unit/gm
Silver Nitrate	Topical Solu.	----------	10% , 25% , 50%
Povidone-Iodine	Solu.	Betadine®	5% , 10%
Fusidic acid	Cream/Oint.	Fucidin®, Fucine®, Fucibact®	2%
Silver Sulfadiazine	Cream	Silvadene®, Floumizine®	1%
Nitrofurazone	Cream	Furacin®	2 mg/gm
Silver Sulfadiazine + Panthenol *	Cream	Argiderm®	15 gm
Silver Sulfadiazine + Kaolin	Spray	Sofargen®	10 gm/125 ml can
Mafenide	Cream , Topical Solu.	Sulfamylon®	----------

* **Panthenol** is used as a **moisturizer and to improve wound healing.**

References

1- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th ed.
2- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition. Ph. Press
3- BNF 82.
4- Handbook of Dermatology: A Practical Manual, 2018 Ed, Margaret W. Mann
5- http://www.ncbi.nlm.nih.gov/pubmed/23138019
6- https://jamanetwork.com/journals/jamadermatology/fullarticle/2753127

BLOOD PRODUCTS AND HEMATOLOGY

Chapter Fifteen: Blood products and Hematology

15.1- Anemia

First: Iron Deficiency Anemia

A. Oral Iron
B. Parenteral Iron

Second: Megaloblastic Anemia

A. Vitamin B_{12} types
B. Folic acid
C. Combination Products for Mixed types of Anemia

Third: Hemolytic Anemia

A. (G6PD) Deficiency
B. Sickle cell anemia
C. Thalassemia

15.2- Recombinant Human Erythropoietins

15.3- Iron Chelating Agents

15.4- Drugs used in platelet disorders

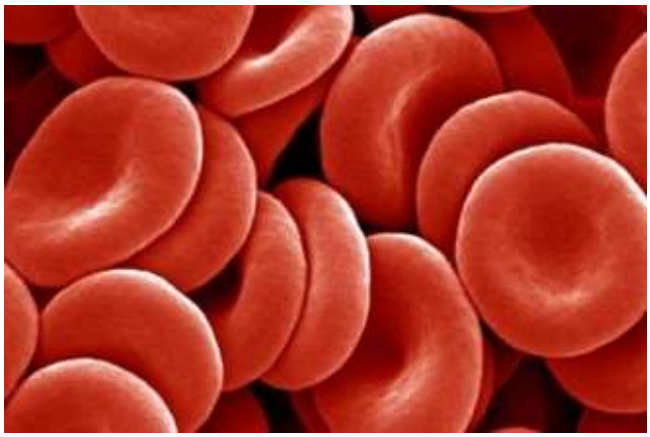
A. Idiopathic thrombocytopenic purpura (ITP)
B. Drugs for Thrombocytopenia (Platelet-stimulating agents)
C. Essential Thrombocythemia

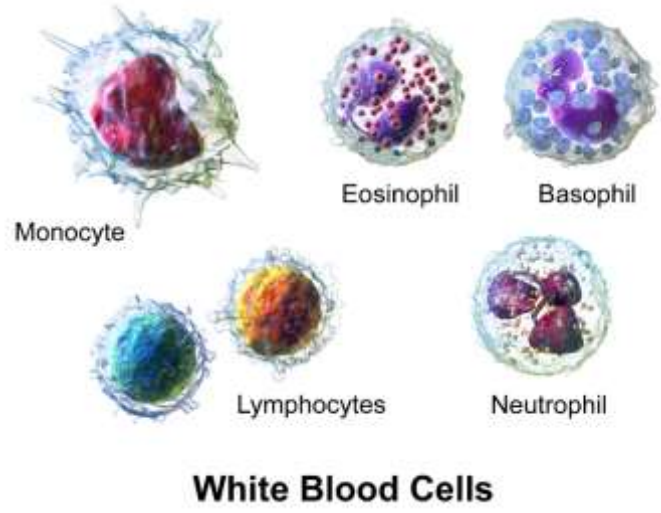
15.5- Drugs for Neutropenia (Colony stimulating factors)

15.6- Hematopoietic stem cell Mobilizers

15.7- Sclerosing agents

15.8- Others Hematological products





White Blood Cells

Chapter Fifteen: Blood products and Hematology

15.1 – Anemia

1. **Anemia** is a group of diseases characterized by a decrease in either hemoglobin (Hb) or the volume of red blood cells (RBCs), which results in decreased oxygen-carrying capacity of the blood.
2. Anemia is defined by the World Health Organization as:
    1. Hb <13g/dL (<130 g/L; <8.07 mmol/L) in men.
    2. Hb <12g/dL (<120 g/L; <7.45 mmol/L) in women.
    3. Newborn: 17 - 19 g/dL.
    4. Children: 14 - 17 g/dL.

Iron salt	Amount	Content of ferrous iron
Ferrous fumarate	200 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous sulphate	300 mg	60 mg
Ferrous sulphate, dried	200 mg	65 mg

First: Iron Deficiency Anemia:

Iron-deficiency anemia (IDA) is characterized by decreased levels of ferritin (most sensitive marker) and serum iron, as well as decreased transferrin saturation. Hb and hematocrit decrease later. RBC morphology includes **hypochromia and microcytosis**.

A) Oral Iron

1. The oral dose of **elemental iron** for iron-deficiency anemia should be 100 to 200 mg daily.
2. The **iron content of various iron salts** is tabulated in the table.
3. Oral iron **preferably taken on an empty stomach** because food, especially dairy products, decreases the absorption by 40% to 50%; (However, many patients must take iron with food because they experience gastrointestinal upset when iron is administered on an empty stomach.) [4], the patient should be told that **oral iron therapy produces dark stools**.
4. **Oral** iron preparations sometimes produce **gastrointestinal irritation** and abdominal pain with nausea and vomiting; **Adverse effects can be reduced by giving it with or after food** or by beginning therapy with a small dose and increasing gradually.
5. **Oral Liquid preparations** containing iron salts should be well **diluted with water and swallowed through a straw to prevent discoloration of the teeth**.
6. Iron should be **stored in a safe place, inaccessible to her young children**; Accidental ingestion of even small amounts (3-4 tabs) of iron can cause serious consequences in small children.
7. Preparations containing **iron and folic acid are used during pregnancy** in women who are at high risk of developing iron and folic acid deficiency.

Scientific name	Dosage form	Trade name	concentration
Ferrous Sulphate	Tab	Ferrosam®	200 mg
	Oral Drops		25 mg/ml
Ferrous Gluconate	Tab	Ferrosam®	300 mg
	Oral Syr.	Ferrosam®	400 mg/15 ml
	Oral Vials	Viofer®	300 mg (37.5 mg Fe^{+2})
Ferrous Fumarate	Tab , Tab ER	Feostat®	63 mg , 150 mg
Polysaccharide Iron	Cap	Niferex® , Ferrex®	150 mg
Iron Protein-succinylate	Oral Vials	Ferplex®	800 mg (equal 40 Fe^{+3})
Dextriferron	Chew Tab	Referum®	100 mg
Ferric Hydroxide Polymaltose Complex	Oral Vials, Syrup	Ferimax®, Ferlos® Veltifer®	100 mg/5 ml
	Syrup	Ferimax®	50 mg/5 ml
Carbonyl Iron	Tab	Feosol® , Icron® , Icar®	45 mg , 66 mg
	Chew Tab	Icar Ped®	15 mg
	Susp.	Icar Ped®	15 mg /1.25 mg

Combination Products			
Iron Gluconate + Manganese Gluconate + Copper Gluconate	Oral Amp	Tot'heme®	50 mg + 1.33 mg + 0.70 mg
Iron Pyrophosphate + Vit. C	Tab	SiderAL Forte®	30 mg + 70 mg

*** Ferric Hydroxide Polymaltose Complex = Dextriferron,** they are the same drug.
* Vit. C enhance the absorption of Iron.

Note: A new study suggests that **iron supplementation** may be a simple solution **to the persistent dry cough** associated with the use of **ACE inhibitors (ACEIs).**

B) Parenteral Iron

1. Parenteral iron is generally reserved for use **when oral therapy is unsuccessful.**
2. **Required Dose calculation:**
   Volume of product required (ml) = [weight (kg) × (14 – actual Hb) × (2.145)] ÷ C
   Where C = concentration of elemental iron (mg/ml) in the product being used:
   For Iron Dextran C= 50 mg/ml, For Iron Sucrose C= 20 mg/ml
3. With the exception of patients with severe renal failure receiving hemodialysis, **parenteral iron does not produce a faster hemoglobin response than oral iron provided,** that the oral iron preparation is taken reliably and is absorbed adequately.
4. **Anaphylactic reactions** occur in less than 1% of patients treated with parenteral iron therapy and are more **commonly associated with iron dextran**.
5. **Test dose**:
   a. It is suggested that all patients considered for iron dextran injection receive a test dose. Patient **should be observed for more than 1 hour** for untoward (chest pain, hypotension), if no reaction occurs, the remainder of the dose can be given.
      - If an anaphylactic–like reaction occurs, it generally responds to (I.V.) epinephrine, diphenhydramine, and corticosteroids.
   b. A Test dose of 0.2 mL (10 mg) has been suggested for children weighing less than 10 kg, 0.3 mL (15 mg) for those weighing 10 to 20 kg, **and 0.5 mL (25 mg) for adults**.
6. It's important to **monitor Iron storage levels** when using chronic or prolonged parenteral iron therapy; to avoid serious toxicity associated with iron over load.
   - **Excess iron** is deposit in the heart, liver, pancreas and other organs; **which can lead to organ failure** and even death.
7. **Iron dextran** is given most commonly **by IM route**; In these cases, undiluted drug should be **administered using a Z-track technique to avoid staining the skin**; (The skin should be pulled laterally before injection; then the drug is injected and the skin is released to avoid leakage of dextran into the subcutaneous tissue).
8. **Iron sucrose** (I.V. only) can be administered **undiluted as a slow IV injection** (rate not to exceed 20 mg/minute) **or as an IV infusion** (dilutes in a maximum of 100 mL of 0.9% NaCl and infuses at a rate of 100 mg for 15 minutes); **A test dose is not indicated** because of the lower incidence of serious anaphylactic reactions.
9. **New Iron Complexes** (Ferumoxytol, Ferric Carboxymaltose and Iron Isomaltoside) can be administered at much higher doses than the older complexes; with very low incidence to iron overload or toxicity, and **they do not require a test dose**.

Scientific name	Dosage form	Trade name	concentration
Iron Dextran	Amp	Dexferrum®, CosmoFer®	50 mg /ml
Iron Sucrose	Amp	Venofer®	20 mg/ml

Ferric Gluconate	Amp	Ferrlecit® , Ferralet®	12.5 mg/ml (10 ml)
Ferric Carboxymaltose	Inj. Solu.	Injectafer®	750 mg/15 ml (50 Fe^{+})
	Inj. Solu.	Ferinject®	50 mg/ml (20 ml vial)
Ferumoxytol *	I.V. Solu.	Feraheme® , Rienso®	30 mg/ml
Ferric Pyrophosphate	Solu.	Triferic®	27.2 mg/5 ml
Iron Isomaltoside **	Inj. Solu.	Monofer®	100 mg/ml (10 ml vial)

*** Ferumoxytol** is indicated in Iron Deficiency Anemia in Chronic Kidney Disease.
** A complex of ferric iron and Isomaltoside containing 10% (100 mg/mL) of iron.

Second: Megaloblastic Anemia (Either B_{12} deficiency or Folate Deficiency, or both)

1. Vitamin B_{12} deficiency, a **macrocytic anemia**, can be due to inadequate intake, malabsorption syndromes, and inadequate utilization; Anemia caused by lack of intrinsic factor, resulting in decreased vitamin B_{12} absorption, is called **pernicious anemia.**
2. Neurologic symptoms can be present and can become irreversible if the vitamin B_{12} deficiency is not treated promptly
3. Risk of Vitamin B_{12} deficiency increases with age, and with the use of gastric acid–suppressing agents (PPIs, H_2 Blockers); which may inhibit the release of Cobalamin from food, Oral or parenteral therapy can be used for replacement.

A) Vitamin B_{12} comes in 3 types

Scientific name	D. form	Trade name	concentration
Cyanocobalamin*	Tab	Cobalamine®	100 mcg , 250 , 500 , 1000 mcg
	Amp	Cobalamine®	1000 mcg/ml
	Amp (oral)	B_{12} Gerda®	1000 mcg/4 ml
	Oral Vial	Maddovit B_{12}®	25 mcg/7 ml
	Nasal Spray	Nascobal® , CaloMist®	25 mcg/spray
Methylcobalamin **	Amp	Methycobal®	500 mcg
	Tab	Methycobal®, Mecobalamine®	250 mcg , 500 mcg
Hydroxocobalamin	Amp	Cobalin-H®	1000 mcg/ml
	Vial	Cyanokit®	5 gm/vial

*** (Cyanocobalamin)** turns inside the body to **(Methylcobalamin) then to (Hydroxocobalamin)** which is the active form of B_{12}
**** Methylcobalamin** ampules and tablets should be **protected from light and moisture**, (Light decreases the active ingredient content and may turn reddish with exposure to moisture)

Notes:

1. **Cyanocobalamin** is the least expensive and least painful type at the injection site, and is used once a week **I.M. ONLY**, but it is the least efficient.
2. **Methylcobalamin,** also called **(Mecobalamin);** is **more efficient than Cyanocobalamin** because it does not need to switch to another form inside the body.
   - **a.** It has a better absorption profile.
   - **b.** More painful at the injection site and **can be given I.M, I.V.**
   - **c. The best choice for smokers,** due to their inability to convert **Cyanocobalamin** to **Methylcobalamin** because of the presence of the heavy metals & toxins in the liver.
   - **d.** Its methyl group stimulates Serotonin production in CNS; (thus has a mood supporting effect).
   - **e.** High doses can be effective in the treatment of Multiple Sclerosis.
3. **Hydroxocobalamin** is the most bioactive form, and is the most type commonly used.
   - **a.** It's better to be given I.V. due to its very painful at injection site unless mixed with local anesthetic, stay inside the body for a longer period, which reduces the no. of injections.
   - **b.** The (5 gm vial) is used in the **treatment of Cyanide poisoning** as I.V infusion.

B) Folic acid

1. Human beings **cannot synthesize Folate endogenously**; thus, it has to be supplied throw diet or by supplementation; the human body needs Folate to make and repair DNA, it also acts as a cofactor in several biological reactions.
2. **Folic acid** is an oxidized form; it must be converted to the active form (**Tetrahydrofolate**) in the body (by the liver) to be beneficial inside the human body.

Notes:

1. **Prevention of neural tube defects (NTD)**
   - **a.** Folic acid supplements taken before and during pregnancy can **reduce the occurrence of neural tube defects**.
   - **b.** For women of child-bearing potential at high risk of having a pregnancy affected by NTD (if they have had a previous pregnancy affected by a neural tube defect), the dose of folic acid is **4 mg or 5 mg daily** starting before pregnancy (in the USA the recommendation is 4 weeks before) and continued through the first trimester (until week 12 of pregnancy).
   - **c.** **For women at a low risk of having a child with a NTD** the dose **is 400 micrograms** daily and continued through the first trimester (until week 12 of pregnancy).
   - **d.** **Higher doses** than 400 mcg of Folic acid is **related** in some studies **to Autism.**
2. **Other indications for folic acid include:**
   A- Folate-deficient **Megaloblastic anemia**.
   B- Prevention of **methotrexate-induced side-effects.**
   C- Prophylaxis of **folate deficiency in dialysis.**
   E- Fertility aid in both men and women.
3. **Folic acid** may **reduce the risk of stroke** in elderly (due **it decreases Homocysteine** conc.), as the patients with heart disease with high homocysteine levels are more than four times as likely to suffer the most common type of stroke compared with those with low homocysteine levels.

Scientific name	Dosage form	Trade name	concentration
Folic Acid	Tab	Folvite®, Folix®	400 mcg, 1 mg , 4 mg , 5 mg
	Oral Solu.	Mega Folic®	400 mcg/5 ml
	Oral Drops		400 mcg/1 ml
	Inj. Solu.		5 mg/ml
L-5 Methyl-Tetrahydrofolate	Tab	FolaPro®, Folimax®	800 mcg , 400 mcg
Folic Acid + Iron	Cap	Fefol® , F.F®	5 mg + 150 mg

*** Folic acid** Inj. Solu. is used in the treatment of methanol toxicity and Methotrexate toxicity
** **L-5-Methyl-Tetrahydrofolate (L-5-MTHF) = Metafolin = Methylfolate**, all are the same.

Combination Products for Mixed types of Anemia

Trade name	D. form	Scientific name(s)	concentration
Quatre B_{12}®	Tab	Methyl-Tetrahydrofolate + Vit. B_{12}	400 mcg + 1000 mcg
SiderAL Folic®	Oral Solu. (Sticks)	Iron Pyrophosphate + Vit. C + Folic acid + Vit. D + Vit. B_6 + Vit. B_{12}	30 mg + 70 mg + 400 mcg + 10 mcg + 1 mg + 1.75 mcg
Soft Iron®	Cap	Iron Bisglycinate + Vit. C + Folic acid + Vit. B_6 + Vit. B_{12}	28 mg + 40 mg + 400 mcg + 1.4 mg + 2.5 mcg
Hema-Plex®	Tab	Iron amino acid complex + Vit. C + Tetrahydrofolate + Vit. B_{12} + (other minerals and vitamins)	85 mg + 300 mg + 400 mcg + 500 mcg

Third: Hemolytic Anemia:

1. These include:
   A. **Glucose 6-phosphate dehydrogenase (G6PD) deficiency** B. **Sickle cell anemia**
   C. **Thalassemia**
2. Those patients **don't need Iron therapy,** they are at **risk of developing iron overload** and require chelation therapy with **(Deferoxamine, Desferiprone** or **Deferasirox).**
3. They are generally **given Folic acid supplementation.**

A) (G6PD) Deficiency:

1. **G6PD** is essential for the production of **(NADPH)** in erythrocytes, and **(NADPH)** is essential for keeping **Glutathione** (**Glutathione** helps erythrocytes to deal with oxidative stress).
2. So, in G6PD deficiency, if the erythrocytes are exposed to an oxidizing agent, the cell membrane becomes damaged; the hemoglobin becomes oxidized and forms what are known as Heinz bodies, some of the red cells undergo hemolysis and others have their Heinz bodies removed by the Spleen to form 'bite cells'.
3. Individuals with G6PD deficiency are susceptible to **developing acute hemolytic anemia when they take a number of common drugs** (1); so it's best to avoid them in such patients.

Box 49.10 Common drugs implicated in causing haemolysis in G6PD deficiency

Drugs to be avoided in all variants
Ciprofloxacin (and probably other quinolones)
Dapsone
Methylene blue
Primaquine (reduced dose may be used in milder variants)
Nalidixic acid
Sulphonamides (including co-trimoxazole)

Drugs to be avoided in more severe variants
Aspirin (low dose used under supervision)
Chloramphenicol
Chloroquine (may be acceptable in acute malaria)
Menadione
Probenecid
Quinidine
Quinine (acceptable in acute malaria)

B) Sickle cell Anemia

1. Patients with sickle cell disease (SCD) have a different form of hemoglobin; Patients with the most common variant of sickle cell disease have hemoglobin S (Hb S).
   - Normal hemoglobin is usually designated as Hb A.
2. The membrane of red cells containing hemoglobin S is damaged, which leads to intracellular dehydration, Also Sickle cells are less flexible than normal cells (flexibility allows normal cells to pass through the micro-circulation), the inflexibility leads to impaired blood flow through the micro-circulation, resulting in local tissue hypoxia.
3. **Vaso-occlusive crisis (VOC)** is the most common clinical manifestation of SCD; it occurs when the microcirculation is obstructed by sickled RBCs, causing ischemic injury to the organ supplied and resultant pain - approximately half of individuals with SCD experience VOC; Pain crises begin suddenly and may last several hours to several days, the pain can affect any body part but often involves the abdomen, bones, joints and soft tissue, VOC result in a decrease in quality of life and an increase in the risk of death.
4. Treatment goal is to decrease hemoglobin S (Hb-S) proportions and increase hemoglobin F; which don't turn into sickle cells; Treatment option include: **Hydroxycarbamide, Hydroxyurea,** and **Recombinant Human Erythropoietins** (see next Section).
5. **Hydroxycarbamide** and **Hydroxyurea** are the same drug, but they differ in the way of manufacturing; **Hydroxyurea is semi-synthetic drug,** while **Hydroxycarbamide is a fully-synthetic drug.**
6. **Hydroxyurea (Hydroxycarbamide)** are antineoplastic drugs**,** used in the treatment of **Polycythemia Vera** and in the treatment of **Essential Thrombocythemia**.
   - In Sickle cell anemia they are used to reduce the rate of painful attacks; they act by increasing hemoglobin F levels; (their effects take a minimum 3 months to appear).

6. **Voxelotor** is an oral, once-daily therapy for the treatment of sickle cell disease (SCD); it's a sickle hemoglobin (Hb S) polymerization inhibitor, Voxelotor works by increasing the affinity of hemoglobin for oxygen, this stabilizes red blood cells in an oxygenated state, preventing hemoglobin polymerization and the resultant sickling and destruction of the red blood cells.
7. **Inclacumab** is a fully human monoclonal antibody designed to bind to and selectively inhibit P-selectin, an adhesion molecule found on endothelial cells and platelets that contributes to the cell-cell interactions that are involved in the pathogenesis of Vaso-occlusive crisis (VOCs).
8. **Crizanlizumab** (an anti-P-selectin antibody); it is approved by the FDA to reduce the frequency of Vaso-occlusive crises (VOCs), or pain crises, in adult and pediatric patients aged 16 years and older with sickle cell disease.

Scientific name	Dosage form	Trade name	concentration
Hydroxycarbamide	Cap	Hydrea®	500 mg
Hydroxyurea	Cap	Hydrine®, Droxia®	300 mg , 500 mg
Voxelotor	Tab	Oxbryta®	500 mg
Crizanlizumab	Inj. Solu.	Adakveo®	10 mg/ml (10 ml)
Inclacumab	Pending FDA approval		

C) Thalassemia

1. In **β thalassemia**, there is a reduced or absent production of the globin β chain, this leads to a relative excess of α chain which when unpaired become unstable and precipitates in the red cell precursors; there is ineffective erythropoiesis and those mature cells that reach the circulation have a shortened life span
2. In **α thalassemia**, the pathology is slightly different, the deficiency of α chains leads to an excess of γ or β chains, this time erythropoiesis is less affected, but the hemoglobin produced (hemoglobin Bart's or Hemoglobin H) is unstable when the cells are in the circulation and precipitates as the cells grow older, this leads to a shortened life span with the spleen trapping many of the cells.
3. Many patients with severe forms are dependent on blood transfusions from an early age; This inevitably leads to iron overload, **Deferoxamine, Deferiprone** and **Deferasirox** are needed for such patients; also, it is likely that a combination of drugs (**Hydroxycarbamide** and **Erythropoietin**) will provide some clinical improvement. (See above).
4. A new drug is developed for the treatment of β thalassemia: **Luspatercept**, the first-in-class **erythroid (red blood cell) maturation agent** used to treat patients who have blood disorders associated with ineffective erythropoiesis (it's a recombinant fusion protein that binds several TGF-beta superfamily ligands, thereby diminishing Smad2/3 signaling).
   - the FDA approved **Luspatercept** for treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusions.

Scientific name	Dosage form	Trade name	concentration
Luspatercept	Vial (Solu.)	Reblozyl®	25 mg , 75 mg

15.2 – Recombinant Human Erythropoietins

1. They stimulate erythropoiesis via division and differentiation of progenitor cells in bone marrow, they are **used in Sickle Cell anemia, Thalassemia** and in **Anemia due chronic renal disease.**
2. The most common side effects include: **hypertension** and **thrombotic complications**.
3. In controlled trials with CKD patients on Erythropoietin therapy, **patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered Erythropoietins to target hemoglobin level of greater than 11 g/dl.**
4. Supplementation with Iron may be required to ensure an adequate response.

Scientific name	Dosage form	Trade name	concentration
Epoetin Alfa	Inj. Solu.	Eprex®, Espogen®	4000 , 10,000 , 20,000 Unit/ml
Epoetin Beta	Inj. Solu.	NeoRecormon®	4000 , 10,000 , 20,000 Unit/ml
Epoetin Theta	Inj. Solu.	Eporatio®	4000 , 10,000 , 20,000 Unit/ml
Epoetin Zeta	Inj. Solu.	Retacrit®	4000 , 10,000 , 20,000 Unit/ml
Darbepoetin Alfa	Prefilled Inj.	Aranesp®	100 , 150 , 200 , 500 mcg
Methoxy polyethylene glycol Epoetin Beta	Prefilled Inj.	Mircera®	120 mcg/0.3 ml , 200 mcg/0.3 ml , 360 mcg/0.3 ml , 800 mcg/0.6 ml
Peginesatide	Vial (Multi-use) , Prefilled Inj.	Omontys®	10 mg , 20 mg (Vials multi-use) , (1, 2, 3, 4, 5, 6 mg/0.5 ml) Prefilled

Notes:

1. **Epoetin Alfa** is given (50-100 units/kg) **3 times a week.**
   - Subcutaneous (SC) administration of **Epoetin Alfa** is preferred because the SC dose that maintains target indices is 15% to 30% lower than the IV dose.
   - Same dosing for Beta, Theta and Zeta types of Epoetin.
2. **MPG Epoetin Beta** is given **every 2 weeks, or in a loading dose every month.**
3. **Darbepoetin** is given (0.45 mcg/kg) **once a week.**
4. **Peginesatide** is given (0.04-0.08 mg/kg) **once monthly.**
   - For patients previously receiving **Epoetin Alfa**, the first dose of **Peginesatide** should be administered 1 week after the last **Epoetin Alfa** dose was administered.
   - For patients previously receiving **Darbepoetin Alfa**, the first dose of **Peginesatide** should be administered at the next scheduled dose in place of **Darbepoetin Alfa.**
   - The Brand Company has **withdrawn Peginesatide** due reports of serious hypersensitivity reactions and deaths.

   Note: Two randomized controlled trials published in 2013 found that the effectiveness of **Peginesatide** was not inferior to **Epoetin** for patients receiving dialysis (the EMERALD study), or to **Darbepoetin** for patients with chronic kidney disease who were not receiving dialysis (the PEARL study) However, **the safety endpoint of cardiovascular events and death was worse for Peginesatide than for Darbepoetin** in the PEARL study.

15.3 – Iron Chelating Agents

1. These chelates iron by forming a stable complex that prevents the iron from entering into further chemical reactions; also chelates iron readily from ferritin and hemosiderin but not readily from transferrin; **does not combine with the iron from cytochromes and hemoglobin**; the chelate is readily soluble and is renally excreted (if parenteral chelating is used), or excreted with stool (if oral chelating is used).
2. Available Chelating agents include: **Deferoxamine** (Parenteral I.M. I.V. or S.C.), **Deferiprone** and **Deferasirox** (both oral), these agents **defer in their chelating affinity**:
   - Deferoxamine 100 parts of weight can bind 8.5 parts of Ferric Iron.
   - Deferiprone 3 molecules can bind 1 atom of Iron.
   - Deferasirox 2 molecules can bind 1 atom of Iron.
3. **Deferiprone** is given 3 times a day; while **Deferasirox** is given once daily.

Scientific name	Dosage form	Trade name	concentration
Deferoxamine	Inj. powder	Desferal®	500 mg , 2 gm (vial)
Deferiprone	Tab, Oral Solu.	Ferriprox®	500 mg (tab) , 100 mg/ml
Deferasirox	Tab	Exjade®	125 mg , 250 mg , 500 mg
	Tab	Jadenu®	90 mg , 180 mg , 360 mg

*** Deferoxamine = Desferrioxamine,** they are the same drug.

* **Deferiprone = Desferiprone,** they are the same drug.

15.4 – Drugs used in platelet disorders

A) Idiopathic thrombocytopenic purpura (ITP)

1. Acute idiopathic thrombocytopenic purpura is usually self-limiting in children.
2. In adults, idiopathic thrombocytopenic purpura can be **treated with a corticosteroid, e.g. prednisolone 1 mg/kg daily,** gradually reducing the dose over several weeks.
   - **Splenectomy** is considered if a satisfactory platelet count is not achieved or if there is a relapse on reducing the dose of corticosteroid or withdrawing it.
   - **Immunoglobulins** are also used in idiopathic thrombocytopenic purpura or where a temporary rapid rise in platelets is needed, **usually by a dose of 0.4 gm/kg/day.**
   - **D(Rh0) immunoglobulin** is effective in raising the platelet count in about 80% of unsplenectomized rhesus-positive individuals; its effects may last longer than normal immunoglobulin for intravenous use, but further doses are usually required.
     - **Dose usually 125 – 250 IU/Kg, infused over 3-5 min.**
   - **Other therapy** that has been tried in refractory idiopathic thrombocytopenic purpura includes **azathioprine, cyclophosphamide, vincristine, cyclosporine, and Danazol**.
   - For patients with chronic severe thrombocytopenia refractory to other therapy, **Tranexamic acid may be given to reduce the severity of hemorrhage.**
3. **Eltrombopag** and **Romiplostim** (see below) are thrombopoietin receptor agonists licensed for the treatment of chronic idiopathic thrombocytopenic purpura in splenectomized patient's refractory to other treatments, such as corticosteroids or immunoglobulins, or as a second-line treatment in non-splenectomized patients when surgery is contra-indicated

B) Drugs for Thrombocytopenia (Platelet-stimulating agents)

1. A normal human platelet counts ranges from 150,000 to 450,000 platelets per microliter of blood, these limits are determined by the 2.5th lower and upper percentile, so values outside this range do not necessarily indicate disease. **One common definition of thrombocytopenia is a platelet count below 50,000 per microliter.**
2. Treatment is guided by etiology and disease severity. The main concept is to eliminate the underlying problem.
3. **Corticosteroids (**usually **prednisolone** or **Dexamethasone)** may be used to increase platelet production. **Lithium carbonate** or **Folate** may also be used to stimulate the bone marrow production of platelets.
4. **Platelet transfusions** may be used to stop episodic abnormal bleeding caused by a low platelet count. However, if platelet destruction results from an immune disorder, platelet infusions may have only a minimal effect and reserved for life-threatening bleeding.
5. Specific treatment plans depend on the underlying etiology of the thrombocytopenia, and **platelet stimulating agents** should be prescribed by professional medical staff only under supervision; since these medications have a wide side effects profile (liver failure, anaphylaxis).

Scientific name	Dosage form	Trade name	concentration
Eltrombopag	Tab	Promacta® , Revolade®	12.5 , 25 , 50 , 75 , 100 mg
Lusutrombopag	Tab	Mulpleta®	3 mg
Romiplostim	Vial (S.C.)	Nplate®	250 mcg , 500 mcg
Oprelvekin	S.C. Inj.	Neumega®, Interleukin 11®	5 mg/vial

Notes:

1. **Eltrombopag** may cause severe liver damage, so routine check for liver functions is required.
2. **Romiplostim** is indicated as a long-term treatment for **chronic ITP** in adults who have not responded to other treatments, such as corticosteroids, intravenous immunoglobulin, Rh^{o} (D) immune globulin or splenectomy.

3. **Oprelvekin** is contraindicated in Patients with severe or decompensated heart failure; because it may cause excessive fluid retention with edema and cardiac decompensation, **it also has caused very serious allergic reaction** (edema of the face and tongue, shortness of breath; wheezing; chest pain; hypotension (including shock); dysarthria; loss of consciousness, rash, urticaria, flushing, and fever.)

☒ A number of potentially serious side-effects may develop when using Platelet stimulation agents including: myalgia, joint and extremity discomfort, insomnia, thrombocytosis, which may lead to potentially fatal clots, and bone marrow fibrosis, the latter which may result in an unsafe decrease in the red blood count.

C) Essential Thrombocythemia

Anagrelide inhibits platelet formation. It is licensed for essential Thrombocythemia in patients at risk of thrombo-hemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs. **Anagrelide** should be initiated under specialist supervision.

Scientific name	Dosage form	Trade name	concentration
Anagrelide	Cap	Xagrid®	500 mcg

15.5- Drugs for Neutropenia (Colony stimulating factors)

1. These drugs are used to **increase the number of white blood cells** when the white blood cell count is low; they act by stimulating the bone marrow to increase production of neutrophils.
2. **Causes of neutropenia** include **chemotherapy** and **bone marrow transplantation**; a reduced level of white blood cells causes an increased susceptibility to infections.
   - Thus; treatment can be used to stimulate bone marrow to produce more neutrophils to fight infection in patients undergoing chemotherapy.
3. Available drugs include: (**Filgrastim**, **Tbo-filgrastim**, **Pegfilgrastim**, **Lenograstim**) which are considered a recombinant human granulocyte colony-stimulating factor (G-CSF) and **Sargramostim**, which differ from the rest as its considered as a human recombinant granulocyte macrophage colony-stimulating factor (GM-CSF).
   - **Filgrastim** and **Tbo-filgrastim** both have half-life of 3-4 hours inside the body.
   - **Pegfilgrastim** has a long half-life 15-80 hours.
4. **Sargramostim** is primarily used for myeloid reconstitution after autologous or allogeneic bone marrow transplantation.
   - It is also used to treat neutropenia induced by chemotherapy during the treatment of acute myeloid leukemia.
   - Used in treating Crohn's disease and other GI inflammatory disorders.
   - This medication is being investigated in trials to treat Autoimmune Pulmonary Alveolar Proteinosis (PAP).

Scientific name	Dosage form	Trade name	concentration
Pegfilgrastim	S.C. Inj.	Neulasta®, Neulastim®, Imupeg®	6 mg/0.6 ml (Prefilled Inj.)
Sargramostim	Inj. Solu.	Leukine®	500 mcg/ml
	Inj. Powder		250 mcg/vial
Filgrastim	Inj. Solu.	Neupogen® , Zarzio®	300 mcg/ml , 480 mcg/1.6 ml
	Prefilled Inj.		300 mcg/0.5 ml , 480 mcg/0.8 ml
Tbo-filgrastim		Granix	
Lenograstim	Inj. Powder	Granocyte®	105 mcg , 263 mcg

15.6 - Hematopoietic stem cell Mobilizers

Hematopoietic stem cell mobilizer binds to the CXCR4 chemokine receptor and inhibits the binding of its ligand, stromal cell-derived factor-1-alpha (SDF-1-alpha), this leads to mobilization of hematopoietic stem cells to the peripheral blood.

Scientific name	Dosage form	Trade name	concentration
Ancestim	Inj. Powder	Stemgen®	1875 mcg/vial
Plerixafor	Inj. Solu.	Mozobil®	24 mg/vial (20 mg/ml)

15.7 - Sclerosing agents

Sclerosing agents are used in sclera-therapy of varicose veins, where the irritant solution is injected into the blood vessels. **(Sclerosing agents are used to treat varicose veins).**

Scientific name	Dosage form	Trade name	concentration
Ethanolamine	Inj. Solu.	Ethamolin®	50 mg/ml
Morrhuate Na	Inj. Solu.	Scleromate®	50 mg/ml
Polidocanol	I.V. Inj.	Asclera® , Varithena®	0.2% , 1% (2 ml amp)
	I.V. Inj.	Aethoxysklerol®	2% (2 ml amp)
Na^+ Tetradecyl Sulfate	Inj. Solu.	Trombovar® , Sotradecol®	1% , 3%

15.8 - Others Hematological products

Scientific name	Dosage form	Trade name	concentration
Icatibant	S.C. Inj.	Firazyr®	30 mg (prefilled Inj.)
Etamsylate	Tab , Amp	Dicynone®	250 mg

Notes:

1. **Icatibant** is a selective and specific antagonist of bradykinin B2 receptors. It has been approved for the treatment of acute attacks of hereditary angioedema (HAE).
2. **Etamsylate** is a hemostatic drug, it acts by increasing capillary endothelial resistance and promoting platelet adhesion; **indicated for Prophylaxis and control of hemorrhages** from small blood vessels, neonatal intra-ventricular hemorrhage capillary bleeding of different etiology, including: menorrhagia, hematuria, epistaxis, prevention of periventricular hemorrhages in prematurely born children.

References

1- BNF 82.
2- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition. Ph.P
3- Mary Anne koda-kimble (ed.), Applied Therapeutics: The clinical use of drugs, 11th ed.
4- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Ed.
5- Lexi-comp: Drug information handbook, 2022 Ed.

IMMUNOLOGICS AND ONCOLOGY

Chapter Sixteen: Immunologics & Oncology

Part One: Immunology

First: Immunosuppressive Agents

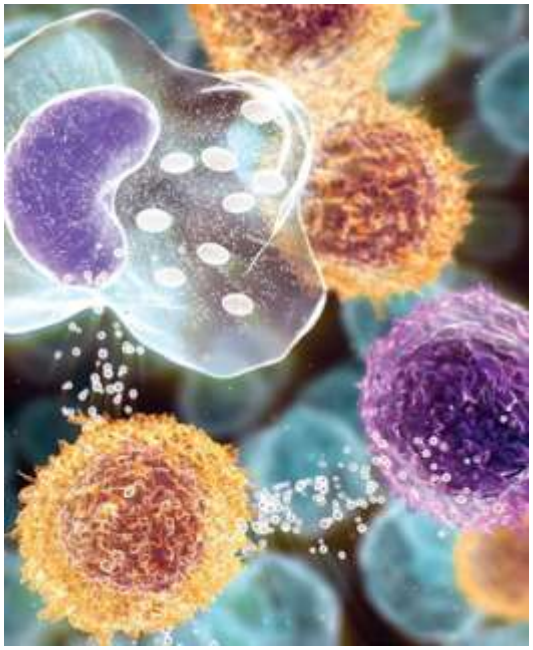
1. Corticosteroids
2. Selective Inhibitors of Cytokine Production and Function
3. Drugs That Disrupt cell metabolism
   a. Alkylating agents
   b. Antimetabolites
   c. Antibodies (Polyclonal and Monoclonal)
      - Anti-Thymocyte globulins (Polyclonal)
      - Muromonab-CD3 (Monoclonal)
      - IL-2-receptor antagonists (Monoclonal)
      - Other Monoclonal Antibodies
4. Other immunosuppressive agents

Second: Immune Globulins

Third: Interferons

Fourth: Immunomodulators

Fifth: Immunostimulants



Part Two: Oncology

First: Introduction

Second: Anti-Cancer Groups

1. Cytotoxic antineoplastics
   - Alkylating Cytotoxic Agents
   - Platinum compound
   - Anthracycline (antibiotics)
   - Microtubule Inhibitors
   - Topoisomerase inhibitors
   - Antimetabolite Cytotoxic Agents
   - Retinoid derivatives
   - Other Cytotoxic agents
   - Drugs for cytotoxic drug-induced side effects
2. Antineoplastic monoclonal antibodies
3. Hormonal Antineoplastics
4. Immunotherapy antineoplastics
5. Proteasome inhibitors antineoplastics
6. Kinase inhibitor antineoplastics
7. Histone deacetylase inhibitors

Chapter Sixteen: Immunologics and Oncology

Part one: Immunology

First: Immunosuppressive Agents

1. Immunosuppressive drugs (or antirejection medications) are drugs that **inhibit or prevent activity of the immune system**; They are used in immune-suppressive therapy to:
   - **a.** Prevent the rejection of transplanted organs and tissues (as in those with bone marrow, heart, kidney and liver transplant).
   - **b.** Treat autoimmune diseases or diseases that are most likely of autoimmune origin (rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, sarcoidosis, focal segmental glomerulo-sclerosis, Crohn's disease ulcerative colitis, Behcet's Disease).
   - **c.** Treat some other non-autoimmune inflammatory diseases (long term allergic asthma).
2. **The principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins**, Because of their severe toxicities when used as monotherapy, **a combination of immunosuppressive agents, usually at lower doses, is generally employed.**
3. Immunosuppressive drug regimens usually consist of anywhere from two to four agents with different mechanisms of action that disrupt various levels of T-cell activation.
4. **A common side-effect of many immunosuppressive drugs is immunodeficiency,** because the majority of them act non-selectively, resulting in **increased susceptibility to infections;** There are also other side-effects, such as hypertension, dyslipidemia, hyperglycemia, peptic ulcers, lipodystrophy, liver and kidney injury.
5. **Immunosuppressive drugs can be categorized** according to their mechanisms of action:
   - **a) Corticosteroids**
   - **b)** Interfere with cytokine production or action.
   - **c)** Disrupt cell metabolism, preventing lymphocyte proliferation.
   - **d) Mono and polyclonal antibodies** that block T-cell surface molecules.
   - **e)** Other immunosuppressive agents

1) Corticosteroids (see chapter 12 for more information)

1. In pharmacologic (supra-physiologic) doses, glucocorticoids are used to suppress various allergic, inflammatory, and autoimmune disorders. They are also administered as post transplantory Immunosuppressants in high doses to prevent the acute transplant rejection and graft-versus-host disease.
2. The steroids are able to rapidly **reduce lymphocyte populations** by lysis or redistribution.
3. The most common agents are **prednisone** or **methylprednisolone**, whereas **prednisone** or **prednisolone** are used for autoimmune conditions; (Note: In transplantation, they are used in combination with other agents).

2) Selective Inhibitors of Cytokine Production and Function

1. Cytokines are soluble, antigen-nonspecific, signaling proteins that bind to cell surface receptors on a variety of cells, the term cytokine includes the molecules known as **interleukins (ILs)**, **interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors**, and **colony-stimulating factors**, these cytokines collectively activate natural killer cells, macrophages, and cytotoxic T lymphocytes.
2. They include: **(Cyclosporine, Tacrolimus, Sirolimus, Everolimus** and **Pimecrolimus)**

Scientific name	Dosage form	Trade name	concentration
Cyclosporine	Cap	Sandimmune® , Gengraf®	25 mg , 50 mg , 100 mg
	Inj. Solu.		50 mg/ml

Tacrolimus	Cap	Prograf® , Hecoria®	0.5 mg , 1 mg , 5 mg
	Inj. Solu.	Prograf®	5 mg/ml
	Oint.	Protopic® , Talimus®	0.03% , 0.1%
Sirolimus	Tab	Rapamune®	0.5 mg , 1 mg , 2 mg
Everolimus	Tab	Afinitor®	0.25 mg , 0.5 mg , 0.75 mg
Pimecrolimus	Cream	Elidel® , Pacroma®	1%

Notes:

1. **Cyclosporine** is an alternative to methotrexate for the treatment of severe, active rheumatoid arthritis, it can also be used for patients with recalcitrant psoriasis that does not respond to other therapies, and it is also used for xerophthalmia.
2. **The antiproliferative action of Sirolimus has found use in cardiology**; Sirolimus-coated stents inserted into the cardiac vasculature inhibit restenosis of the blood vessels by reducing proliferation of the endothelial cells.
3. **Sirolimus** and **Everolimus** both cause hyperlipidemia.

3) Drugs That Disrupt cell metabolism

They inhibit cell division; **in immunotherapy they are used in smaller doses than in the treatment of Cancers;** They affect the proliferation of both T cells and B cells. Due to their highest effectiveness, purine analogs are most frequently administered.

1. Alkylating agents

1. The only alkylating agent that maybe used as immunosuppressant is the nitrogen mustard (cyclophosphamide); **others are used to treat cancers** (mentioned in the next part, page 390).
2. **Cyclophosphamide** is probably the most potent immunosuppressive compound.
   In small doses, it is very efficient in the therapy of systemic lupus erythematosus, autoimmune hemolytic Anemias, Wegener's granulomatosis, and other immune diseases. High doses cause pancytopenia and hemorrhagic cystitis.
3. **Cyclophosphamide decreases the immune system's response to various diseases and conditions;** Therefore, it has been used in autoimmune diseases where disease-modifying anti-Rheumatic drugs (DMARDs) have been ineffective, as in: systemic lupus erythematosus, severe rheumatoid arthritis, Wegener's granulomatosis and multiple sclerosis.
   a. **It is also used to treat some types of cancer.**
   b. **Cyclophosphamide is itself carcinogenic,** potentially causing transitional cell carcinoma of the bladder as a long-term complication, and other serious potential side effect is acute myeloid leukemia, referred to as secondary AML.
   c. The risk may be dependent on dose and a number of other factors, including the condition being treated, other agents or treatment modalities used (including radiotherapy), treatment intensity and length of treatment.

Scientific name	Dosage form	Trade name	concentration
Cyclophosphamide	Tab	Cytoxan®	25 mg , 50 mg
	Inj. Powder		

2. Antimetabolites

Antimetabolites interfere with the synthesis of nucleic acids. These include:

a. Folic acid analogues, such as **Methotrexate**
b. Purine analogues, such as **Azathioprine** and **Mercaptopurine**
c. Pyrimidine analogues, such as **Fluorouracil**
d. Others, such as **Mycophenolate.**

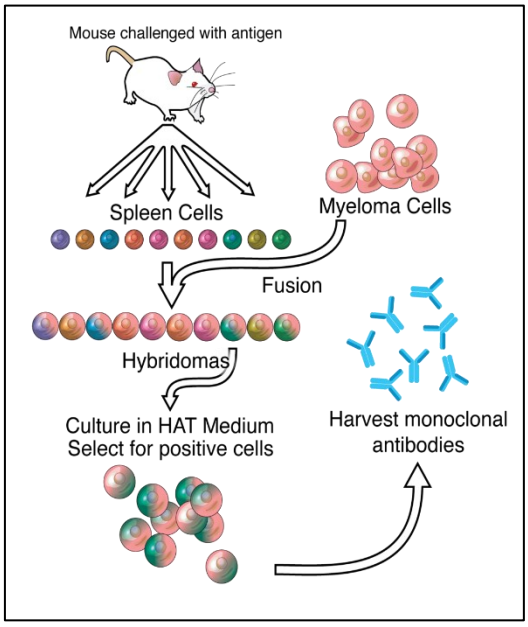
Scientific name	Dosage form	Trade name	concentration
Methotrexate	Tab	Rheumatrex® , MTX®	2.5 mg , 5 mg , 10 mg
	Inj. Solu.	Trexall®	25 mg/ml
Azathioprine	Tab	Imuran®	50 mg , 75 mg , 100 mg
	Inj. Powder		100 mg/Vial
Mercaptopurine	Tab	6MP® , Puri-nethol®	50 mg
Fluorouracil	Inj. Solu.	Adrucil®	50 mg/ml
Mycophenolate	Cap , Tab	CellCept® , Myfortic®	250 mg , 500 mg
	Inj. Powder		500 mg/vial

Notes:

1. **Methotrexate** is a folic acid analogue. It binds dihydrofolate reductase and prevents synthesis of tetrahydrofolate, it is used in the treatment of autoimmune diseases (for example Rheumatoid Arthritis, Crohn's disease, Behcet's Disease) and in transplantations.
2. **Azathioprine** is extensively used to control transplant rejection reactions, it is non-enzymatically cleaved to **Mercaptopurine**, which acts as a purine analogue and an inhibitor of DNA synthesis, **Mercaptopurine** itself can also be administered directly; it is also efficient in the treatment of autoimmune diseases.
   - Concomitant use with (ACEIs) or co-trimoxazole in patients with renal diseases can lead to an exaggerated leukopenic response.
3. **Mycophenolate** has replaced azathioprine because of its safety and efficacy; the most common adverse effects include diarrhea, nausea, vomiting, abdominal pain, leukopenia, and anemia. Higher doses of Mycophenolate (3 gm/day) were associated with a higher risk of CMV infection.

4) Antibodies (Polyclonal and Monoclonal)

1. Antibodies are sometimes used as a quick and potent immunosuppressive therapy to prevent the acute rejection reactions as well as a targeted treatment of lymphoproliferative or autoimmune disorders (Psoriasis, Eczema, Asthma, Multiple Sclerosis, Osteoporosis, etc.).
2. They are prepared either by immunization of rabbits, mice and horses with human lymphoid cells (producing a mixture of polyclonal antibodies directed against a number of lymphocyte antigens), or by Hybridoma technology (producing antigen-specific, monoclonal antibodies). Hybridomas are produced by fusing mouse antibody-producing cells with immortal malignant plasma cells; they are generally prepared in the below method:



   a. In the laboratory, scientists analyze a specific antigen on the surface of the target cells to determine a protein to match the antigen.
   b. Then using protein from mice (murine) or humans (humanized) to create a special antibody that will attach to the target antigen (on the target cells).
   c. Monoclonal antibodies are produced by immunizing an animal (usually a mouse), multiple times with a specific antigen.
   d. B cells from the spleen of the immunized animal are then removed, and they are fused with cancerous B cells called myeloma cells; to yield Hybridoma cells.
   e. The Hybridoma cells (which are capable of growing continuously in culture while producing antibodies) are then screened for the desired monoclonal antibody.
   f. This process is very expensive and time consuming; thus, Monoclonal antibodies are generally expensive.

3. The names of monoclonal antibodies conventionally contain **"muromab"** if they are from a murine (mouse) source, and **"ximab"** if they are chimerized (65% human-mouse), and "**zumab**" if they are humanized (95% human), and "**umab**" if they are fully 100% human; The suffix "**mab**" (monoclonal antibody) identifies the category of drug.
4. Monoclonal antibodies are directed towards exactly defined antigens; Therefore, they cause fewer side-effects than Polyclonal antibodies, especially the IL-2 receptor-(CD25-) and CD3-directed antibodies.

A) Anti-Thymocyte globulins (Polyclonal)

1. Thymocytes are cells that develop in the thymus and serve as T-cell precursors. The antibodies developed against them are prepared by immunization of large rabbits or horses with human lymphoid cells and, thus are polyclonal.
2. **Rabbit formulations** (1.5 mg/kg) of polyclonal anti-Thymocyte globulin are more commonly used over the **horse preparation** (10-30 mg/kg) due to greater potency.
3. Their adverse effects include chills and fever, leukopenia and thrombocytopenia, infections due to CMV or other viruses and skin rashes.

Scientific name	D. form	Trade name	concentration
Anti-Thymocyte globulin Equine	Inj. Solu.	Atgam® , ATG equine®	50 mg/ml
Anti-Thymocyte globulin Rabbit	Inj. Solu.	Thymoglobulin® , ATG Rabbit®	25 mg/vial

B) Muromonab-CD3 (Monoclonal)

1. Muromonab-CD3 is a mouse monoclonal antibody that is synthesized by Hybridoma technology and directed against the glycoprotein CD3 antigen of human T cells.
2. The antibody is administered IV. Initial binding of muromonab-CD3 to the antigen transiently activates the T cell and results in cytokine release (cytokine storm). It is, therefore, customary to pre-medicate the patient with methylprednisolone, diphenhydramine, and acetaminophen to alleviate the cytokine-release syndrome.
3. The symptoms can range from a mild, flu-like illness to a life-threatening, shock-like reaction. High fever is common. Central nervous system effects, such as seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache, may occur. Infections can increase, including some due to CMV.
4. Muromonab-CD3 is contraindicated in patients with a history of seizures, in those with uncompensated heart failure, in pregnant women, and in those who are breast-feeding; **Because of these muromonab-CD3 is rarely used today.**

Scientific name	Dosage form	Trade name	concentration
Muromonab-CD3	Inj. Solu.	Orthoclone® , OKT3®	1 mg/ml

C) IL-2-receptor antagonists (Monoclonal)

1. Interleukin-2 is an important immune system regulator necessary for the clone expansion and survival of activated lymphocytes T; the IL-2a is expressed only by the already-activated T lymphocytes.
2. **Basiliximab** and **Daclizumab**, act by binding the IL-2a receptor's α chain, preventing the IL-2 induced clonal expansion of activated lymphocytes and shortening their survival. They are used in the prophylaxis of the acute organ rejection after bilateral kidney transplantation, both being similarly effective and with only few side-effects.
3. Both antibodies are given IV, **Basiliximab** is about 10-fold more potent than **Daclizumab** as a blocker of IL-2 stimulated T-cell replication, but the serum half-life of **Daclizumab** is about 20 days, and the blockade of the receptor is 120 days. Five doses of
4. **Daclizumab** are usually administered, and the serum half-life of Basiliximab is about 7 days, usually two doses of this drug are administered.

Scientific name	Dosage form	Trade name	concentration
Basiliximab	Inj. Powder	Simulect®	10 mg , 20 mg
Daclizumab	Inj. Solu.	Zenapax®	5 mg/ml

D) Other Monoclonal Antibodies (Monoclonal)

These drugs vary in their uses, ranges from the treatment of cancers to immunosuppressive therapies and auto-immune diseases treatments (Psoriasis, Arthritis, Asthma .. etc.).

- Note: there are a lot of other Monoclonal antibodies that is mainly used for the treatment of cancers, they are mentioned in the next oncology part, page 395.

Scientific name	Dosage form	Trade name	concentration
Etanercept	Inj. Solu.	Enbrel®	50 mg/ml
	Inj. Powder		25 mg/vial
Infliximab	Inj. Powder	Remicade®	100 mg/vial
Adalimumab	Prefilled Inj.	Humira®	40 mg/0.8 ml
Certolizumab	Inj. Powder	Cimzia®	200 mg/vial
Natalizumab	Inj. Solu.	Tysabri®	300 mg/15 ml
Golimumab	Prefilled Inj.	Simponi®	50 mg/0.5 ml
Abatacept	Prefilled Inj.	Orencia®	125 mg/Inj.
	I.V. infusion		250 mg/vial
Tocilizumab	Inj. Solu.	Actemra®	20 mg/ml
	Prefilled Inj.		162 mg/0.9 ml
Rituximab	Inj. Solu.	Rituxan®	10 mg/ml
Canakinumab	Inj. Powder	ILaris®	180 mg/vial
Raxibacumab	Inj. Solu.	Raximab®	50 mg/ml
Ustekinumab	Inj. Solu.	Stelara®	45 mg/0.5 ml
Alemtuzumab	Inj. Solu.	CamPath®	10 mg/ml , 30 mg/ml

Notes:

1. **Infliximab, Adalimumab, Certolizumab** and **Natalizumab** are FDA Approved for the treatment of Crohn's disease and Ulcerative colitis, and are also used in the treatment of Psoriasis (Psoriatic Arthritis and Plaque Arthritis), Rheumatoid Arthritis, and Ankylosing Spondylitis.
2. **Golimumab** is indicated for all the above except Crohn's disease and Ulcerative colitis.
3. **Tocilizumab** is indicated for Rheumatoid Arthritis and systemic sclerosis.
4. **Etanercept** is used in the treatment of Psoriasis and Rheumatoid Arthritis.
5. **Rituximab** is also used in the **management of NH Lymphoma, CL Leukemia.**
6. **Raxibacumab** is indicated for treatment of inhalation anthrax in combination with antibiotics.
7. **Ustekinumab** is used in the treatment of Psoriasis (Psoriatic Arthritis and Plaque Arthritis).
8. **Alemtuzumab** is approved for the treatment of refractory B-cell chronic lymphocytic leukemia.

5) Other immunosuppressive agents:

Scientific name	D. form	Trade name	concentration
Auranofin	Cap	Ridaura®	3 mg
Gold Na^+ Thiomalate	Inj. Solu.	Aurothiomalate®	25 mg/ml , 50 mg/ml
Belatacept	Inj. Powder	Nulojix®	250 mg/vial
Hydroxychloroquine	Tab	Plaquenil®	200 mg
Leflunomide	Tab	Arava®, Vamid®	10 mg , 20 mg , 100 mg

*** Hydroxychloroquine** is also an antimalarial, its uses as a **DMARD** in Rheumatoid Arthritis.

**** Leflunomide** is mainly used in Rheumatoid Arthritis.

Second: Immune Globulins:

1. Immunoglobulin (also called gamma globulin or immune globulin) is a substance made from human blood plasma. The plasma, processed from donated human blood, contains antibodies that protect the body against diseases. When you are given an immunoglobulin, your body uses antibodies from other people's blood plasma to help prevent illness; and even though immunoglobulins are obtained from blood, they are purified so that they can't pass on diseases to the person who receives them.
2. Specific types of immunoglobulin are made to protect against specific diseases, such as hepatitis, chickenpox, or measles. Immunoglobulin injections may:
   - **a.** Give short-term protection against or reduce the severity of certain diseases.
   - **b.** Protect your fetus if you are pregnant and at risk for Rh sensitization.
   - **c.** Decrease the immune system's ability to attack body tissues in some cases of autoimmune disease.
   - **d.** Help people who have an inherited problem making their own antibodies or those who are having treatment for certain types of cancer (such as leukemia).
   - **e.** Treatments for some cancers can cause the body to stop producing its own antibodies, making immunoglobulin treatment necessary.

1. Disease prevention

1. You may be given an immunoglobulin if you are exposed to certain infectious diseases, such as hepatitis A, rubella, or measles. The immunoglobulin may prevent or reduce the severity of the illness if given shortly after exposure. The time period during which an injection provides this benefit ranges from days to months, depending on the disease.
2. Immunoglobulins do not provide long-term protection in the same way as a traditional vaccine. The protection they provide is short-term, usually lasting a few months. It is still possible to get the disease after the immunoglobulin has worn off.

2. Rh sensitization

1. When a Rh-negative woman becomes pregnant with a Rh-positive fetus (which can occur when the father's blood is Rh-positive), the pregnant woman's immune system makes antibodies that can destroy the fetus's blood in a future pregnancy. This antibody response is called Rh sensitization and occurs only if the fetus's blood mixes with the pregnant woman's, which can happen during birth.
2. To prevent Rh sensitization during pregnancy, you must have a Rh immunoglobulin injection if you are Rh-negative. This is done during your pregnancy and after delivery to protect the fetus of a future pregnancy. **(See chapter 7, section 1, for more information).**

3. Idiopathic thrombocytopenic purpura (ITP)

1. Immunoglobulin is sometimes used to treat idiopathic thrombocytopenic purpura (ITP), an immune disorder in which the body attacks the cells responsible for blood clotting (platelets), resulting in bleeding; The cause of ITP is not known (idiopathic).
2. People who have this disorder may have bruises or black-and-blue marks (purpura) on the skin. Internal bleeding is a more serious complication that can occur.
3. Some cases of ITP may go away on their own and do not require treatment. In other cases, treatment may be needed to control bleeding. Some medicines can help the body make more platelets. Steroids (such as prednisone) or other medicines may be needed to suppress the immune system. An intravenous (IV) infusion of a substance made from human blood plasma (immunoglobulin) may be given. Sometimes you will need to have platelet transfusions. In rare cases, the spleen may need to be removed.

Scientific name	D. form	Trade name	concentration
Immune Globulin I.V.	Inj. Solu.	Flebogamma® , Gamunex®	1 gm , 5 gm
Immune Globulin I.M.	Inj. Solu.	Gamastan®	150-180 mg/ml
Immune Globulin S.C.	Inj. Solu.	Hizentra®	20% , 10%
Hepatitis B Immune Globulin	Inj. Solu.	HepaGam B®, HyperHep®	
Rabies Immune Globulin	Inj. Solu.	HyperRAB®, Imogam®	150 IU/ml
Tetanus Immune Globulin	Inj. Powder	HyperTET®	250 IU
Vaccinia Immune Globulin	Inj. Solu.	VIGIV®	50 mg/ml
Varicella Zoster Immune Globulin	Inj. Powder	VariZIG®	125 IU/vial
Cytomegalovirus Immune Globulin	Inj. Solu.	CytoGam®	50 mg/ml
Botulism Immune Globulin *	Inj. Powder	BabyBIG®	100 mg/vial
Anti-D Immune Globulin (Rho(D) IG)	Inj. Solu.	Rhoclone® , RhoGAM®	150 mcg , 300 mcg
	Inj. Solu.	WinRho SDF®	120 mcg , 300 mcg
Antithymocyte globulin Equine	Inj. Solu.	Atgam®, ATG equine®	50 mg/ml
Antithymocyte globulin Rabbit	Inj. Solu.	Thymoglobulin®, ATG Rabbit®	25 mg/vial

*** Botulism Immune Globulin** is only indicated for infants below 1-year-old.

Note: There are five major types of antibodies are:

1. **IgA antibodies** are found in areas of the body such the nose, breathing passages, digestive tract, ears, eyes, and vagina. IgA antibodies protect body surfaces that are exposed to outside foreign substances. This type of antibody is also found in saliva, tears, and blood. About 10% to 15% of the antibodies present in the body are IgA antibodies. A small number of people do not make IgA antibodies.
2. **IgG antibodies** are found in all body fluids. They are the smallest but most common antibody (75% to 80%) of all the antibodies in the body. IgG antibodies are very important in fighting bacterial and viral infections. IgG antibodies are the only type of antibody that can cross the placenta in a pregnant woman to help protect her baby (fetus).
3. **IgM antibodies** are the largest antibody. They are found in blood and lymph fluid and are the first type of antibody made in response to an infection. They also cause other immune system cells to destroy foreign substances. IgM antibodies are about 5% to 10% of all the antibodies in the body.
4. **IgE antibodies** are found in the lungs, skin, and mucous membranes. They cause the body to react against foreign substances such as pollen, fungus spores, and animal dander. They are involved in allergic reactions to milk, some medicines, and some poisons. IgE antibody levels are often high in people with allergies.
5. **IgD antibodies** are found in small amounts in the tissues that line the belly or chest. How they work is not clear.

Third: Interferons:

1. Interferons are a family of naturally-occurring proteins that are made and secreted by cells of the immune system (for example, white blood cells, natural killer cells, fibroblasts, and epithelial cells); Three classes of interferons have been identified:
   1. Alpha 2. Beta 3. Gamma
2. Each class has many effects, though their effects overlap. Commercially available Interferons are human Interferons manufactured using recombinant DNA technology. The mechanism of action of interferon is complex; **Interferons modulate the response of the immune system** to viruses, bacteria, cancer, and other foreign substances that invade the body. Interferons do not directly kill viral or cancerous cells; they boost the immune system response and reduce the growth of cancer cells by regulating the action of several genes that control the secretion of numerous cellular proteins that affect growth.
3. Although Interferons are very similar, they affect the body differently, therefore, different Interferons are used for different conditions.
   a. **Interferon Alphas** are used for treating cancers and viral infections.
   b. **Interferon Betas** are used for treating multiple sclerosis
   c. **Interferon Gamma** is used for treating chronic granulomatous disease.
4. Since Interferons enhance the immune system in many ways, they are used for many diseases that involve the immune system. For example:
   1. **Interferon alfa-2a** is FDA-approved to treat hairy cell leukemia, AIDS-related Kaposi's sarcoma, and chronic myelogenous leukemia.
   2. **Interferon alfa-2b** is approved for the treatment of hairy cell leukemia, malignant melanoma, condylomata acuminata, AIDS-related Kaposi's sarcoma, chronic hepatitis C, and chronic hepatitis B.
   3. **Ribavirin combined with interferon alfa-2b, interferon alfacon-1**, **Pegylated interferon alfa-2b, or Pegylated interferon alpha-2a**, all are approved for the treatment of chronic hepatitis C.
   4. **Interferon beta-1b** (Betaseron®) and interferon beta-1a (Avonex®) are approved for the treatment of multiple sclerosis.
   5. **Interferon alfa-n3** (Alferon-N®) is approved for the treatment of genital and perianal warts caused by human papillomavirus (HPV).
   6. **Interferon gamma-1B** (Actimmune®) is approved for the treatment of chronic granulomatous disease, and severe, malignant osteoporosis.
5. **Side effects** include Flu-like symptoms following each injection (fever, chills, headache, muscle aches and pains, malaise), occur with all of the Interferons. These symptoms vary from mild to severe and occur in up to half of all patients; The symptoms tend to diminish with repeated injections and may be managed with analgesics such as acetaminophen and antihistamines such as diphenhydramine.

Scientific name	Dosage form	Trade name	concentration
Interferon Alfa-2a	Vial	Roferon A	18 million IU
Interferon Alfa-2b	Inj. Solu.	Intron A®	6 , 10 million IU/ml
	Inj. Powder		10 , 18 , 30 million IU/vial
Interferon Alfa-n3	Inj. Solu.	Alferon N®	5 million IU/ml
Interferon Alfacon-1	Inj. Solu.	Infergen®	9 mcg/0.3 ml , 15 mcg/0.5 ml
Interferon Beta-1a	Prefilled Inj.	Avonex®	30 mcg/0.5 ml
	Prefilled Inj.	Rebif®	22 mcg/0.5 ml , 44 mcg/0.5 ml
Interferon Beta-1b	Inj. Powder	Betaseron® , Extavia®	0.3 mg/vial
Interferon Gamma 1b	Inj. Solu.	Actimmune®	100 mcg/0.5 ml

Scientific name	Dosage form	Trade name	concentration
Peg-Interferon Alfa-2a	Vial	***Pegasys®***	180 mcg/ml (single use)
	Prefilled Inj.		180 mcg/0.5 ml (single use)
Peg-Interferon Alfa-2b	Inj. Powder	Sylatron®	444 mcg/vial , 888 mcg/vial
	Prefilled Inj.	PEG Intron®	80 mcg , 120 mcg , 180 mcg

Notes:

1. **Peg-Interferon alfa-2b,** comes in combination pack with (**Ribavirin** 200 mg cap.); for the treatment of chronic hepatitis C.
2. **The dose of Peg-INF alfa-2b is weight dependent, while the alfa-2a dose is fixed.**
3. Conventional **IFN** therapy has been virtually replaced with **PEG-IFN**, because of the ease of administration (once-weekly injections), fewer side effects, and improved efficacy.
4. **Lamivudine** (100 mg daily given orally) in combination with PEG-IFN resulted in greater HBV DNA suppression.

Fourth: Immunomodulators:

Immunomodulators are medications used to help regulate or normalize the immune system. They can be used as an add-on therapy to treat asthma or to **treat hereditary angioedema.**

Scientific name	Dosage form	Trade name	concentration
C1 inhibitor	Inj. Powder	Berinert®, Cinryze®	500 Unit/vial
Ecallantide	Inj. Solu.	Kalbitor®	10 mg/ml (single use)
Icatibant	Prefilled Inj.	Firazyr®	30 mg (10 mg/ml)
Rilonacept	Inj. Powder	Arcalyst®	220 mg/vial

Notes:

1. **C1 inhibitor** is also indicated for routine prophylaxis against angioedema attacks in adolescent and adult, and for Capillary Leakage Syndrome.
2. **Rilonacept** is indicated for Cryopyrin Associated Periodic Syndrome.

Fifth: Immunostimulants:

1. Immunostimulators are substances (drugs and nutrients) that stimulate the immune system by inducing activation or increasing activity of any of its components.
2. **There are two main categories of Immunostimulants:**
   a. Specific Immunostimulants provide antigenic specificity in immune response, such as vaccines or any antigen.
   b. Non-specific Immunostimulants act irrespective of antigenic specificity to augment immune response of other antigen or stimulate components of the immune system without antigenic specificity, such as adjuvants and non-specific Immunostimulators.
3. Many endogenous substances are non-specific Immunostimulators. For example, female sex hormones are known to stimulate both adaptive and innate immune responses
4. Some autoimmune diseases such as lupus erythematosus strike women preferentially, and their onset often coincides with puberty.
5. Some publications point towards the effect of deoxycholic acid (DCA) as an immunostimulant of the unspecific immune system, activating its main actors, the macrophages. According to these publications, a sufficient amount of DCA in the human body corresponds to a good immune reaction of the unspecific immune system.

Types of Immunostimulants:

1. **Colony stimulating factors:** are glycoproteins that promote production of white blood cells (mainly granulocytes such as neutrophils), in response to infection. Administration of exogenous colony stimulating factors stimulates the stem cells in the bone marrow to produce more of the particular white blood cells; The new white blood cells migrate into the blood and fight the infection.
   - Colony stimulating factors are used in patients who are undergoing cancer treatment that causes low white blood cell counts (neutropenia) and puts the patient at risk of infection. Colony stimulating factors tend to reduce the time where patients are neutropenic.
   - **These include: Filgrastim, Pegfilgrastim, Sargramostim** and **Lenograstim** (See chapter 15, section 5 for more info)

2. **Interleukins:**
   A group of cytokines which are synthesized by lymphocytes, monocytes, macrophages, and certain other cells; they function especially in regulation of the immune system.

Scientific name	Dosage form	Trade name	concentration
Aldesleukin	Vial	Proleukin®	22 million IU/vial (1.3 mg)
Oprelvekin	S.C. Inj.	Neumega®, Interleukin 11®	5 mg/vial

Notes:

- **Aldesleukin** has been shown to possess the biological activities of human native interleukin-2, the immunoregulatory properties include:
  - **a.** Enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines and Enhancement of lymphocyte cytotoxicity.
  - **b.** Induction of killer cell - lymphokine-activated (LAK) and natural (NK) – activity and Induction of interferon-gamma production.
- **Oprelvekin** is indicated for the prevention of severe thrombocytopenia.

3. **Bacterial vaccines:** Contain killed or attenuated bacteria that activate the immune system. Antibodies are built against that particular bacteria, and prevents bacterial infection later.

4. **Viral vaccines:** Contain either inactivated viruses or attenuated viruses. **(Alive but not capable of causing disease)**, Inactivated or killed viral vaccines contain viruses, which have lost their ability to replicate and in order for it to bring about a response it contains more antigen than live vaccines; Attenuated or live vaccines contain the live form of the virus. These viruses are not pathogenic but are able to induce an immune response.

5. **Vaccine combinations** merge antigens that prevent different diseases or that protect against multiple strains of infectious agents causing the same disease, into a single product. This reduces the number of injections required to prevent some diseases.

6. **Therapeutic vaccines:** are vaccines which are intended to treat or cure a disorder or disease by stimulating the immune system; Therapeutic vaccines may be used to treat certain types of cancer, by stimulating the body's immune system to help it respond against certain cancer cells. They may also be used in the prevention of tuberculosis in persons not previously infected with M. tuberculosis who are at high risk for exposure.

Part Two: Oncology

First: Introduction:

1. New cells are continuously needed by the body to replace those that wear out and die naturally and to repair injured tissue. Normally, the rate at which cells are created is carefully regulated; However, sometimes abnormal cells are formed that multiply uncontrollably, and they may form lumps of abnormal tissue.

2. These tumors are usually confined to one place and cause few problems; these are **benign growths**, such as warts; while in other types of tumors, the cells may invade or destroy the structures around the tumors, and abnormal cells may spread to other parts of the body, forming satellite or **metastatic tumors**; These are **malignant growths**, also called cancers.

3. Uncontrolled multiplication of cells leads to the formation of tumors that may be benign or malignant; **Benign tumors do not spread** to other tissues**;** while **malignant (cancerous) tumors does spread** to other tissues.
   - **Carcinomas**: affect the skin and cells in the tissue lining internal organs.
   - **Sarcomas**: affect muscles, bones, and fibrous tissues and lining cells of blood vessels.
   - **Leukemia**: affects white blood cells.
   - **Lymphomas**: affect the lymph glands.

4. Cancer is a general term that covers a wide range of disorders, ranging from the leukemias (blood cancers) to solid tumors of the lung, breast, and other organs; In all cancers, a group of cells escape from the normal controls on cell growth and multiplication; As a result, the malignant (cancerous) cells begin to crowd out the normal cells and a tumor develops.
   - Cancerous cells are frequently unable to perform their usual functions, and this may lead to progressively impaired function of the organ or area concerned.
   - Cancers may develop from cells of the blood, skin, muscle, or any other tissue.
   - Malignant tumors spread into nearby structures, blocking blood vessels and compressing nerves and other structures.
   - Fragments of the tumor may become detached and carried in the bloodstream to other parts of the body, where they form secondary growths (**Metastases**).

5. A single cause for cancer has not been identified, and an individual's risk of developing cancer may depend both upon **genetic predisposition** (some families seem prone to cancers of one or more types) and upon exposure to external risk factors, known as **carcinogens**; These include chronic **tobacco smoking** (which increases the risk of lung cancer), chronic **heavy alcohol consuming**, and **ultraviolet light** (which makes skin cancer more likely in those who spend long periods in the sun), **Radiation** (X-Rays) and **Environmental Pollution**.
   - Long-term suppression of the immune system by disease (as in AIDS) or by drugs (those given to prevent rejection of transplanted organs) increases the risk of developing infections and also certain cancers.

6. In cancer treatment, conventional chemotherapy involves using **cytotoxic** (cell-killing drugs) to eliminate abnormally dividing cells; These **slow the growth rate of tumors and sometimes lead to their complete disappearance**.
   - Because these drugs **act against all rapidly dividing cells** (including Hair; which explains severe hair loss in patients receiving cytotoxics), they also reduce the number of normal cells, including blood cells, being produced from bone marrow; This can produce serious adverse effects, such as anemia and neutropenia in cancer patients.
   - Newer anticancer drugs are more selective in the cells they target; For ex: **Trastuzumab** targets a specific protein produced by certain types of breast cancer cells.

7. Treating cancer is a complicated process that depends on the type of cancer, its stage of development, and the patient's condition and psychology; Any of the following treatments may be used alone or in combination with the others: surgery, radiation treatment, and drug therapy.

8. Hormone treatments are suitable for only a few types of cancer and cytotoxic drugs, although valuable, can have severe side effects because of the damage that they do to normal tissues.
9. In recent years, as understanding of cancer biology has increased, new anticancer drugs have been developed, these drugs include **Cytokines**, such as **Interferon** and **Interleukin-2**, that stimulate the immune system to attack certain cancers, and **Monoclonal Antibodies** and **Growth Factor Inhibitors** that attack the cancer cells much more selectively.

Second: Treatment Types:

1. **Induction Chemotherapy:** the first line treatment for cancer with chemotherapeutic agent.
2. **Combined Modality Chemotherapy:** the use of drugs with other cancer treatments as (surgery, radiation, or hyperthermia therapy).
3. **Consolidation Chemotherapy:** the drug treatment that is given after remission in order to prolong the overall disease-free time, and to improve overall survival, the drug is the same drug used in the Induction Chemotherapy.
4. **Intensification Chemotherapy:** same as Consolidation; but a different drug is used than the one being used in the Induction Chemotherapy.
5. **Adjuvant chemotherapy**: drug treatment used after surgery, especially for breast and bowel tumors, to prevent regrowth of the cancer from cells left behind after surgery.
6. **Neoadjuvant** or **(Primary Chemotherapy):** drug treatment that is used before surgery to reduce the size or shrink the tumor.
7. **Hormone treatment** is offered in cases of hormone-sensitive cancer, such as breast, uterine, and prostatic cancers, where it can be used to relieve disease symptoms or provide palliative treatment in advanced disease.
8. **Salvage Chemotherapy** or **(Palliative Chemotherapy):** the drug treatment that is given without the intent of cure, but simply to increase life expectancy as long as possible; while having the most possible life quality.
9. **Cytokines, Monoclonal Antibodies**, and **Growth Factor Inhibitors** are increasingly used alongside or instead of conventional chemotherapy; Sometimes these can be curative but often they produce or prolong disease remission.

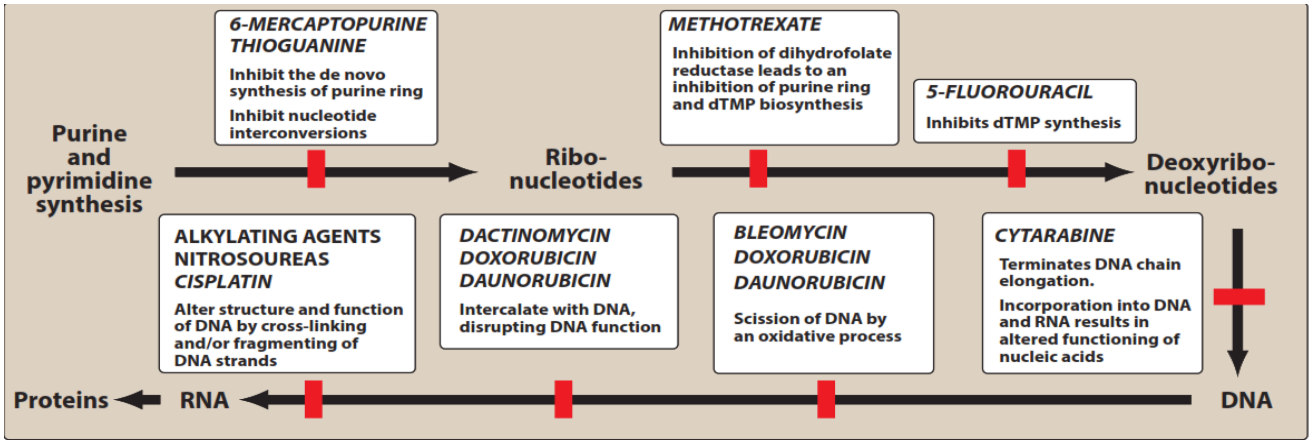
Notes:

1. The **Efficacy of chemotherapy** greatly depends on the **type and stage of Cancer**.
2. Most anticancer drugs, especially cytotoxic drugs, have side effects, which are sometimes severe, and so **treatment decisions have to balance possible benefits against the side effects**, and often a combination of several drugs is used.
   - Common side effects include: Severe vomiting, stomatitis, bone marrow suppression (which predisposes to infections) and Alopecia (hair loss).
3. Special regimes of different drugs that are used together and in succession have been devised to maximize their activity and minimize the side effects; also, Certain anticancer drugs are also used for their effect in suppressing immune system activity.
4. Some cancer cells (as melanoma) are inherently resistant to most anti-cancer drugs; some tumor types may acquire resistance to the cytotoxic effects of anti-cancer drugs by mutating (usually after prolonged administration of sub-optimal drug doses).
5. Also, Tumor resistance to chemotherapy can develop by: (decreased drug uptake into the cells, increased drug efflux outside the cells, activation of detoxifying systems, activation of DNA repair mechanisms, and by evasion of drug-induced apoptosis).
   - Some drugs as (Verapamil) in high doses, can interfere with the pumps that cause the efflux of anti-cancer drugs outside the cells; thus, reducing drug resistance.

Third: How Anti-Cancer drugs work:

Anticancer drugs work in many different ways; the main groups of drugs and how they work:

1. **Cytotoxic drugs:** There are several classes of cytotoxic drugs, including the **Alkylating Agents**, **Anthracyclines (Cytotoxic Antibiotics)**, **Antimetabolites**, **Taxanes Platinum compounds** and **Vinca Alkaloids,** and; Each class has a different mechanism of action, but all act by interfering with basic processes of cell replication and division.
   - They are particularly potent against rapidly dividing cells; These include cancer cells but also certain normal cells, especially those in the hair follicles, gut lining, and bone marrow.
   - This explains their side effects and why treatment needs careful scheduling.



2. **Hormone therapies:** Hormone treatments act by counteracting the effects of the hormone that is encouraging growth of the cancer; for example, some breast cancers are stimulated by the female sex hormone estrogen; the action of estrogen is opposed by the drug **Tamoxifen**, other cancers are damaged by very high doses of a particular sex hormone; An example is **Medroxyprogesterone**, a progesterone that is used to halt the spread of endometrial cancer.
3. **Cytokines**: The **Cytokines**, **Interferon Alfa** and **Interleukin-2**, stimulate the immune system to attack certain cancers.
4. **Monoclonal antibodies:** Antibodies are a fundamental building block of the immune system, they recognize and bind very specifically to foreign proteins on the surface of bacteria, viruses, and parasites, marking them out for destruction by other parts of the immune system.
   - Monoclonal antibodies are produced in tissue culture using cells genetically engineered to make antibodies against a particular target protein; If the target is carefully selected, the antibodies can be used to identify cancer cells for destruction; If the target is found only on cancer cells, or on the cancer cells and the normal tissue from which it arose, the damage to healthy tissues during treatment is limited.
   - These antibodies are very specific for certain types of cancer, and they cause little of the toxicity of conventional chemotherapy; They can, however, cause allergy-type reactions, especially at the beginning of treatment.
5. **Growth factor inhibitors:** The growth of cells is controlled by a complex network of growth factors that bind very specifically to receptor sites on the cell surface, this triggers a complex series of chemical reactions that transmit the "grow" message to the nucleus, triggering cell growth and replication. In many cancers, this system is faulty and there are either too many receptors on the cell surface or other abnormalities that result in inappropriate "grow" messages. The extra or abnormal cell surface receptors can be used as targets for monoclonal antibodies.
   - Another new area of cancer treatment is the use of drugs that inhibit the growth of new blood vessels to tumors **(anti-angiogenesis agents)**, thereby depriving the tumors of the nutrients and oxygen they need to grow.

Notes:

1. Cytotoxic drugs are generally associated with more side effects than other anticancer drugs, at the start of treatment, adverse effects of the drugs may be more noticeable than benefits; the most common side effect is nausea and vomiting, for which an anti-emetic drug will usually be prescribed, effects on the blood are also common; many cytotoxic drugs cause hair loss because of their effect on the hair follicle cells, but the hair usually starts to grow back after chemotherapy has been completed; Individual drugs may produce other side effects.
   - In some cases, they cause symptoms of anemia (weakness and fatigue) and an increased risk of abnormal or excessive bleeding may develop as a result of treatment with anticancer drugs.
   - Reduction in the number of white blood cells may result in an increased susceptibility to infection. A simple infection such as a sore throat may be a sign of depressed white cell production in a patient taking anticancer drugs.
   - Also, some wounds may take longer to heal, and susceptible people can develop gout as a result of increased uric acid production due to cells being broken down.
2. Cytotoxic drugs are, in most cases, administered in the highest doses that can be tolerated in order to kill as many cancer cells as quickly as possible.
3. The unpleasant side effects of intensive chemotherapy, combined with a delay of several weeks before any beneficial effects are seen and the seriousness of the underlying disease, often lead to depression in those who are receiving anticancer drugs.
   - Thus; Specialist counselling, support from family and friends may have huge beneficial effects on the therapy, and in some cases, treatment with antidepressant drugs may be helpful.
4. **Not all cancers respond to treatment with anticancer drugs**; Some cancers can be cured by drug treatment; In other cancers, drug treatment can only slow or temporarily halt the disease's progress, in certain cases, drug treatment has no beneficial effect but other treatments, such as surgery, often produce significant benefits.
   The main cancers that fall into each of the first two groups are described here:
   a. **Cancers that can often be cured by drugs:** (Some cancers of the lymphatic system (including Hodgkin's disease), Acute leukemias (forms of blood cancer), Choriocarcinoma (cancer of the placenta), Germ cell tumors (cancers affecting sperm and egg cells), Wilms' tumor (a rare form of kidney cancer that affects children), and Cancer of the testis.
   b. **Cancers in which drugs may produce worthwhile benefits:** Breast cancer, Ovarian cancer, some leukemias, Multiple myeloma (a bone marrow cancer), Many types of lung cancer, Head and neck cancers, Cancer of the stomach, Cancer of the prostate, some cancers of the lymphatic system, Bladder cancer, Endometrial cancer (cancer affecting the lining of the uterus), Cancer of the large intestine, Cancer of the esophagus, Cancer of the pancreas, and Cancer of the cervix.
5. Successful drug treatment of cancer usually **requires repeated courses of anticancer drugs** because the treatment needs to be halted periodically to allow the blood-producing cells in the bone marrow to recover.
6. Imaging (CT, MRI, PET) is frequently done after 2 to 3 cycles of therapy to evaluate response; Therapy continues if there is a clear response.
   - If the tumor progresses despite therapy, the regimen is often changed or stopped.
   - If the disease remains stable with treatment and the patient can tolerate therapy, then a decision to continue is reasonable with the understanding that the disease will eventually progress.

Fourth: Anti-Cancer Groups

A. Cytotoxic antineoplastics

1. Alkylating Cytotoxic Agents

a. Compounds that work by adding an alkyl group to the guanine base of the DNA molecule, preventing the strands of the double helix from linking as they should; This causes breakage of the DNA strands, affecting the ability of the cancer cell to multiply.

b. Alkylating agents are used to treat several cancers, but they are also toxic to normal cells, particularly cells that divide frequently, such as those in the gastrointestinal tract, bone marrow, hair follicles, testicles and ovaries, which can cause loss of fertility.

c. Alkylating agents are **mutagenic** and **Carcinogenic**, and can lead to secondary malignancies such as acute Leukemia.

Scientific name	Dosage form	Trade name	concentration
Bendamustine	Vial	Treanda® , Ribomustin®	100 mg
Busulfan	Vial	Myleran® , Busulfex®	60 mg/10 ml
	Tab		2 mg
Carmustine	Vial	BiCNU® , Gliadel®	100 mg
Chlorambucil	Tab	Leukeran®	2 mg
Cyclophosphamide	Vial	Cytoxan® , Endoxan®	500 mg , 1 gm
	Tab		25 mg , 50 mg
Procarbazine	Tab	Matulane® , Natulan®	50 mg
Dacarbazine	Vial	DTIC® , Celdaz®	100 mg , 200 mg
Estramustine	Cap	Estracyt®	140 mg
Ifosfamide	Vial	Ifex®	1 gm/20 ml , 3 gm/60 ml
Lomustine	Cap	Gleostine®	10 mg , 40 mg , 100 mg
Melphalan	Vial	Alkeran®	50 mg
	Tab		2 mg
Temozolomide	Cap	Temodal®	100 mg , 140 mg
	Vial		100 mg
Thiotepa	Vial	Thioplex® , Tespa®	15 mg
Treosulfan	Vial	Trecondi®	1 gm , 5 gm
Streptozocin	Vial	Zanosar®	1 gm
Altretamine	Cap	Hexalen®	50 mg

2. Platinum compound Cytotoxic agents

a. They are coordination complexes of platinum; These are a heavy-metal complex that exerts a cytotoxic effect by binding DNA, forming cross-links which disrupt the ability of replication and transcription, thus inducing cell apoptosis.

b. Platinum-based antineoplastic agents are sometimes described as (alkylating-like) due to similar effects as alkylating antineoplastic agents, although they do not have an alkyl group.

c. Common side effects include neurotoxicity, which is manifested by **peripheral neuropathies** including polyneuropathy.

d. Have a synergistic effect when combined with other Alkylating agents and Taxanes.

Scientific name	Dosage form	Trade name	concentration
Carboplatin	Vial	Paraplatin® , Kemocarb®	150 mg , 450 mg , 600 mg
Cisplatin	Vial	Platamin®	50 mg , 100 mg , 200 mg
Oxaliplatin	Vial	Eloxatin®	50 mg , 100 mg
Nedaplatin	Vial	Aqupla®	10 mg
Dicycloplatin	Pending FDA approval		

3. Anthracycline (antibiotics) Cytotoxic Agents

a. They are extracted from Streptomyces bacterium; They are derived from antibiotics that inhibit DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand; Cytotoxicity is primarily due to inhibition of topoisomerase II after the enzyme induces a break in DNA, preventing religation of the break and leading to cell death.

b. They also produce free radicals, which plays a major role in their cytotoxic effect.

c. Two major dose limiting toxicities of Anthracyclines include **myelosuppression** and **cardiotoxicity**; which is dose-dependent and cumulative.

- **Dexrazoxane** is used with Anthracyclines to reduce their cardio-toxic effect, it's a derivative of EDTA (chelates Iron and thus reducing metal iron complexed with Anthracyclines; which leads to decrease in the formation of superoxide radicals).
- **Liposomal Doxorubicin** has lower cardio-toxic effects than the older formulation.

d. They may cause a **red color urine**; and the veins at the site of injection may become dark red.

Scientific name	Dosage form	Trade name	concentration
Daunorubicin	Vial	Daunomycin® , Cerubidine®	20 mg/4 ml , 50 mg/10 ml
Doxorubicin	Vial (Solu.)	Adriamycin® , Rubex®	20 mg , 50 mg , 100 mg
Doxorubicin (Liposomal)	Vial	Doxil®	20 mg , 50 mg
Epirubicin	Vial	Ellence®	10 mg , 20 mg , 100 mg
Idarubicin	Vial	Idamycin®	5 mg , 10 mg , 20 mg
Mitoxantrone	Vial	Novantrone®	20 mg , 25 mg , 30 mg
Pixantrone	Vial	Pixuvri®	29 mg
Bleomycin	Vial	Blenoxane®	15 units , 30 units
Mitomycin	Vial	Mutamycin®	10 mg , 20 mg , 40 mg
Dactinomycin *	Vial	Cosmegen®	500 mcg

* Dactinomycin = Actinomycin D, they are the same drug.

4. Microtubule Inhibitors

1. Mitotic spindle is an intracellular skeleton (cytoskeleton), that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells; the mitotic spindle consist of chromatin and microtubules (which is composed of tubulin protein); the mitotic spindle is essential for all cell division.

2. Several anti-cancer groups act to disturb the microtubules; usually affecting the equilibrium between the polymerized and depolymerized forms of the microtubules; thus, causing cytotoxicity, these groups include: **Vinca Alkaloids** and **Taxanes**.

A) Vinca Alkaloid Cytotoxic agents

a. They disrupt microtubule formation; they also have many effects on cellular activities, including inhibition of mitotic spindle formation and mitotic arrest; All Vinca alkaloids bind to tubulin, a protein comprised of α and β subunits, inhibiting its polymerization. Polymerization of tubulin is responsible for the formation of the mitotic spindle during the metaphase period of mitosis

b. Thus, Vinca alkaloids inhibit cell division in the M phase of the cell cycle.

c. **Vinblastine** and **Vincristine** are natural alkaloids, while **Vindesine**, **Vinorelbine** and **Vinflunine** are semisynthetic derivatives.

d. The most common side effect is **Neurotoxicity**, including peripheral neuropathy, also **SIADH** may occur (syndrome of inappropriate secretion of antidiuretic hormone).

- **Liposomal Vincristine** has a lower neurotoxicity side effect.

Scientific name	Dosage form	Trade name	concentration
Vinblastine	Vial	Velban®	10 mg/10 ml
Vincristine *	Vial	Oncovin® , Vincasar®	1 mg , 2 mg
Vincristine Liposomal	Vial	Marqibo®	5 mg
Vindesine	Vial	Eldisine®	5 mg
Vinorelbine	Vial	Navelbine®	10 mg , 50 mg
Vinflunine	Vial	Javlor®	50 mg , 250 mg

* Vincristine = Leurocristine, they are the same drug.

B) Taxanes Cytotoxic agents

a. As their name suggests, Taxanes were first derived from natural sources, but some have been synthesized artificially; Taxanes present difficulties in formulation as medicines because they are poorly soluble in water.

b. Also called **Cytoskeletal disruptors** or **anti-microtubulars**, they produce antitumor activity by causing stabilization of cellular microtubules, thereby inhibiting cell division.

c. They have high binding affinity to microtubules with enhancement of tubulin polymerization.

d. Limitations to Taxanes use include the risk of **life-threatening hypersensitivity reactions**, hematopoietic toxicity and **cumulative neurotoxicity**.

Scientific name	Dosage form	Trade name	concentration
Cabazitaxel	Vial	Jevtana®	60 mg
Docetaxel	Vial	Taxotere® , Docax®	20 mg , 80 mg , 120 mg , 160 mg
Paclitaxel	Vial	Taxol®	30 mg , 100 mg , 300 mg
Other Microtubules inhibitors			
Ixabepilone *	Vial	Ixempra®	15 mg , 45 mg
Eribulin	Amp , Vial	Halaven®	0.5 mg , 1 mg

* **Ixabepilone** is also an Epothilone B analog; which is a **highly potent agent**, capable of damaging cancer cell in very low concentrations; it retains activity in cases were tumor cells are insensitive to Taxanes or Anthracyclines.

5. Topoisomerase inhibitors

a. Topoisomerase enzymes aids in the DNA unwinding, thus inhibiting them prevents re-ligation of the DNA strands; and by doing so, DNA strand break down, (Cancer cells rely on this enzyme more than healthy cells, because they divide more rapidly).

b. Groups inhibiting these enzymes include: Podophyllotoxin derivatives and Camptothecins.

- **Podophyllotoxin derivatives** forms a complex with **Topoisomerase II** forming single stranded DNA breaks, prevents repair by topoisomerase II binding; Accumulated breaks in DNA prevent entry into the mitotic phase of cell division, and lead to cell death.
- **Camptothecins** inhibits **Topoisomerase I** resulting in the stabilization of the cleavable complexes, causing reversible single stranded DNA breaks, preventing DNA re-ligation and therefore causes DNA damage which results in apoptosis.

Scientific name	Dosage form	Trade name	concentration
Podophyllotoxin derivatives			
Etoposide	Cap	Toposar® , Etopophos®	50 mg
	Vial		100 mg , 500 mg
Teniposide	Vial	Vumon®	50 mg
Camptothecins			
Irinotecan	Vial	Camptosar®	40 mg , 100 mg
Topotecan	Vial	Hycamtin®	4 mg

6. Antimetabolite Cytotoxic Agents

a. Antimetabolites are drugs that interfere with one or more enzymes or their reactions that are necessary for DNA synthesis; They affect DNA synthesis by acting as a substitute to the actual metabolites that would be used in the normal metabolism (antifolates as methotrexate interfere with the use of folic acid); competitive inhibition can occur, and the presence of antimetabolites can have toxic effects on cells, such as halting cell growth and cell division,

b. They are structurally similar to normal compounds that exist within the cell; they interfere with the availability of normal Purine or Pyrimidine Nucleotides; thus inhibiting synthesis of DNA and RNA (Antimetabolites generally impair DNA replication machinery, either by incorporation of chemically altered nucleotides or by depleting the supply of deoxynucleotides needed for DNA replication and cell proliferation).

c. Many Antimetabolites are available; they differ in their mechanism of action, indications and their side effects profile.

Scientific name	Dosage form	Trade name	concentration
Folate Analogs			
Methotrexate	Tab	Rheumatrex® , MTX®	2.5 mg , 5 mg , 10 mg
	Vial	Trexall®	25 mg/ml
Pemetrexed	Vial	Alimta®	100 mg , 500 mg
Pralatrexate	Vial	Folotyn®	20 mg/ml , 40 mg/2 ml
Purine Analogs			
Mercaptopurine	Tab	Purinethol® , 6-MP®	50 mg
Fludarabine	Vial	Fludara®	50 mg/2 ml
Cladribine	Vial	Leustatin®	10 mg/10 ml
	Tab	Mavenclad®	10 mg
Nelarabine	Vial	Arranon®	50 mg
Tioguanine *	Tab	Tabloid® , 6-TG®	40 mg
Clofarabine	Vial	Clolar®	20 mg/10 ml
Pentostatin **	Vial	Nipent®	10 mg
Pyrimidine Analogs			
Fluorouracil *	Vial	Adrucil® , 5-FU®	50 mg/ml (1gm , 2.5 gm)
Capecitabine	Tab	Xeloda®	500 mg
Floxuridine	Vial	Fudr®	500 mg
Cytidine Analogs			
Cytarabine	Vial	Cytosar® , Ara-C®	500 mg , 1 gm , 2 gm
Azacitidine	Vial	Vidaza® , Xpreza®	100 mg
Gemcitabine	Vial	Gemzar® , Gemsiban®	200 mg , 1 gm , 2 gm
Decitabine	Vial	Dacogen®	50 mg
Combination Products			
Tegafur + Gimeracil + Oteracil	Cap	Teysuno® **	(15 mg + 4.35 mg + 11.8 mg), (20 mg + 5.8 mg + 15.8 mg)
Trifluridine + Tipiracil	Tab	Lonsurf®	(15 mg + 6.14 mg), (20 mg + 8.19 mg)

Notes:

1. **Fluorouracil** is also available as a topical cream.
2. **Tioguanine = Thioguanine**; and **Pentostatin = Deoxycoformycin**, they are the same drug.
3. **Tegafur** is a prodrug of **Fluorouracil** (5-FU), **Gimeracil** inhibits the degradation of Fluorouracil which results in higher 5-FU levels and a prolonged half-life; **Oteracil** reduces the production of 5-FU and Lowers 5-FU levels in the gut resulting in a lower gastrointestinal toxicity.
4. **Trifluridine** is a nucleoside analog; **Tipiracil** is a thymidine phosphorylase inhibitor, it prevents rapid metabolism of Trifluridine, increasing the drug bioavailability.

7. Retinoid derivatives Cytotoxic agents

The retinoic acid receptors (RARs) regulate cell differentiation and proliferation whereas retinoid X receptors (RXRs) regulate apoptosis.

- These agents bind to RXRs and induce cell apoptosis.

Scientific name	Dosage form	Trade name	concentration
Bexarotene	Cap	Targretin®	75 mg
	Gel		1%
Tretinoin	Cap	Vesanoid®	10 mg
Alitretinoin	Gel	Panretin®	0.1%

8. Other Cytotoxic agents

Scientific name	Dosage form	Trade name	concentration
Arsenic trioxide	Amp , Vial	Trisenox®	10 mg
Asparaginase	Vial	Leunase®	5,000 IU , 10,000 IU
Crisantaspase	Vial	Erwinase®	5,000 IU , 10,000 IU
Hydroxyurea (Hydroxycarbamide)	Cap	Hydrea®, Hydrine® Droxia®	500 mg
Mitotane	Tab	Lysodren®	500 mg
Panobinostat	Cap	Farydak®	20 mg
Pegaspargase	Vial	Oncaspar®	3,750 IU
Raltitrexed	Vial	Tomudex®	2 mg
Trabectedin	Vial	Yondelis®	0.25 mg , 1 mg
Olaparib	Cap , Tab	Lynparza®	50 mg , 100 mg , 150 mg
Venetoclax	Tab	Venclexta®	10 mg , 100 mg
Vismodegib	Cap	Erivedge®	150 mg

Note:

Drugs for **cytotoxic drug-induced side effects** are listed below:

Scientific name	D. form	Trade name	concentration	Indications
Dexrazoxane	Vial	Zinecard®, Cardioxane®	250 mg, 500 mg	Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or Epirubicin, Anthracycline extravasation
Palifermin	Vial	Kepivance®	6.25 mg	Management of oral Mucositis in patients with hematological malignancies
Mesna	Vial	Mesnex®	1 gm	Cytotoxic induced urothelial toxicity associated with cyclophosphamide
	Amp		200 mg , 400 mg	
Amifostine	Vial	Ethyol®	500 mg	To prevent Xerostomia, and to protect against nephropathy and bone marrow damage.
Palifermin	Vial	Kepivance®	6.25 mg	For severe oral Mucositis
Folinic acid	Tab	Leucovorin®	800 mcg	Prevention of methotrexate-induced adverse effects, As an antidote to methotrexate, Adjunct to fluorouracil in colorectal cancer
Levofolinic acid	Vial	Leucovorin Inj. ®	50 mg, 100 mg 200 mg, 350 mg	
Glucarpidase	Vial	Voraxane®	1000 unit	Converts methotrexate to glutamate and di-amino methylpteroic acid, used for prevention of methotrexate-induced adverse effects
Rasburicase	Vial	Fasturtec®, Elitek®	1.5 mg, 7.5 mg	Prophylaxis and treatment of acute hyperuricemia, before and during initiation of chemotherapy

B. Antineoplastic monoclonal antibodies

1. Monoclonal antibodies are a type of **targeted cancer therapy**; they are directed at specific targets and they usually have fewer adverse effects (compared to other cancer medications).
   - For more info on monoclonal antibodies see the previous part (immunology page 378)
2. Monoclonal antibodies can be used alone, or to carry drugs, toxins or radioactive substances directly to the cancer cells.
3. Most recently, anticancer monoclonal antibodies that target 2 or even 3 antigens have been developed; These monoclonal antibodies target a cancer-related antigen and a normal antigen on T cells with the objective of enhancing T-cell killing of cancer cells.
4. Monoclonal antibodies **differ greatly in their exact mechanism of action**; and thus, differ in their indications and their side effects profile; below some of the most common notes about them:
   - **Rituximab** has the risk of severe infusion reactions (fatal) and Tumor Lysis Syndrome risk.
   - Both **Trastuzumab** and **Pertuzumab** have the risk of causing Heart Failure (risk is increased or worsen when combined with Anthracyclines).
   - **Bevacizumab** has a high risk of causing internal bleeding.

Scientific name	Dosage form	Trade name	concentration
Alemtuzumab *	Vial	Lemtrada®, Campath®	12 mg/1.2 ml , 30 mg/ml
Atezolizumab	Vial	Tecentriq®	1200 mg
Avelumab	Vial	Bavencio®	200 mg
Bevacizumab	Vial	Avastin®	100 mg , 400 mg
Blinatumomab	Vial	Blincyto®	35 mcg
Brentuximab	Vial	Adcetris®	50 mg
Catumaxomab	Prefilled Inj.	Removab®	10 mcg , 50 mcg
Cetuximab	Vial	Erbitux®	100 mg , 200 mg
Cemiplimab	Vial	Libtayo®	350 mg
Daratumumab	Vial	Darzalex®	100 mg , 400 mg
Denosumab **	Vial	Xgeva®	120 mg
Durvalumab	Vial	Imfinzi®	120 mg , 500 mg
Dinutuximab	Vial	Unituxin®	17.5 mg
Elotuzumab	Vial	Empliciti®	300 mg , 400 mg
Gemtuzumab	Vial	Mylotarg®	4.5 mg
Ipilimumab	Vial	Yervoy®	50 mg , 200 mg
Mogamulizumab	Vial	Poteligeo®	20 mg
Necitumumab	Vial	Portrazza®	800 mg
Nivolumab	Vial	Opdivo®	40 mg , 100 mg
Obinutuzumab	Vial	Gazyva®	1000 mg
Olaratumab	Vial	Lartruvo®	190 mg , 500 mg
Ofatumumab	Vial	Arzerra®	1000 mg
Panitumumab	Vial	Vectibix®	100 mg
Pembrolizumab	Vial	Keytruda®	50 mg , 100 mg
Pertuzumab	Vial	Perjeta®	420 mg
Ramucirumab	Vial	Cyramza®	100 mg , 500 mg
Rituximab	Vial	Rituxan®, MabThera®	100 mg , 500 mg
Siltuximab	Vial	Sylvant®	100 mg , 400 mg
Tositumomab	Vial	Bexxar®	35 mg , 225 mg
Trastuzumab	Vial	Herceptin® , Herzuma®	150 mg , 440 mg
Ado-Trastuzumab	Vial	Kadcyla®	100 mg , 160 mg

***** Alemtuzumab is also used for Multiple Sclerosis**.**

** Denosumab is also used for osteoporosis (Prolia).

Monoclonal antibodies Combinations			
Ado-Trastuzumab Emtansine	Vial	Kadcyla®	100 mg , 160 mg
Inotuzumab Ozogamicin	Vial	Besponsa®	0.9 mg
Gemtuzumab Ozogamicin	Vial	Mylotarg®	4.5 mg

*** Emtansine** is a **microtubule inhibitor** (Cytotoxic agent).
* **Ozogamicin** is a cytotoxic agent

C. Hormonal Antineoplastics

1. A Hormone-sensitive cancer or (hormone-dependent cancer) is a type of cancer that depends on hormone for growth; as in **Breast cancer** (which depends on Estrogens like Estradiol), or **Prostate cancer** (which depends on Androgens like Testosterone).
2. Hormonal anticancer drugs are used to reduce or prevent proliferation of cancers that are responsive to specific levels of hormones.
3. Hormones are signaling molecules that bind to target cells receptors and stimulates or blocks the cells function; Hormonally responsive cancer can be treated by reducing the level of hormone that is needed for tumor cell growth and survival, by using inhibitors of hormone synthesis or hormone receptor antagonist, some cancers may be inhibited by increased level of a specific hormone therefore supplementing with a hormone agonist is used to treat these types of cancer.
4. Hormonal therapy is particularly useful in prostate cancer, which grows in response to androgens; Other cancers with hormone receptors on their cells (breast, endometrium) can often be palliated by hormone antagonist therapy or hormone ablation.
5. Hormonal agents may block the secretion of pituitary hormones (luteinizing hormone–releasing hormone agonists), block the androgen (Bicalutamide, Enzalutamide) or estrogen receptor (Tamoxifen), suppress the conversion of androgens to estrogens by aromatase (Letrozole), or inhibit the synthesis of adrenal androgens (Abiraterone).
6. All hormonal blockers can cause symptoms related to hormone deficiency (such as hot flashes) and the androgen antagonists also induce a metabolic syndrome that increases the risk of diabetes and heart disease.

Scientific name	Dosage form	Trade name	concentration
Anti-androgens Antineoplastics			
Abiraterone	Tab	Zytiga®	250 mg , 500 mg
	UM Tab	Yonsa®	125 mg
Apalutamide	Tab	Erleada®	60 mg
Bicalutamide	Tab	Casodex®	50 mg , 150 mg
Enzalutamide	Cap	Xtandi® , Azel®	40 mg
Flutamide	Tab	Eulexin® , Cytomid®	250 mg
	Cap		125 mg
Nilutamide	Tab	Nilandron®	150 mg
Degarelix *	Vial	Firmagon®	80 mg , 120 mg
Estrogens antineoplastics			
Diethylstilbestrol	Tab	Distilbene®	1 mg , 5 mg , 25 mg
Somatostatin analogues antineoplastics			
Lanreotide	Prefilled Inj.	Sumatuline Depot®	60 mg , 90 mg , 120 mg
Octreotide	Inj. Solu.	Sandostatin®	0.1 mg , 0.5 mg , 1 mg
	Depot Inj.	Sandostatin LAR®	10 mg , 20 mg , 30 mg
Pasireotide	S.C Inj.	Signifor®	0.2 mg/ml, 0.6 mg/ml, 0.9 mg/ml

Progestogens antineoplastics			
Megestrol acetate	Tab	Megace®	40 mg , 160 mg
Gonadotropin releasing hormone (GnRH) analogs			
Goserelin	Implant (S.C)	Zoladex®, Zoladex LA®	3.6 mg (for 1 month), 10.8 mg (for 3 months)
Leuprolide **	Inj.	Lupron®	5 mg/ml
Triptorelin	Inj. (S.C.)	Decapeptyl®	0.1 mg/ 1ml
	Inj. Powder	Trelstar®, Trelstar depot®	3.75 mg , 11.25 mg , 22.5 mg
Anti-Estrogens antineoplastics			
Fulvestrant	Prefilled Inj.	Faslodex®	250 mg
Tamoxifen	Tab	Nolvadex®	10 mg , 20 mg
Toremifene	Tab	Fareston®	20 mg , 60 mg
Aromatase inhibitors antineoplastics			
Anastrozole	Tab	Arimidex®	1 mg
Exemestane	Cap	Aromasin®	25 mg
Letrozole	Tab	Femara®	2.5 mg

* Degarelix is also an Anti-gonadotrophin releasing hormones antineoplastics.
** Leuprolide = Leuprorelin, they are the same drug.

D. Immunotherapy antineoplastics

1. Immunotherapy is the artificial stimulation of the immune system to treat cancer, improving on the immune system's natural ability to fight the cancer., by **enabling it to recognize, target, and eliminate** cancer cells throughout the body.
2. Immunotherapy **can be given alone, or in combination** with other types of cancer treatments. It's already proven to be an effective treatment for patients with various types of cancers.
3. Solid tumors produce growth factors that form new blood vessels necessary to support ongoing tumor growth; the drugs that inhibit this process is called **(Angiogenesis inhibitors)**, they include: **Thalidomide**, **Lenalidomide** and **Pomalidomide**

Scientific name	D. form	Trade name	concentration
Talimogene Laherparepvec	Vial	Imlygic® , TVEC®	1 million PFU, 100 million PFU (PFU = Plaque-Forming Unit)
Interferon Alfa 2b	Vial	Multiferon® , Intron A®	3 million IU , 5 M , 10 M IU
Interferon Alfa 2a	Vial	Roferon A®	18 million IU
Aldesleukin	Vial	Proleukin®	22 million IU
Bacillus Calmette-Guérin (BCG)	Vial	Onco BCG®	40 mg/ml
Histamine dihydrochloride	Vial	Ceplene®	0.5 mg/0.5 ml
Mifamurtide	Vial	Mepact®	4 mg
Lenalidomide	Tab	Revlimid® , Lenalid®	10 mg , 25 mg
Pomalidomide	Cap	Pomalyst® , Imnovid® Pomalid®	1 mg , 2 mg , 4 mg
Thalidomide	Cap	Thalomid® , Thalix®	50 mg , 100 mg

* **Thalidomide** is a sedative drug discovered at the end of the 50s, which caused a worldwide tragedy; The drug has been prescribed to many pregnant women in order to relieve pregnancy nausea, it was later found that thalidomide caused irreversible damages to the fetus and thousands of children were born with severe congenital malformations, many of them did not survive more than a few days after they were born.

E. Proteasome inhibitors antineoplastics

Proteasome is an enzyme that degrades unwanted cellular proteins; thus, inhibition of this enzyme results in accumulation of polyubiquinated proteins, which may cause cell cycle arrest, apoptosis and inhibition of tumor growth.

Scientific name	Dosage form	Trade name	concentration
Bortezomib	Vial	Velcade®	1 mg , 2 mg , 3.5 mg
Carfilzomib	Vial	Kyprolis®	10 mg , 30 mg , 60 mg
Ixazomib	Cap	Ninlaro®	2.3 mg , 3 mg , 4 mg

F. Kinase inhibitor antineoplastics

1. A **Tyrosine Kinase** is an enzyme that can transfer a phosphate group from ATP to a protein in a cell; it functions as an "on" or "off" switch in many cellular functions.
2. Phosphorylation of proteins by kinases is an important mechanism in communicating signals within a cell (signal transduction) and regulating cellular activity, such as cell division.
3. Receptor tyrosine kinases have been shown not only to be key regulators of normal cellular processes but also to have a critical role in the development, progression of many types of cancer.
4. Protein kinases can become mutated, stuck in the "on" position, and cause unregulated growth of the cell, which is a necessary step for the development of cancer; Therefore, kinase inhibitors, (such as Imatinib) are often effective cancer treatments.
5. Many Tyrosine Kinase inhibitors are available (they differ in their exact cellular mechanism; and thus, differ in their indications and their side effect profile), and these agents have a wide variety of applications in the treatment of cancer.
6. Some notes regarding **Tyrosine Kinase inhibitor** antineoplastics:
   - **Imatinib** may cause fluid retention, and has a risk of causing sever congestive heart failure.
   - **Nilotinib** may cause fluid retention and prolong QT interval.
   - **Dasatinib** has the risk of causing Pulmonary Arterial Hypertension.
   - **Erlotinib** may cause Pneumonitis and Pulmonary Fibrosis.

Scientific name	Dosage form	Trade name	concentration
Tyrosine Kinase inhibitor antineoplastics			
Acalabrutinib	Cap	Calquence®	100 mg
Afatinib	Tab	Gilotrif® , Xovoltib®	20 mg , 30 mg , 40 mg , 50 mg
Alectinib	Cap	Alecensa®	150 mg
Avapritinib	Tab	Ayvakit®	100 mg , 200 mg , 300 mg
Axitinib	Tab	Inlyta®	1 mg , 5 mg
Brigatinib	Tab	Alunbrig®	30 mg , 90 mg , 180 mg
Bosutinib	Tab	Bosulif®	100 mg , 500 mg
Cabozantinib	Tab	Cabometyx®	20 mg , 40 mg , 60 mg
Ceritinib	Cap	Zykadia® , Spexib® , Noxalk®	150 mg
Cobimetinib	Tab	Cotellic®	20 mg
Crizotinib	Cap	Xalkori®	200 mg , 250 mg
Dacomitinib	Tab	Vizimpro®	15 mg , 30 mg , 45 mg
Dasatinib	Tab	Sprycel®	20 mg , 50 , 70 , 100 mg
Entrectinib	Cap	Rozlytrek®	100 mg , 200 mg
Erlotinib	Tab	Tarceva®	100 mg , 150 mg
Gefitinib	Tab	Iressa® , Geftinat®	250 mg
Gilteritinib	Tab	Xospata®	40 mg

Ibrutinib	Tab	Imbruvica®	140 mg , 280 mg , 420 mg
	Cap		70 mg , 140 mg
Idelalisib	Tab	Zydelig®	100 mg , 150 mg
Imatinib	Tab	Gleevec®	100 mg , 400 mg
Lapatinib	Tab	Tykerb® , Herduo®	250 mg
Lenvatinib	Cap	Lenvima®	4 mg , 10 , 14 , 20 , 24 mg
Lorlatinib	Tab	Lorbrena®	25 mg , 100 mg
Midostaurin	Cap	Rydapt®	25 mg
Neratinib	Tab	Nerlynx®	40 mg
Nilotinib	Cap	Tasigna®	150 mg , 200 mg
Osimertinib	Tab	Tagrisso® , Osicent®	80 mg
Pacritinib	Pending FDA approval		
Pazopanib	Tab	Votrient®	200 mg , 400 mg
Pexidartinib	Cap	Turalio®	200 mg
Ponatinib	Tab	Iclusig®	15 mg , 45 mg
Quizartinib	Pending FDA approval		
Regorafenib	Tab	Stivarga® , Nublexa®	40 mg
Ruxolitinib	Tab	Jakavi®	5 mg , 10 mg , 15 mg , 20 mg
Sorafenib	Tab	Nexavar®	200 mg , 400 mg
Sunitinib	Cap	Sutent®	12.5 mg , 25 mg , 50 mg
Trametinib	Tab	Mekinist®	0.5 mg , 2 mg
Vandetanib	Tab	Caprelsa®	300 mg
Nintedanib	Cap	Ofev® , Vargatef®	100 mg , 150 mg
Zanubrutinib	Cap	Brukinsa®	80 mg
Ziv-Aflibercept	Vial	Zaltrap®	100 mg , 200 mg
Cyclin Dependent Kinase inhibitor antineoplastics			
Abemaciclib	Tab	Verzenio®	100 mg , 150 mg , 200 mg
Palbociclib	Cap	Ibrance®	75 mg , 125 mg
Ribociclib	Tab	Kisqali®	200 mg
BRAF Kinase inhibitor antineoplastics			
Dabrafenib	Cap	Tafinlar®	50 mg , 75 mg
Encorafenib	Cap	Braftovi®	50 mg , 75 mg
Vemurafenib	Tab	Zelboraf®	240 mg
mTOR Kinase inhibitor antineoplastics			
Everolimus	Tab	Afinitor®	5 mg , 10 mg
	Tab	Zortress®	0.25 mg , 0.5 mg
Temsirolimus	Vial	Torisel®	25 mg/ml

G. Histone deacetylase inhibitors

1. The Histone deacetylase inhibitors are a new class of cytostatic agents that inhibit the proliferation of tumor cells by inducing cell cycle arrest, differentiation and/or apoptosis; Histone deacetylase inhibitors exert their anti-tumor effects via the induction of expression changes of oncogenes or tumor suppressor, through modulating the acetylation/deactylation of histones and/or non-histone proteins such as transcription factors.
2. Several compounds act on the Histone deacetylate system, these include:
   - **Romidepsin** (which is obtained naturally from **Chromobacterium Violaceum** bacterium, and acts by blocking Histone deacetylase enzymes; thus, inducing apoptosis.
   - **Vorinostat, Belinostat, Entinostat** and **Mocetinostat** (which are synthetic Histone deacetylase inhibitors).

Scientific name	Dosage form	Trade name	concentration
Romidepsin	Vial	Istodax®	10 mg
Vorinostat	Cap	Zolinza®	100 mg
Belinostat	Vial	Beleodaq®	500 mg
Entinostat	Pending FDA approval		
Mocetinostat			

Note: Nobel Prize in Physiology or Medicine 2018

The 2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo "for their **discovery of cancer therapy by inhibition of negative immune regulation**". Their pioneering work on the CTLA4 and PD1 immune checkpoints revealed that these pathways act as so-called 'brakes' on the immune system, and showed that inhibition of these checkpoint pathways allows T cells to more effectively eradicate cancer cells. This research laid the foundation for the clinical development of immune checkpoint inhibitors, which have dramatically improved outcomes for many people with cancer.

References

1- Lexi-comp: Drug information handbook, 2022 Ed.
2- Sean C. Sweetman. Martindale: The Complete Drug Reference, 38th Edition. Ph. Press
3- Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Ed.
4- Lippincott's Pharmacology, 7th Ed.

TOXICOLOGY

Chapter Seventeen: Toxicology

17.1- General care

17.2- Techniques for reducing the Toxicological effects

- **A.** Prevention of absorption
- **B.** Active elimination
- **C.** Hemodialysis
- **D.** Alkalization of the urine
- **E.** Removal from the GIT

17.3- Intoxications

1. Acute Intoxication of Ethyl Alcohol
2. Acute Intoxication of Methyl Alcohol (Methanol), Ethylene Glycol
3. Methemoglobinemia
4. Cocaine intoxication
5. Organophosphorous Poisoning
6. Inhaled Carbon Monoxide
7. Tear Gas intoxication
8. Cyanide Poisoning
9. Poisonous Bites
    a. Supportive measures
    b. Scorpion Bites
    c. Snake Bites
    d. Insect stings

17.4- Toxicity with Drugs

A. Anticoagulants
B. Atropine
C. Paracetamol
D. Salicylates (Aspirin and NSAIDs)
E. Benzodiazepines
F. Antidepressants
G. Opiates (opioids)
H. Digoxin
I. Beta-blockers
J. Calcium-channel blockers
K. Theophylline
L. Amphetamine and Related Drugs
M. Phenothiazines and Related Drugs
N. Iron salts

17.5- Chelation Agents

17.6- Monograph that Summarize Toxicology

Chapter Seventeen: Toxicology

Patients who have features of poisoning should generally be admitted to hospital, and Patients who have taken poisons with delayed action should also be admitted, even if they appear well, Delayed-action poisons include aspirin, iron, Paracetamol, tricyclic antidepressants, (Diphenoxylate + atropine); the effects of modified-release preparations are also delayed.

17.1- General care

It is often impossible to be certain of the identity of the poison and the size of the dose.

- Respiration

Respiration is often impaired in unconscious patients, an obstructed airway requires immediate attention, and an oropharyngeal or nasopharyngeal airway may be useful in patients with reduced consciousness to prevent obstruction, provided ventilation is adequate.

Intubation and ventilation should be considered in patients whose airway cannot be protected or who have respiratory acidosis because of inadequate ventilation.

Most poisons that impair consciousness also depress respiration, assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed.

Oxygen is not a substitute for adequate ventilation, although it should be given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

- Blood pressure

Hypotension is common in severe poisoning with central nervous system depressants.

A systolic blood pressure of less than 70 mmHg may lead to irreversible brain damage or renal tubular necrosis, Hypotension should be corrected initially by raising the foot of the bed and administration of an infusion of either sodium chloride or a colloid.

Fluid depletion without hypotension is common after prolonged coma and after aspirin poisoning due to vomiting, sweating, and hyperpnoea.

- Heart

Cardiac conduction defects and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines.

Arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities, but ventricular arrhythmias that causes serious hypotension require treatment, **Supraventricular arrhythmias are seldom life-threatening and drug treatment is best withheld** until the patient reaches hospital.

- Body temperature

Hypothermia may develop in patients of any age who have been deeply unconscious for some hours, particularly following overdose with barbiturates or Phenothiazines. It may be missed unless core temperature is measured using a low-reading rectal thermometer.

Hyperthermia can develop in patients taking CNS stimulants; children and the elderly are also at risk when taking therapeutic doses of drugs with Antimuscarinic properties. Hyperthermia is initially managed by removing all unnecessary clothing and using a fan. Sponging with tepid water will promote evaporation, both hypothermia and hyperthermia require urgent hospitalization for assessment and supportive treatment.

- Convulsions

Single short-lived convulsions (lasting less than 5 minutes) do not require treatment. If convulsions are protracted or recur frequently, **lorazepam 4 mg or diazepam (preferably as emulsion) 10 mg** should be given by slow intravenous injection into a large vein.

Benzodiazepines should not be given by the intramuscular route for convulsions. If the I.V. route is not readily available, **midazolam [unlicensed use] can be given by the buccal route or diazepam can be administered as a rectal solution.**

17.2- Techniques for reducing the Toxicological effects

A) Prevention of absorption:

By using **Activated Charcoal**, when given by mouth; it can bind many poisons in the gastro-intestinal system, thereby reducing their absorption, **the sooner it is given the more effective it is, but it may still be effective up to 1 hour after ingestion of the poison.**

- **Dose:** in adults **50 gm initially then 50 gm every 4 hours**, Vomiting should be treated (e.g. with an antiemetic drug) since it may reduce the efficacy of charcoal treatment.
- In cases of intolerance, **the dose may be reduced and the frequency increased** (e.g. 25 gm every 2 hours or 12.5 g every hour) but this may compromise efficacy.
- In children under 12 years of age, activated charcoal is given in a dose of 1 gm/kg (max. 50 gm) every 4 hours; the dose may be reduced and the frequency increased if not tolerated.

Scientific name	Dosage form	Trade name	concentration
Activated Charcoal	Granules	Carbomix®	50 gm/pack
	Oral Susp.	Charcodote®	1 gm/5 ml (100 ml)

B) Active elimination:

Repeated doses of activated charcoal by mouth enhance the elimination of some drugs after they have been absorbed; repeated doses are given after over dosage with: **Carbamazepine, Dapsone, Phenobarbital, Quinine and Theophylline.**

C) Hemodialysis

Generally used for ethylene glycol, lithium, methanol, phenobarbital, salicylates, and sodium valproate. And for severe cases of hyperkalemia.

D) Alkalization of the urine: (for acidic drugs such as salicylates)

E) Removal from the gastro-intestinal tract:

- **By Gastric lavage**, it's used for substances that cannot be removed effectively by other means, it may occasionally be considered in patients who have ingested drugs that are not adsorbed by charcoal (such as iron or lithium).
  - **It should be considered only if a life-threatening amount** has been ingested within the previous hour.
  - **It should be carried out only if the airway can be protected adequately.**
  - **It is contraindicated if a corrosive substance or a petroleum distillate** is ingested.

- **By Induction of emesis,** (e.g. with Ipecacuanha) is **not recommended** because there is no evidence that it affects absorption and **it may increase the risk of aspiration**.
  - **Dose:** 15 to 30 mL followed by 3 to 4 glasses of water.
  - May repeat dose within 20 min if vomiting does not occur.

Scientific name	Dosage form	Trade name	concentration
Ipecacuanha	Syrup	Ipecac®	30 ml

- **By Whole bowel irrigation** (by means of a bowel cleansing preparation), it has been used in poisoning with certain modified-release or enteric-coated formulations.

17.3- Intoxications:

1) Acute Intoxication of Ethyl Alcohol

Treatment:

- Stomach wash
- **Mild cases:** observation until recovery
- **Severe cases:**
  - Circulatory collapse: plasma expanders + positive Inotropics.
  - Hemodialysis is indicated in severe cases not responding to above treatment.
- Put on ventilator if signs of respiratory depressions persist in severe cases.
  - **Nikethamide Amp** (a CNS stimulant which mainly affects the respiratory cycle as a Respiratory stimulant) I.V. repeated as necessary
- **Glucose 20 % 500 ml** to correct hypoglycemia and ketoacidosis
- **Add insulin** if the patient is diabetic
- **Sod bicarbonate** 1.4% or 5% 500 ml to correct lactic acidosis
- **Thiamine** 25 mg Amp I.V daily. (Given to prevent Wernicke syndrome).

Scientific name	Dosage form	Trade name	concentration
Nikethamide	Amp	Coramina®	375 mg/1.5 ml , 500 mg/2 ml
Thiamine	Tab , Cap	Vit B_1®	50 mg , 100 mg
	Inj. (amp)		25 mg/ml , 100 mg/ml

2) Acute Intoxication of Methyl Alcohol (Methanol), Ethylene Glycol

Treatment:

- Stomach wash and Warm the patient.
- Sodium bicarbonate infusion (for acidosis): 5% 500 ml bottle.

Antidote:

- **Fomepizole** is the treatment of choice for Ethylene glycol and Methanol poisoning.
  - LD 15 mg/kg I.V infusion over 30 min, then 10 mg/kg I.V every 12 hr. for 4 doses, then 15 mg/kg every 12 hr.

- **Ethyl alcohol** which should be given early (inhibits alcohol dehydrogenase which converts methyl alcohol to its toxic metabolites).
  - 50 gm orally followed by 8 to 10 gm/hr. I.V. to produce blood Concentration of 1-2 gm/L
  - OR: 60 gm orally followed by 9 gm/15 minute (1 gm = 5 ml 20 % ethyl alcohol)
- **Folinic acid** 30 mg vial I.V. every 6 hours to protect against ocular toxicity.
- **Pyridoxine**, **Thiamine** I.V for Ethylene Glycol.
- **Hemodialysis: for severe cases** – Ethanol 1-2 gm added to 1 liter of dialysis fluid.

Scientific name	Dosage form	Trade name	concentration
Fomepizole	Inj. Solu.	Antizol®	1.5 gm/1.5 ml
Folinic acid	Inj. Solu	Leucovorin®	50 mg/ml

3) Methemoglobinemia

Drug (aniline, Dapsone) or chemical-induced Methemoglobinemia should be treated with **Methylthioninium chloride (Methylene blue)** if the methemoglobin concentration is 30% or higher, or if symptoms of tissue hypoxia are present despite oxygen therapy, **Methylthioninium chloride** reduces the ferric iron of methemoglobin back to the ferrous iron of hemoglobin.

In high doses, Methylthioninium can itself cause Methemoglobinemia.

- **Dose:** 1–2 mg/kg, repeated after 30–60 minutes if necessary, (max. cumulative dose per course 7 mg/kg.

Scientific name	Dosage form	Trade name	concentration
Methylene Blue	Inj.	Proveblue®	5 mg/ml (10 ml amp)

4) Cocaine intoxication

Symptoms: causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hyperthermia, hypertonia and hyperreflexia; cardiac effects include chest pain, myocardial infarction, and arrhythmias.

Treatment:

- Maintain airways - Put to ventilator if necessary.
- **cooling measures for hyperthermia**
- Convulsions: **Diazepam** Amp 10 mg I.V + **Phenytoin** Amp may be added
- **Propranolol** 1 mg Amp: 2-4 Amp I.V to control tachyarrhythmia

Scientific name	Dosage form	Trade name	concentration
Diazepam	Amp	Valium®	10 mg
Phenytoin	Amp	Epantuin®	50 mg/ml
Propranolol	Amp	Inderal®	1 mg/ml

5) Organophosphorus Poisoning

Symptoms:

Mild: Nausea, Vomiting, abdominal pain, Dizziness, irritability, hyper salivation and Bradycardia

Severe: Flaccid paralysis, including ocular and respiratory, pulmonary edema and copious secretions from mouth, Convulsions, Cyanosis, Hyperglycemia.

Treatment:

- Remove contaminated clothes & wash skin by soap and water to prevent further absorption from skin and Give the following:

B. **Atropine** (blocks receptors and reverse the Antimuscarinic effects): 2 mg (2 Amp) I.V at once, Repeat the same dose every 5- 10 minutes until signs of atropine side effects appear: dry mouth, dilatation of pupils – heart rate 70 to 80 bpm.

C. **Palidoxime** (Cholinesterase reactivator, to improve muscle tone): 1 gm vial, indicated in moderate to severe cases: 2 vials diluted with 10 – 15 ml water and given by slow I.V, Improvement in muscle power expected within 30 minutes

- Exact dose 30 mg/kg over 20 minutes, followed by 8 mg/kg/hour
- Continued until the patient has not required **Atropine** for 12 hours.
- Repeat if necessary, in severe cases: 1-2 doses.
- Maximum dose = 12 gm I.V. or I.M/ 24 hr.

- **Supportive measures**:
  - Convulsions: **Diazepam** Amp 10 mg I.V or I.M
  - Pulmonary edema: Oxygen inhalation – put to ventilator.

Scientific name	Dosage form	Trade name	concentration
Atropine	Tab	Atreza®	0.4 mg
	Amp	AtroPen®	1 mg/ml
Palidoxime	Inj. powder	Protopam®	1 gm/vial

6) Inhaled Carbon Monoxide

Carbon monoxide poisoning is usually due to inhalation of smoke, car exhaust, or fumes caused by blocked flues or incomplete combustion of fuel gases in confined spaces.

Treatment:

- Pure oxygen inhalation (100%)
- Put on ventilator if necessary
- Packed red cell transfusion
- **Mannitol** 10-20% + **Dexamethasone** 8 mg I.V **if cerebral edema is suspected**.

7) Tear Gas intoxication

Also called CS spray, which is used for riot control, irritates the eyes (hence 'tear gas') and the respiratory tract, which may lead to respiratory complications.

Treatment:

Symptoms normally settle spontaneously within 15 minutes.

- If symptoms persist, the patient should be removed to a well-ventilated area
- The exposed skin washed with soap and water after removal of contaminated clothing.
- The Eye should be treated by irrigating the eyes with physiological saline (or water if saline is not available).

8) Cyanide Poisoning

Treatment:

- Cardio-respiratory support, as necessary
- **Oxygen should be administered to patients with cyanide** poisoning (Pure oxygen).
- The choice of antidote depends on the severity of poisoning.
- **Dicobalt Edetate** is the antidote of choice when there is a strong clinical suspicion of severe cyanide poisoning, **But Dicobalt Edetate itself is toxic**, associated with anaphylactic reactions, and **is potentially fatal if administered in the absence of cyanide** poisoning.
- Regimen of **sodium nitrite** followed by **sodium thiosulfate** is an alternative if **Dicobalt Edetate** is not available.

Antidote:

- Kelocyanor® (**Dicobalt Edetate**) is the antidote of choice: 20 ml amp (300 mg) I.V over 1 min followed by 50 ml glucose 50%. Repeated if necessary.
- **Sodium nitrate**: 10 ml Amp I.V over 3 min followed by **sodium thiosulphate** 25 ml 50% given over 10 min. if Dicobalt Edetate is not available.
- **Amyl nitrate vitrille** inhalation: (Amp crushed)/12 sec for 2-3 min until the antidote is available.
- **Hydroxocobalamine** (Cyanokit®) can be considered for use in victims of smoke inhalation who show signs of significant cyanide poisoning.

Scientific name	Dosage form	Trade name	concentration
Dicobalt Edetate	Amp	Kelocyanor®	15 mg/ml (20 ml amp)
Sodium nitrate	Amp	Sodium nitrate®	30 mg/ml (10 ml amp)
Sodium thiosulphate	Amp	Sodium thiosulphate®	500 mg/mL
Amyl nitrate vitrille	Amp (inhale)	Amyl nitrate®	0.3 ml
Hydroxocobalamin	Inj. Powder	Cyanokit®	5 gm/vial

9) Poisonous Bites:

A) Supportive measures for Bites (Snake and Scorpion)

- Pain: **Tramadol** amp, if still persistent **Pethidine** 50 mg amp
- Nausea/Vomiting: **Largactil®** 50 mg amp I.V
- Shock: plasma or Dextran + Positive Inotropics (**Norepinephrine** 0.1 % Amp or **Dobutamine** infusion) + **Hydrocortisone** inj. I.V up to 200 mg.
- Bleeding tendency: Fresh blood or Plasma.

B) Scorpion Bites

Symptoms:

- **Local:** pain, swelling and tender enlargement of regional lymph nodes.
- **Systemic:** Ranging from early anaphylactic symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhea, and vomiting), with later persistent or recurrent hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure.

Treatment:

A. **Lidocaine 2%:** 2 ml injected at the site of the bite (immediate relief of pain).
B. Early anaphylactic symptoms should be treated with Adrenaline (epinephrine)
C. To **delay absorption of the poison**: Press firmly on site of bite, and Immobilize limb with a splint.
D. **Antidote**: **Anti-scorpion serum Vial (Anascorp®)**:

- 3 vials added to 50-100 ml 0.9% Normal Saline and infused I.V slowly over 10 min.
- From 3 to 10 vials may be required to neutralize the poison.
- Hypersensitivity reactions are very common: One Amp adrenaline may be given S.C as prophylaxis, if reactions appear another amp of adrenaline + 2 amp 100 mg hydrocortisone added to solution.

C) Snake Bites

Symptoms:

- **Local:** pain, swelling and tender enlargement of regional lymph nodes.
- **Systemic:** Ranging from early anaphylactic symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhea, and vomiting), with later persistent or recurrent hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure.

Treatment:

A. **Lidocaine 2%:** 2 ml injected at the site of the bite (immediate relief of pain).
B. Early anaphylactic symptoms should be treated with **Adrenaline (epinephrine)**
C. To **delay absorption of the poison**: Press firmly on site of bite, and Immobilize limb with a splint.
D. **Antidote:**

- **Anti-snake venom (Favirept®):** 10 ml amp, Start with 2 Amp added to 250 ml 0.9% Normal Saline – 5% Glucose and infused I.V slowly over 10 min.
- From 2 to 10 Amp may be required to neutralize the poison.
- Hypersensitivity reactions are very common: One Amp adrenaline may be given S.C as prophylaxis, if reactions appear another amp of adrenaline + 2 amp 100 mg hydrocortisone added to solution.

D) Insect stings

Stings from ants, wasps, hornets, and bees cause local pain and swelling but seldom cause severe direct toxicity unless many stings are inflicted at the same time.

Treatment:

- Anaphylactic reactions require immediate treatment with I.M **Adrenaline (epinephrine)**
- A short course of an **oral antihistamine** or a **topical corticosteroid** may help to reduce inflammation and relieve itching.
- **A vaccine** containing extracts of bee and wasp venom can be used to reduce the risk of anaphylaxis and systemic reactions in patients with systemic hypersensitivity to bee or wasp stings.

17.4- Toxicity with Drugs

A) Anticoagulants

Treatment:

- Stop drugs given
- Oral anticoagulants: **Vit. K amp** 10 - 50 mg I.V slowly.
- Heparin antidote: **Protamine Sulphate** 50 mg I.V Slowly.

Scientific name	Dosage form	Trade name	concentration
Vit. K	Amp	Phytonadione®	2 mg/ml , 10 mg/ml
	Tab		100 mcg , 5 mg
Protamine Sulphate	I.V Solu.	Protamine®	10 mg/ml (10 ml amp)

B) Atropine intoxication

Treatment:

- Follow stomach lavage with **sodium Sulphate** 30 g in 200 ml water.
- Fever and hyperthermia: apply cold water and ice bags.
- If Severe tachycardia: **Neostigmine** 2.5 mg I.V. very slowly over 10 min with ECG monitoring.

Scientific name	Dosage form	Trade name	concentration
Neostigmine	Inj. Solu.	Prostigmin® , Bloxiverz®	0.5 mg/ml , 1 mg/ml , 2.5 mg/ml
	Tab		15 mg

C) Paracetamol

The Main fear is liver necrosis, **N-Acetylcysteine** and **Methionine** protect the liver if given in 10 -12 hrs., Liver damage is maximal 3-4 days after Paracetamol overdose and may lead to encephalopathy, hemorrhage, hypoglycemia, cerebral edema, and death.

- Hepatotoxicity may occur after a single ingestion of more than 150 mg/kg Paracetamol taken in less than 1 hour.

Treatment:

- **Acetylcysteine (also called Cysteamine)** is given in a total dose (based on patient weight) that is divided into 3 consecutive I.V infusions over a total of 21 hours.
  - **1st dose:** loading dose 150 mg/kg, infused in 1 hour with 200 ml D5W.
  - **2nd dose:** 50 mg/kg, in 500 ml D5W over 4 hours.
  - **3rd dose:** 100 mg/kg in 1000 ml D5W over 16 hours.
  - **Maybe administered orally,** as 140 mg/kg loading dose, then 70 mg/kg every 4 hours for 17 doses.
- Hepsan® (**acetyl methionine**) Amp/4 hours, Repeat for 4 doses.
- **Methionine** 250 mg tab: 10 Tab (2.5 gm) ingested/4 hours for 12 hrs.)

Scientific name	Dosage form	Trade name	concentration
Acetylcysteine	Inj. Solu.	Parvolex®	200 mg/ml (10 ml amp)
Acetyl Methionine	Amp	Hepsan®	10 ml amp
Methionine	Tab	Methon ®	250 mg

D) Salicylates (Aspirin and NSAIDs)

Symptoms: Hyperventilation, Tinnitus, deafness, Vasodilatation and Sweating.

Treatment:

- Stomach Wash: in all cases (mild and severe) even after the lapse of several hours.

Mild cases:

- High intake of oral fluids + activated charcoal and Observe for 12 – 24 hours

Severe cases: When serum salicylates is greater than 50 mg/dl (in adults), 30 mg/dl (in children)

- Forced alkaline diuresis to reach urine PH more than 8
- 50 gm **Activated charcoal** (charcoal or ultracarbon) 0.25 gm tab every 4 hrs.
- Convulsions: **Diazepam** 10 gm Amp
- **Vit. K** 10 mg I.V to prevent hypoprothrombinemia.

Very severe: when plasma-salicylate concentration exceeds 70 mg/dl, with failure of the above-mentioned measures or development of cerebral edema or renal failure = **peritoneal dialysis or hemodialysis.**

E) Benzodiazepines

Symptoms: Drowsiness, Weakness, ataxia, Respiratory depression, nystagmus, Hypotension, hypothermia and Coma

Treatment:

- **Activated charcoal** can be given within 1 hour of ingesting.
- **Stomach wash** in all cases

Mild cases: Recovery without specific treatment, discharge after a short period of obs.

Severe cases:

- Oxygen in high concentrations
- Insert an endotracheal tube (allows suction of mucus) + ready to connect to a mechanical ventilator if cyanosis is not relived.
- Hypotension: raise foot of bed + **Dopamine** Amp I.V Infusion

Antidote: Flumazenil 0.5 mg Amp given in increasing doses of 0.2 – 0.3 – 0.5 mg at 1 min intervals until a good response is obtained or a total dose of 3 to 5 mg is given.

- **VIP Note: Flumazenil can be hazardous**, particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients. Flumazenil may prevent the need for ventilation, particularly in patients with severe respiratory disorders; **thus, it should be used on expert advice only.**

Scientific name	Dosage form	Trade name	concentration
Flumazenil	Amp	Romazicon®	0.1 mg/ml (5 ml amp)

F) Antidepressants

Symptoms:

- Anti-cholinergic manifestations: fever, Mydriasis flushing, retention of urine, decreased bowel motility
- CNS manifestation: restlessness, myoclonus, confusion, convulsions, coma.
- Cardiac manifestation: A-V blockade, cardiac arrhythmias
- Delirium with confusion, agitation, and visual and auditory hallucinations are common during recovery.

Treatment: (Essentially supportive measures)

- Stomach wash is followed by activated charcoal with cathartics / 2-4 hours.
- CNS manifestation: **Neostigmine** Amp 2 mg I.V very slowly over 2 minutes.
- Convulsions: **Diazepam** 10 mg Amp , or **Lorazepam** 1 mg amp
- Cardiac manifestation :Arrhythmias = **Lignocaine** infusion.
- Hypotension = **Dopamine** infusion
- **Hemodialysis has no effect because of the large V_d of these drugs.**

G) Opiates (opioids) Intoxication

Symptoms: Drowsiness, Respiratory depression and Pin-point pupil.

Also has cardio-toxic effects which may require treatment with sodium bicarbonate, or magnesium sulfate, or both; arrhythmias may occur for up to 12 hours.

Treatment: Antidote:

A. Naloxone:

- 1 to 3 Amp (0.8 mg amp) I.V every 5 minutes until evident of clinical response or until 12 Amp (9.6 mg) has been given, Effect lasts 1-4 hrs.
- Do not exceed 10 mg.
- Repeat within 1 to 4 hours if signs of toxicity (papillary constriction, depression of respiration) still persist.

B. Naltrexone:

It's approved only for opioid dependence and Alcohol dependence (not used in Opioids toxicity).

Scientific name	Dosage form	Trade name	concentration
Naloxone	Amp	Narcan®	400 mcg/ml (2 ml amp)
	Amp	Prenoxad®	1 mg/ml (2 ml amp)
	Auto-Inj.	Evzio®	0.4 mg/0.4 ml

H) Digoxin

Mild cases: Nausea + Ectopic beats

- **Potassium Chloride** orally: Potassium syrup: 1 teaspoonful x 3 day or slow Potassium tab for 2 days.

More severe cases: Persistent vomiting, confusion, heart block (all degrees) or arrhythmia (all types), vision disturbances

Potassium changes:

- Hyperkalemia occurs with acute intoxication
- Hypokalemia is common with chronic intoxication

Treatment:

- Discontinue drug

-**If there is hyperkalemia**:

- 500 ml glucose 25 % + insulin soluble 30 Units
- **Kayexalate®** (sodium polystyrene) A Cation-Exchange Resin, (it act by enhancing excretion of potassium ions), dose 15 gm orally 1-4 times daily, or 30-50 gm rectally.

- **If there is hypokalemia:**

- KCL 0.2% in 5 % dextrose (500 ml) infused over 1 hour with continuous ECG monitoring, stop drip immediately if sinus rhythm is restored, or if peaking of T waves returns to normal.
- Repeat if necessary up to 1 gm potassium chloride.

- Severe cases of Digoxin Toxicity:

- **Digoxin antibodies** 40 mg vials: Empiric dosing for acute poisoning 10 -20 vials in both adults and children, Empiric dosing for chronic poisoning adults 3-6 vials, while children 1-2 vials only.
- **Propranolol** 1 mg Amp I.V (to counteracts ectopic beats and tachycardia), Repeated if necessary
- **Atropine** 1 mg Amp I.V (to counteract bradycardia).

Scientific name	Dosage form	Trade name	concentration
Sodium Polystyrene	Oral powder	Kayexalate®	453.6 gm (total)
	Rectal Susp.		15 gm/60 ml
Digoxin antibodies	Vail (Solu.)	DigiBind®	38 mg , 40 mg

I) Beta-blockers

Symptoms: light headedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. **Propranolol over dosage in particular may cause coma and convulsions.**

Treatment:

- Bradycardia: I.V Inj. of **Atropine** (3 mg for an adult, 40 mcg/kg (max. 3 mg) for a child).
- Convulsions: **Diazepam** 10 mg Amp , or **Lorazepam** 1 mg amp
- **Insulin 30 units and 5% glucose 500 ml infusion** may be required in the management of hypotension and myocardial failure.
- **Glucagon** 2-10 mg in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an I.V infusion of 50 mcg/kg/hour.

Scientific name	Dosage form	Trade name	concentration
Glucagon	Vial (powder)	GlucaGen®	1mg/vial

J) Calcium-channel blockers

Symptoms: nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycemia may occur.

Treatment:

- **Activated charcoal** should be considered if the patient presents within 1 hour, repeated doses of activated charcoal are considered for a modified-release preparation.
- **Calcium chloride** inj. or **Calcium gluconate** inj.
- **Atropine** is given to correct symptomatic bradycardia.
- **Insulin 30 units and 5% glucose 500 ml infusion** may be required.
- **Glucagon** 2-10 mg in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an I.V infusion of 50 mcg/kg/hour.

K) Theophylline

Symptoms: vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycemia.

More serious effects are hematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalemia may develop rapidly.

Treatment:

- Repeated doses of **activated charcoal** can be used to eliminate theophylline even if more than 1 hour has elapsed after ingestion.
- **Ondansetron** as an antiemetic.
- Hypokalemia is corrected by I.V infusion of **Potassium Chloride (KCL)** and may be so severe as to require 60 mmol/hour (high doses require ECG monitoring).
- Convulsions should be controlled by I.V administration of **Lorazepam** or **Diazepam.**
- If the patient does not suffer from asthma, a **short-acting beta-blocker** can be administered I.V to reverse severe tachycardia, hypokalemia, and hyperglycemia.

L) Amphetamine and Related Drugs

Symptoms:

- Moderate: wakefulness, excessive activity, paranoia, hallucinations, hypertension, Insomnia and Hallucinations.
- Severe: exhaustion, convulsions, hyperthermia, and coma.

Treatment:

a. The early stages can be controlled by **Diazepam** or **Lorazepam**

b. Largactil® (**Chlorpromazine**) + Inderal® (**Propranolol**) 1 mg Amp

c. **In severe Cases:** Epantuin® (**phenytoin**) Amp + ice packs + artificial ventilator may be needed, also **acid diuresis to help excretion**.

M) Phenothiazines and related drugs

Symptoms: Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. Dystonic reactions can occur with therapeutic doses (particularly with Prochlorperazine and Trifluoperazine), and convulsions may occur in severe cases.

Treatment:

- Arrhythmias may respond to correction of hypoxia, acidosis.
- Dystonic reactions are rapidly abolished by injection of drugs such as **Procyclidine** or **Diazepam 10 mg amp.**

N) Iron salts

Symptom: nausea, vomiting, abdominal pain, diarrhea, hematemesis, and rectal bleeding. Hypotension and hepatocellular necrosis can occur later, Coma, shock, and metabolic acidosis indicate severe poisoning.

Treatment:

- **I.V. Deferoxamine** given to chelate absorbed iron in excess of the expected iron binding capacity, dose 15 mg/kg/hour, reduced after 4–6 hours; max 80 mg/kg in 24 hours.

Scientific name	Dosage form	Trade name	concentration
***Deferoxamine** **	Inj. powder	Desferal®	500 mg , 2 gm (vial)
Desferiprone	Tab, Oral Solu.	Ferriprox®	500 mg (tab) , 100 mg/ml
Deferasirox	Tab	Exjade®	125 mg , 250 mg , 500 mg
	Tab	Jadenu®	90 mg , 180 mg , 360 mg

*** Deferoxamine = Desferrioxamine,** they are the same drug.

* **Deferiprone = Desferiprone,** they are the same drug.

17.5- Chelation Agents

Chelators are drugs that will form covalent bonds with cationic metals, the chelator-metal complex is then excreted in urine, thereby greatly facilitating the excretion of the heavy metal. Unfortunately, Chelators are not specific to heavy metals, and essential metals, such as zinc, often can also be chelated, additionally, some Chelators have potentially serious adverse effects themselves, and their use in treatment of heavy metal intoxication is undertaken only when the benefits of chelation therapy outweigh the associated risks.

1. **Dimercaprol** used by itself to **chelate mercury and arsenic** and **in combination with Edetate calcium disodium to treat lead intoxication**. It is **not effective orally** and is usually given I.M., its **use is limited by its capacity to increase blood pressure and heart rate.**
2. **Succimer** (dimercaptosuccinic acid) is a derivative of Dimercaprol that is **effective upon oral administration**, a second advantage of Succimer over Dimercaprol is **the lack of increased blood pressure and heart rate during treatment**. Some elevation of serum levels of hepatic enzymes can be observed with Succimer treatment; Succimer is currently approved for **treatment of lead intoxication**, but may be effective in chelation of other metals as well.
3. **Edetate calcium disodium** is used primarily for **treatment of lead intoxication**, but it can also be used for poisoning by other metals. It is **not effective orally** and is given I.V or I.M., it can cause renal damage that is reversible upon cessation of the drug.

Scientific name	D. form	Trade name	concentration
Dimercaprol	Inj. Solu.	BAL®	100 mg/ml
Succimer	Cap	Chemet®	100 mg
Edetate Calcium Disodium	Inj. Solu	Versenate®	200 mg/ml
Pentetate Zinc Trisodium	Inj. Solu.	Zn DTPA®	1gm/5 ml

17.6- Monograph that Summarize Toxicology

Common Drugs and Antidotes

Antidote	Indication	Mode of Action
acetylcysteine (Mucomyst)	Acetaminophen/ Tylenol/ Paracetamol	Restores depleted glutathione stores and protects against renal and hepatic failure.
Activated charcoal	Non-specific poisons except cyanide, iron, lithium, caustics and alcohol.	Absorption of drug in the gastric and intestinal tracts. Interrupts the entero-hepatic cycle with multiple dose.
albuterol inhaler, insulin & glucose, $NaHCO_3$, kayexalate	Potassium	
anticholinesterase agents	Neuromuscular blockade (paralytics)	
atropine sulfate or pralidoxime	Anticholinesterase	Competitive inhibition of muscarinic receptors.
Benzylpenicillin	Amanita phalloides (Death cap mushroom)	Not known; partial protection against acute hepatic failure; may displace amatoxin from protein-binding sites allowing increased renal excretion; may also inhibit penetration of amatoxin to hepatocytes.
Calcium salts	Fluoride ingestion	Rapidly complexes with fluoride ion.
deferoxamine	Iron	Deferoxamine acts by binding free iron in the bloodstream and enhancing its elimination in the urine.
digibind digoxine immune fab	Digoxin	Binds molecules of digoxin, making them unavailable for binding at their site of action on cells in the body.
dimercapol, edetate calcium, disodium,	Lead	Chelation of lead ions and endogenous metals (e.g., zinc, manganese, iron, copper).
diphenhydramine (Benadryl)	Extrapyramidal symptoms (EPS)	A potent antagonist to acetylcholine in muscarinic receptors.
flumazenil	Benzodiazepines	Reverses the effects of benzodiazepines by competitive inhibition at the benzodiazepine binding site on the $GABA_A$ receptor.
fomepizole	Ethylene glycol	A competitive inhibitor of the enzyme alcohol dehydrogenase found in the liver. This enzyme plays a key role in the metabolism of ethylene glycol and methanol.
glucagon	Beta blockers and calcium channel blockers	Stimulates the formation of adenyl cyclase causing intracellular increase in cycling AMP and enhanced glycogenolysis and elevated serum glucose concentration.
Glucose (Dextrose 50%)	Insulin reaction	Dextrose (the monosaccharide glucose) is used, distributed and stored by body tissues and is metabolized to carbon dioxide and water with the release of energy.
Heparin	Ergotamine	Reverses hypercoagulable state by interacting with antithrombin III. Used in combination with vasodilator phentolamine or nitroprusside to prevent local thrombosis and ischemia.
Hydroxocobalamin	Cyanide	Forms cyanocobalamin, a non-toxic metabolite that is easily excreted through the kidneys.
leucovorin calcium	Fluorouracil	
	Methotrexate	Protects the healthy cells from the effects of methotrexate while allowing methotrexate to enter and kill cancer cells.

2 sna	Cyclophosphamide	A "chemoprotectant" drug that reduces the undesired effects of certain chemotherapy drugs.
Methylene blue	Chemical producing severe methemoglobinemia. Ifosamide-induced encephalopathy.	Reduces methemoglobin to hemoglobin.
nalmefene or naloxone	Opioid analgesics	Prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension.
naloxone (Narcan)	Narcotics	Naloxone is believed to antagonize opioid effects by competing for the μ, κ and σ opiate receptor sites in the CNS, with the greatest affinity for the μ receptor.
Neostigmine	Anticholinergics	Anticholinesterase which causes accumulation of acetylcholine at cholinergic receptor sites.
Nitrite, sodium and glycerytrinitrate	Cyanide	Oxidizes hemoglobin to methemoglobin which binds the free cyanide and can enhance endothelial cyanide detoxification by producing vasodilation.
Penicillamine	Copper, gold, lead, mercury, zinc, arsenic	Chelation of metal ions.
phentolamine (Regitine)	Dopamine	Regitine produces an alpha-adrenergic block of relatively short duration. It also has direct, but less marked, positive inotropic and chronotropic effects on cardiac muscle and vasodilator effects on vascular smooth muscle.
phyostigmine or $NaHCO_3$	Tricyclic antidepressants	A reversible anticholinesterase which effectively increases the concentration of acetylcholine at the sites of cholinergic transmission.
Phytomenadione (Vitamin K.)	Coumadin/Warfarin	Bypasses inhibition of Vitamin K epoxide reductase enzyme.
protamine sulfate	Heparin	Protamine that is strongly basic combines with acidic heparin forming a stable complex and neutralizes the anticoagulant activity of both drugs.
Pyridoxine	Isoniazid, theophylline, monomethyl hydrazine. Adjunctive therapy in ethylene glycol poisoning.	Reverses acute pyridoxine deficiency by promoting GABA synthesis. Promotes the conversion of toxic metabolite glycolic acid to glycine.
Snake anti-venin	Cobra bite	Neutralizes venom by binding with circulating venom components and with locally deposited venom by accumulating at the bite site.
Sodium Bicarbonate	Iron	Prevents convertion of ferrous to ferric.
	Cardiotoxic drug affecting fast sodium channel (TCA, cocaine)	Decreases affinity of cardiotoxic drugs to the fast sodium channel.
	Weak acids	Promotes ionization of weak acids.
	Chlorine gas inhalational poisoning	Neutralization of hydrochloric acid formed when chlorine gas reacts with water in the airways.
Sodium thiosulphate	Cyanide	Replenishes depleted thiosulphate stores by acting as sulfur donor necessary for the conversion of CN-O to thiocyanate through the action of sulfur transferase enzyme rhodanese.
Thiamine	Alcohol, Wernicke-Korsakoff Syndrome	Reverses acute thiamine deficiency
	Adjunctive in ethylene glycol	Enhances detoxification of glyoxylic acid.
Vitamin C	Chemicals causing methemoglobinemia in patients with G6PD deficiency	Reduces methemoglobin to hemoglobin.

References:

1- Lippincott's pharmacology 7 Ed .
2- Lexi-comp: Drug information handbook, 2022 Ed.
3- Goldfrank's Toxicological Emergencies, 10th Ed.

MISCELLANEOUS TOPICS

Chapter Eighteen: Miscellaneous Topics

First: Smoking Cessation

Second: Anesthetics and related drugs

1. I.V Anesthetics
2. Inhalational Anesthetics
3. Nitrous Oxide
4. Neuromuscular blocking drugs
   a. Depolarizing Neuromuscular Blockers
   b. Non-Depolarizing Neuromuscular Blockers
5. Drugs for reversal of neuromuscular blockade

Third: Appetite stimulants

Fourth: Obesity and weight reducing agents

Fifth: Vitamins, Medical Supplements

1. Minerals and Electrolytes
2. Vitamins
3. Multivitamin preparations

Sixth: Medical Dried Milk

Chapter Eighteen: Miscellaneous Topics

First: Smoking Cessation

1. An average cigarette yields about 2 mg of absorbed nicotine, which **act as a stimulant and improves attention**, high amounts (50–100 mg) can be very harmful.
2. The **stimulant effect** is the major contributing factor to the addictive properties of tobacco smoking, it also **causes feelings of relaxation, sharpness, calmness,** and **alertness**.
3. It also **reduces the appetite** and **raise the metabolism**; thus, some smokers may lose weight.
   - **Nicotine is associated with cardiovascular disease**, it increases blood pressure and heart rate, and can also induce potentially atherogenic genes in human coronary artery endothelial cells, it elevates serum cholesterol levels, supports clot formation, and aids in plaque formation by enhancing vascular smooth muscle.
   - **Abrupt and sudden cessation of smoking has worst effects than smoking itself**; thus, a gradual cessation is always recommended.
4. Treatment approaches include: **Nicotine replacement therapy** (NRT), **Bupropion**, and **Varenicline** are effective aids to smoking cessation.
   - Nicotine replacement therapy should be started 2 weeks after a cardiovascular event (such as acute coronary syndrome); sudden cessation of smoking cause CVS deteriorations.
5. **Smoking cessation** is the **most important** therapeutic intervention for **COPD** and **Asthma**.

A) Bupropion

1. Bupropion is an **antidepressant drug**, a weak norepinephrine dopamine reuptake inhibitor [(1)].
2. For smoking cessation, treatment should be **started about 1 to 2 weeks before the patient attempts to stop smoking**, to allow steady-state blood levels of bupropion to be reached, and normally continues for 7 to 12 weeks; if there is no significant progress towards smoking abstinence by the seventh week, then therapy should be stopped.
3. Should not be prescribed for patients with epilepsy, (it **lowers the seizure threshold**).

B) Varenicline

1. Varenicline is a **selective nicotinic receptor partial agonist** that is used as an aid for smoking cessation, Patients are advised to set a date to stop smoking and **start Varenicline 1 to 2 weeks before**; Treatment is normally given for 12 weeks.
2. In patients who successfully stop smoking, a further 12 weeks of treatment has been recommended to reduce the risk of relapse.

C) Nicotine replacement therapy (NRT)

1. **The first-line pharmacological intervention is NRT**.
2. NRT is available in numerous formulations: chewing gum, transdermal patches, inhalators, nasal sprays, sublingual tablets, and lozenges.
3. Choice of formulation is based on patient preference, tolerance, and previous treatments:
   a. The **transdermal patch is easiest to use and compliance is greatest** with this route but local effects may be troublesome.
   b. The **gum** has an unpleasant taste initially and some find the chewing action difficult.
   c. The **sublingual tablet** may be useful for those who have difficulty chewing the gum.
   d. The **nasal spray has a fast onset of action** but may cause local irritation.
   e. The **inhalator has the advantage of simulating cigarette smoking** but may cause local irritation of the mouth and throat.
   f. The **lozenges** have the advantage that it can be sucked discreetly.
4. **NRT for is usually continued for about 3 months before being withdrawn**.

Scientific name	Dosage form	Trade name	concentration
Bupropion	Tab	Wellbutrin® , Zyban®	150 mg , 300 mg
Varenicline	Tab	Champix® , Chantix®	0.5 mg , 1 mg

Second: Anesthetics and related drugs

- Several types of drug are given together during general anesthesia, which usually contain 2 steps, **induced phase and maintenance phase**.
  - **Anesthesia is induced** with either a volatile drug given by inhalation or with an IV administered drug.
  - **Anesthesia is maintained** with an IV or inhalational anesthetic.
  - **Analgesics**; usually short-acting opioids, are also used.
  - **Neuromuscular blocking drugs** used in anesthesia are also known as muscle relaxants, by specific blockade of the neuromuscular junction they enable light anesthesia to be used with adequate **relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and allow the passage of a tracheal tube.**
  - **Antimuscarinic drugs** are used (less commonly nowadays) as pre-medications to **dry bronchial and salivary secretions** which are increased by intubation, upper airway surgery, or some inhalational anesthetics.
  - **Antimuscarinics** are also used before or with **Neostigmine** to prevent bradycardia, excessive salivation, and other muscarinic actions of **Neostigmine**, and also used to prevent bradycardia and hypotension associated with drugs such as **Propofol** and **Suxamethonium.**

1) I.V Anesthetics

- May be used either to induce anesthesia or for maintenance of anesthesia throughout surgery, they can cause apnea and hypotension, and so adequate resuscitative facilities must be available when giving them to patients.

A) Propofol, can be used in adults and children, but it is not commonly used in neonates, it is associated with rapid recovery and less hangover effect than other IV anesthetics, it causes pain on I.V injection (which can be reduced by IV lidocaine).

- **Onset of action is 30-40 seconds** of IV injection, duration about 5-10 minutes.
- Has a **direct anti-emetic effect**.
- It Has a **full recovery** characteristics profile.

B) Thiopental sodium is a barbiturate that is used for induction of anesthesia, but has no analgesic properties, dose related cardiovascular and respiratory depression can occur.

- **Thiopental** Along with **Pancuronium** and **KCL**, is used to execute prisoners by lethal injection, (Cause death without pain).

C) Etomidate have a rapid recovery without a hangover effect, it causes less hypotension than **thiopental** and **Propofol** during induction.

- Onset of action is 30-60 seconds of IV injection.
- **Etomidate suppresses adrenocortical function,** particularly during continuous administration, thus it should not be used for maintenance of anesthesia.
- **Has the most stable cardiovascular profile,** associated with minimal CVS depression, thus; preferred in patients with cardiovascular dysfunction.

D) Ketamine causes less hypotension than thiopental and Propofol during induction, **it is used mainly for pediatric anesthesia**, the main disadvantage of **ketamine** is the high incidence of hallucinations, nightmares, and other transient psychotic effects.

- **Doesn't cause respiratory depression, useful in asthmatic patient.**
- **Produce a dissociative stare** (eyes are open but the patient doesn't respond).

Scientific name	Dosage form	Trade name	concentration
Etomidate	Inj.	Hypnomidate®	2 mg/ml (10 ml amp)
Ketamine	Inj.	Ketalar®	10 mg , 50 mg , 100 mg (per ml)
Propofol	Inj.	Diprivan®	1% (10 mg/ml) , 2% (20 mg/ml)
Fospropofol	Inj.	Lusedra®	35 mg/ml (30 ml Vial)
Thiopental sodium *	Inj. powder	Thiopental®	500 mg/vial

*** Thiopental = Thiopentone, they are the same drug.**

2) Inhalational Anesthetics

- These include gases and volatile liquids; Gaseous anesthetics require suitable equipment for storage and administration; Volatile liquid anesthetics are administered using calibrated vaporizers, using air, oxygen, or nitrous oxide-oxygen mixtures as the carrier gas, **to prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times.**
- Higher concentrations of oxygen (greater than 30%) are usually required during inhalational anesthesia when nitrous oxide is being administered.
- **Volatile liquid anesthetics** can **trigger malignant hyperthermia** and are contra-indicated in those susceptible to malignant hyperthermia; They can **increase cerebrospinal pressure** and should be used with caution in those with raised intracranial pressure.
    a. **Isoflurane** is the preferred inhalational anesthetic **for use in obstetrics**.
    b. **Desflurane** have about one-fifth the potency of **Isoflurane,** it is not recommended for induction of anesthesia as it is irritant to the upper respiratory tract.
    c. **Sevoflurane** is more potent than **Desflurane**, and it is non-irritant and is therefore often used for inhalational induction of anesthesia

Scientific name	Dosage form	Trade name	concentration
Isoflurane	Inhale Solu.	Forane®	100 ml , 250 ml
Desflurane	Inhale Solu.	Suprane®	240 ml
Sevoflurane	Inhale Solu.	Ultane®	100%
Enflurane	Inhale Solu.	Ethrane®, CMPND 347®	125 ml , 250 ml

3) Nitrous Oxide (N_20)

- Commonly Known as **Laughing gas** (due its euphoretic effect when inhaled), Nitrous oxide is used for **maintenance of anesthesia** and in sub-anesthetic concentrations **for analgesia**.
- For anesthesia, **nitrous oxide** is commonly used in a concentration of 50-66% in oxygen as part of a balanced technique in association with other inhalational or intravenous agents, **for analgesia** (without loss of consciousness), a mixture of nitrous oxide and oxygen containing 50% of each gas (Entonox®, Equanox®) is used.
- **Nitrous oxide** should not be given continuously for longer than 24 hours or more frequently than every 4 days without close supervision and hematological monitoring (prolonged exposure may cause megaloblastic anemia).

4) Neuromuscular blocking drugs

- These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular endplate of skeletal muscle.
- They enable light anesthesia to be used with adequate **relaxation of the muscles of the abdomen and diaphragm**, they also relax the vocal cords and **allow passage of a tracheal tube.**
- **Classified into Depolarizing (Agonist) and Non-Depolarizing (Antagonist).**

A) Depolarizing Neuromuscular Blockers:

- **Succinylcholine (or Suxamethonium)** is the only depolarizing muscle relaxant in use today, all other family members are discontinued, it is more resistant to degradation by AChE, and can thus more persistently depolarize the muscle fibers.
    - Because of its **rapid onset** and **short duration** of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia.
    - It is also used during electroconvulsive shock treatment.
    - Can **trigger malignant hyperthermia**.
    - **Cause Hyperkalemia** and **Apnea**.

Scientific name	Dosage form	Trade name	concentration
Succinylcholine	Amp	Anectine®	50 mg/ml (2 ml amp)

*** Succinylcholine = Suxamethonium, they are the same drug.**

B) Non-Depolarizing Neuromuscular Blockers

- These drugs compete with acetylcholine for receptor sites at the neuromuscular junction and their action can be reversed with anticholinesterases such as **Neostigmine,** they have a **slower onset** of action than **Succinylcholine,** they have **no sedative or analgesic effects** and are **not considered to trigger malignant hyperthermia.**
- **All have intermediate duration of action,** except **Pancuronium** (has a long duration of action), and **Mivacurium** (has a short duration of action).

1. **Atracurium** has a **high cardiovascular side effects profile** and it's **associated with significant histamine release**.
2. **Cisatracurium** is **more potent** and has a **slightly longer duration** of action than **Atracurium** and provides greater cardiovascular stability because **Cisatracurium** lacks histamine-releasing effects.
3. **Rocuronium** exerts an effect **within 2 minutes** and has **the most rapid onset.**

Note: Cisatracurium and **Vecuronium** are devoid of clinically significant cardiovascular effects and are the **agents of choice for patients with unstable cardiovascular profiles**.

Scientific name	Dosage form	Trade name	concentration
Atracurium	Amp	Tracrium®	10 mg/ml (2.5 ml , 5 ml amp)
	Vial		10 mg/ml (25 ml vial)
Cisatracurium	Amp	Nimbex®	2 mg/ml (10 ml amp)
	Vial	Nimbex Forte®	5 mg/ml (30 mlvial)
Mivacurium	Amp	Mivacron®	2 mg/ml (5 ml , 10 ml amp)
Pancuronium	Amp	Pavulon®	2 mg/ml (2 ml amp)
Rocuronium	Vial	Esmeron®	10 mg/ml (5 ml , 10 ml vial)
Vecuronium	Vial (powder)	Norcuron®	10 mg/vial

Note: An important point to remember is that **neuromuscular blocking agents have no known effect on consciousness or pain threshold.**

5) Drugs for reversal of neuromuscular blockade

There are 3 drugs available for this purpose: **Neostigmine, Pyridostigmine** and **Sugammadex**.

a. **Neostigmine (Acetylcholinesterase inhibitor)** is used specifically for reversal of non-depolarizing (competitive) blockade. It acts within one minute of IV injection and its effects last for 20 to 30 minutes; a second dose may then be necessary.

b. **Pyridostigmine** is a pro-drug of **Neostigmine.**
- **Glycopyrronium** or **Atropine** given before or with **Neostigmine and Pyridostigmine** to prevent bradycardia, excessive salivation, and other muscarinic effects of those drugs.

c. **Sugammadex** (selective relaxing binding agent) can be used for rapid reversal of neuromuscular blockade induced by **Rocuronium** or **Vecuronium** (used mainly for rapid reversal of neuromuscular blockade in an emergency).

Scientific name	Dosage form	Trade name	concentration
Neostigmine	Inj. Solu.	Prostigmin® , Bloxiverz®	0.5 mg/ml , 1 mg/ml , 2.5 mg/ml
	Tab		15 mg
Pyridostigmine	Inj. Solu.	Mestinon®	5 mg/ml
	Tab		60 mg , 180 mg (CR tab.)
Sugammadex	Amp	Bridion®	100 mg/ml (2 ml , 5 ml amp)
Combination products			
Neostigmine + Glycopyrronium	Amp	Glyco-Prostigmin®	(2.5 mg + 500 mcg)/ml (1 ml amp)

Third: Appetite stimulants

- There are several appetite stimulants available worldwide, **only those below has a scientific support as an appetite stimulant**; all other claimed stimulants are not recommended to be used, especially those herbal combinations or local made combinations
  - **Local made combinations can be very harmful** since some contain a large amount of Dexamethasone, Cyproheptadine and starch.
- Some tries to gain weight throw using Proteins and amino-acids formulas (which are made for Body-Building Athletes) without going to the Gym or even training, such behavior can be harmful since the body's intake of energy is much more than its usage, and also those high protein formulas tend to cause renal stones.

Available Appetite stimulants include:

1. **Lysine is an essential amino-acid,** which plays a role in appetite stimulation by contributing in the pathway of the digestive enzymes, **considered the best option for children.**
   - There are some Multivitamins combinations which contain **Lysine** in its components, which makes them ideal for children growth support.
   - Examples of those combinations: **Vitan®, Predine®**

2. **Cyproheptadine**, which is an **antihistamine drug**; has been used to increase weight, it's not recommended for routine use because of the anticholinergic side effects, including dizziness, sedation, and dry mouth.
   - It was approved for appetite stimulate in the 1960s, but in 1971, the U.S. FDA withdrew approval for the use of (Cyproheptadine) as an appetite stimulant for children - and approval for adult use was never given.
   - The withdrawal was due to the American Medical Association reports that the effect of Cyproheptadine on children is "inconsistent, transient, and quickly reversible on withdrawal of the drug", besides its side effects.

3. **Pizotifen** (an **anti-migraine medication**) is also used for appetite stimulation, it's observed as a side effect of **Pizotifen**, publication and studies of Pizotifen observes only that "a slight increase in body weight is observed in some patients"
   - Long term use will do more harm than good.

4. **Dronabinol** has been shown to increase weight in a small placebo control study of Alzheimer's patients, but its use is limited because of the risk of seizures, confusion, sleepiness, and euphoria.
   - It's also used as an **anti-emetic** for chemotherapy-induced Nausea and vomiting.

Scientific name	D. form	Trade name	concentration
Lysine	Tab	----------	----------
Pizotifen	Tab	Sadnomigran® , Mosegor®	0.5 mg
Cyproheptadine	Tab	Periactin®, Ciptadine®, Cyprodad®, Nebor®	4 mg
	Syr.	Cyprodine® , Citadine®	2 mg/5 ml
Dronabinol	Tab	Marinol®	2.5 mg , 5 mg , 10 mg
Combination products			
Cyproheptadine Alpha-Ketoglutarate + Arginine Aspartate	Amp (for oral intake)	Dynamogen®	3 mg + 1 gm

Fourth: Obesity and weight reducing agents

- Obesity is also defined as a BMI (body mass index) over 30 kg/m^2, Patients with a BMI between 25 and 29.9 are considered overweight.
- There is a lot of weight reduction formulations found in our markets; none of them has a proven or reliable clinical study to prove their efficacy and safety, so please; as a responsible pharmacist don't give these medications without being sure of their safety and benefits.
- **Remember that weight reduction products have caused disasters in health and many products of this category are withdrawn** (see the table below).

Drug	Introduced	Mechanism	FDA status
Fenfluramine	1973-U.S.	Sympathomimetic amine (appetite suppression)	Withdrawn 1997: valvular heart disease, pulmonary hypertension
Dexfenfluramine	1996-U.S.	As above	Withdrawn 1997: valvular heart disease, pulmonary hypertension
Rimonabant	2006-Europe	Selective CB1 receptor blocker	Not approved in U.S.: concern over psychiatric side effects Withdrawn 2009: potential of serious psychiatric disorders Temporarily withdrawn 2002
Sibutramine	1997-U.S. 2001-Europe	Selective combined serotonin and noradrenaline reuptake inhibitor (appetite suppression)	Withdrawn 2010: increased risk of heart attack and stroke in high-risk cardiac patients

The safest anti-obesity drug is Orlistat:

1. **Orlistat** is a gastric and pancreatic lipase inhibitor that limits the absorption of dietary fat, it is used together with dietary modification in the management of obesity; (in **patients with a BMI of 30 kg/m^2 or greater**); it may also be used in overweight patients with a BMI of 27 kg/m^2 or more if there are associated risk factors (such as type 2 DM, hypertension).
2. **Orlistat** is given in a usual dose of 120 mg orally three times daily, **immediately before, during, or up to 1 hour after meals**. If a meal is missed or contains no fat, the dose should **be omitted, Orlistat** therapy should be stopped if the patient does not lose at least 5% of their body-weight during the first 12 weeks of therapy.

Other Agents include:

Drug	Mechanism	Effects on weight	Adverse effects	Status	Comments
Medications for short-term weight management or selected medications used off-label to promote weight loss					
Phentermine[a]	Sympathomimetic amine (appetite suppressant)	3.6 kg placebo-subtracted weight loss in studies ranging from 2-24 weeks	Insomnia, tremor, ↑ blood pressure and pulse rate, headache, palpitation, constipation	Currently approved drug for short-term weight management (≤12 weeks) in U.S., Korea and some countries, withdrawn 2000 in U.K.	Diffusion controlled release preparation is available
Diethylpropion[a]	As above	3.0 kg placebo-subtracted weight loss in studies ranging from 6-52 weeks	As above	Currently approved drug for short-term weight management	
Zonisamide[a]	Anti-convulsant agent	5.0% placebo-subtracted weight loss at 12 weeks	↑ Nervousness, sweating, tremors, gastrointestinal adverse effects, hypersomnia, fatigue, and insomnia	Used off-label	No enough clinical trials; should not exceed 400 mg/day
Topiramate[a]	As above	6.5% placebo-subtracted weight loss at 24 weeks	Paresthesia, dizziness, altered taste, fatigue, memory impairment, somnolence, anorexia, and abdominal pain	Used off-label	Associated with teratogenicity; should not exceed 400 mg/day

Table showing current anti-obesity drugs:

Mechanism of action	Drug	Effects and safety concerns	Efficacy	Status
Appetite suppressant. Stimulates anorexic signaling in hypothalamus or dopamine receptor in the hippocampus. Sympathomimetic agents similar to norepinephrine with central nervous system (CNS) stimulatory activity.	Phentermine	Appetite suppression and weight loss. *Side effects include dizziness, dry mouth, difficulty sleeping, irritability, nausea, vomiting, diarrhea, or constipation. This drug has withdrawal symptoms.	Weight loss greater than placebo was 3.6 kg [CI] 0.6---6.0 kg	FDA---approved in 1959
	Amphetamine	Anorexia and weight loss. *Side effects include nervousness, restlessness, excitability, dizziness, headache, fear, anxiety, and tremor. Blood pressure and heart rate may increase. Chronic use may lead to dependence. These drugs have withdrawal symptoms.	Weight loss greater than placebo was less than 1 kg [CI] 0.5---1.6 kg	Off---label usage Approved for ADHD
Serotonin, dopamine and norepinephrine reuptake inhibitor (SNRI) that potentiates the neurotransmitter activity in the central nervous system (CNS).	Lorcaserin (Belviq)	Limited weight loss efficacy and possible increase in cancer risk. *Side effects include headache, infection, sinusitis, nausea, depression, anxiety and suicidal thoughts. Possible concerns of cancer risk.	Mean body weight loss: Lorcaserin 5.8 ± 0.2 kg; Placebo 2.2 ± 0.1 kg	FDA---approved in 2012
	Desvenlafaxine (Pristiq)	Anorexia but effect on body weight is unclear. *Vision problem, headache, low libido, dry mouth, dizziness, insomnia, taste problems, vomiting, anxiety, Sexual dysfunction, depression, high blood pressure, stomach ache, numbness and tingling, fatigue, and involuntary quivering.	Mean body weight loss greater than placebo was 0.22---1.41 kg	Off---label usage Approved for depression
	Sibutramine (Meridia)	Limited weight loss efficacy. *Increased risk for cardiovascular events and stroke.		FDA---approved in 1997, but withdrawn in 2010 due to cardiovascular effects
Inhibits the neuronal uptake of dopamine, norepinephrine, and serotonin.	Bupropion (Wellbutrin, Zyban)	Modest weight loss. *Nausea, vomiting, dry mouth, headache, constipation, increased sweating, joint aches, sore throat, blurred vision, strange taste in the mouth, agitation and insomnia, tremer or dizziness may occur. Rare side effects includes cardiovascular	% weight loss greater than placebo: Bupropion SR 400 mg/d 5.1% [CI] 6.9---3.2% Bupropion SR 300 mg/d 2.2% [CI] 4.0---0.4%	Off---label usage Approved for depression

Mechanism of action	Drug	Effects and safety concerns	Efficacy	Status
Reversible inhibitor of intestinal lipases.	Orlistat (Xenical)	Weight loss. *increased number of bowel movement and potential changes in the bowel function and microbiota.	Mean body weight loss greater than placebo was 4.2 kg	FDA---approved drug in 1999
Enhancing GABA singaling to promote anorexigenic signaling. Inhibiting voltage---gated channels and AMPA receptor in the orexigenic neurons.	Topiramate (Topamax)	Appetite suppression and weight loss. *Tiredness, drowsiness, dizziness, loss of coordination, tingling of the hands/feet, bad taste in the mouth, diarrhea. Mental problems such as confusion, slowed thinking, trouble concentrating or paying attention, nervousness, memory problems, or speech/language problems may also occur. Rare side effects include kidney stones, depression, suicidal thoughts/attempts, and vision loss.	Weight loss greater than placebo was 6.5 kg [CI] 4.8---8.3 kg	Off---label usage Approved for epilepsy
Glucagon---like peptide---1 (GLP---1) receptor agonist.	Exenatide (Byetta, Bydureon)	Decreased blood glucose level and body weight. * Side effects include GI symptoms, acute pancreatitis, dizziness and headache. It might increase risks of sulfonylurea---induced hypoglycemia and thyroid cancer.	Mean body weight change: Exenatide --- (2.49 ± 0.66) kg, placebo + (0.43 ± 0.63) kg	Off---label usage Approved for diabetes
	Liraglutide (Victoza)	Maintained normal blood glucose and body weight. *Increased risks of C---cell carcinoma and thyroid C---cell focal hyperplasia were observed in rats and mice.	Weight loss greater than placebo was 4.4 kg [CI] 2.9---6.0 kg	Off---label usage Approved for diabetes
Amylin analog.	Pramlintide (Symlin)	Decreased blood glucose level and body wieght. * Side effects include nausea, hypoglycemia, vomiting, headache, abdominal pain and fatigue.	%weight loss greater than placebo was 2.2 ± 0.7%	Off---label usage Approved for diabetes
Cocktail drug.	Phentermine/topiramate (Osymia)	See above effects from individual drugs	%weight loss from baseline was placebo −2.2%, (PHEN 7.5 mg/TPM 46 mg) CR −9.3%, and (PHEN 15 mg/TPM 92 mg) CR −10.7%	FDA---approved in 2012

Fifth: Vitamins and Medical Supplements

1. Minerals and Electrolytes:

a. Calcium supplements

1. Calcium salts are used in the management of **hypocalcemia** and **calcium deficiency states** resulting from dietary deficiency or ageing.
2. **Intravenous calcium (calcium gluconate)** salts are also used to reverse the toxic cardiac effects of potassium in the emergency treatment of severe **hyperkalemia (calcium act to protect the heart from hyperkalemia)**.
3. **Calcium SC inj**. is used in cases **of HCL acid burns** (because it forms un-harmful CaCL salt).
4. **Used** in cases of **hyper-Mg+**
5. **Used as antidote** for overdose of Calcium Channel Blocker **(CCBs).**
6. **Used** for treatment in the **neurotoxicity of Aminoglycosides**.
7. Calcium **carbonate** or acetate are **effective phosphate binders** and are given orally (with food) to **reduce phosphate absorption from the gut in** patients with **hypophosphatemia**; this is particularly relevant to patients with **chronic renal failure**
8. Oral calcium supplements can also be used adjunct in the management of **osteoporosis**.

b. Phosphate-binding agents

1. Calcium-containing preparations are used as phosphate-binding agents in the management of hypophosphatemia complicating renal failure.
2. **Sevelamer hydrochloride** and **Sevelamer carbonate** are both licensed for the treatment of hypophosphatemia in patients on hemodialysis or peritoneal dialysis.

c. Potassium

1. Potassium salts are used for the prevention and treatment of **hypokalemia**.
2. An **I.V. Potassium** salt (KCL) may be required in **severe acute hypokalemia**.
3. When I.V. Potassium is added to I.V. fluid, it is important to mix thoroughly; if the solutions are not mixed; a concentrated layer of potassium chloride may form (layering effect) owing to differences in density; if such a mixture is administered it may have a serious effect.

d. Zinc

1. Zinc supplement is **used for zinc deficiency**.
2. Zinc supplements have been shown to **reduce the incidence, intensity, or duration of acute diarrhea in children** in developing countries, (it enhances the absorption of water and electrolytes)**.**
   - **The WHO/UNICEF** recommend that children with acute diarrhea also receive zinc (10 mg of elemental zinc/day for infants younger than 6 months; 20 mg of elemental zinc/day for older infants and children) for 10 to 14 days.
3. **Zinc prevents the absorption of copper in Wilson's disease**.
4. **Zinc supplementation can cause a Copper deficiency.**

e. Magnesium

1. Magnesium Deficiency will cause **ringing in the ears** or hearing loss, **muscle cramps** or tremors, **depression**, **abnormal heart function** and **kidney stones**.
2. **Sever Magnesium Deficiency** can be treated by using a nebulizer filled with magnesium Sulphate or magnesium chloride dissolved in water; Nebulizing has the advantage of taking effect within minutes, relieving muscle pain, tension or breathing difficulties.
3. Magnesium is indicated for Emergency treatment of serious arrhythmias (torsade de pointes); and in Severe acute asthma, and in the Prevention and treatment of seizures in pre-eclampsia in pregnancy.

2. Vitamins:

a. Vitamin A:

1. Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision.
2. Vitamin A is used in the treatment and prevention of vitamin A deficiency, **Vitamin A has also been used to treat various skin disorders including acne and psoriasis**.
3. It has two forms **Retinol** and **Beta-Carotene**.
   - 1 IU vitamin A equals 0.3 mcg Retinol, 0.6 mcg Beta-Carotene.
4. In view of evidence suggesting that high levels of vitamin A may cause birth defects (**teratogenic**), women who are (or may become) **pregnant are advised not to take vitamin A supplements** (except on the advice of a doctor); nor should they eat liver.

(The American College of Obstetricians and Gynecologists has recommended that women who are pregnant or planning pregnancy should ensure that any vitamin supplements they take contain a daily dose of vitamin A of no more than 5000 units, The Australian Adverse Drug Reactions Advisory Committee has advised women in this category to avoid vitamin A supplements and to not exceed the recommended daily allowance of 2500 units from all sources)

b. Vitamin B:

There are several type of vitamin B, which include the following:

Vitamin B	Scientific name	Uses
B_1	**Thiamine**	- Thiamine is used in the treatment and prevention of thiamine deficiency (Beriberi).
B_2	**Riboflavin**	Riboflavin is used in the treatment and prevention of riboflavin deficiency.
B_3	**Niacin**	Used for the treatment of hyperlipidemia.
B_5	**Pantothenic acid**	- Plays a role in synthesis and maintenance of Coenzyme A. - Its deficiency causes depression. - Also used as a dietary supplement.
B_6	**Pyridoxine**	- Pyridoxine is used in the treatment and prevention of pyridoxine deficiency states [2]. - Prevention of **isoniazid-induced neuropathy**. - Treatment of **premenstrual syndrome**. - Maybe useful as an **antiemetic.**
B_7 (or Vit H)	**Biotin**	- Helping the body metabolize proteins, fats and carbohydrates - Helping the body process glucose - It also contributes towards healthy nails, skin and hair. It is therefore found in many cosmetic and health products for the skin and hair, **it cannot be absorbed through hair or skin.**
B_9	**Folic acid**	- used as a supplementation for pregnancy to prevent Neural tube defect. - Also used in Megaloblastic anemia caused by folic deficiency.
B_{12}	**Cobalamins**	- Vitamin B_{12} is used in the treatment and prevention of vitamin B_{12} deficiency. - Treatment of B_{12}**- deficient Megaloblastic anemias**. - Useful in **neuropathic pain**.

c. Vitamin C: (Ascorbic acid)

Usually used in combination products for Common cold and Flu, but Claims that vitamin C ameliorates colds or promotes wound healing **have not been proved**.

- **Scurvy** is an avitaminosis resulting from lack of vitamin C, since without this vitamin, collagen made by the body is too unstable to perform its function.
- **Scurvy** leads to the formation of brown spots on the skin, spongy gums, and bleeding from all mucous membranes.

d. Vitamin D:

1. A diet deficient in vitamin D in conjunction with inadequate sun exposure causes **osteomalacia** (or **rickets** when it occurs in children), which is a softening of the bones.
2. The term Vitamin D is used for a range of compounds which possess the property of preventing or curing rickets. They include **Ergocalciferol** (Calciferol, vitamin D2), **Cholecalciferol** (vitamin D3), **Alfacalcidol** (1-α hydroxycholecalciferol), and **Calcitriol** (1, 25-dihydroxycholecalciferol)
3. Vitamin D requires hydroxylation by the kidney to its active form, **therefore the hydroxylated derivatives Alfacalcidol or Calcitriol should be prescribed if patients with severe renal impairment require vitamin D therapy**.
4. Preparations containing calcium with Vitamin D are available for the management of combined calcium and vitamin D deficiency.
   - 1 IU Vit. D = 0.025 mcg Cholecalciferol or Ergocalciferol.
5. **Note: How to calculate the required Vit D3 dose for patients**
   - Use the following equation; (75 – lab test ng/ml) × (Age in yrs.) × (wt. in kg) = dose per month IU
   - Divide by 30 = dose per day, divide by 4 = dose per week, given for at least 2 months.
6. Available **in combination with Vit. A, as a topical product** (emollient).
7. Vitamin D overdose causes hypercalcemia, which is a strong indication of vitamin D toxicity – this can be noted with an **increase in urination and thirst**; If hypercalcemia is not treated, it results in excess deposits of calcium in soft tissues and organs such as the kidneys, liver, and heart, resulting in pain and organ damage including renal failure.

e. Vitamin E: (Tocopherol)

1. Vitamin E is used in the treatment and prevention of vitamin E deficiency.
2. It has an **anti-Oxidant effect**, and also plays a role in preventing oxidation of Vitamin A and C.
3. Can be **used in Post Herpetic Neuralgia** (off-label), Vitamin E has been tried for various other conditions **but there is little scientific evidence of its value**.
4. Available as **a topical product** (emollient).
5. Regular consumption of more than 1,000 mg (1,500 IU) of Vitamin E per day may be cause **hypervitaminosis E**
   - **Vitamin E can act as an anticoagulant**, increasing the risk of bleeding.
   - **Hypervitaminosis E** may also counteract vitamin K, leading to a vitamin K deficiency.

f. Vitamin K:

1. Vitamin K is necessary for the **production of blood clotting factors**.
2. Vitamin K compounds are used in the **treatment and prevention of hemorrhage associated with vitamin K deficiency**.
3. The body also **needs Vitamin K for controlling binding of calcium in bones** and other tissues; thus, it's important in treating or preventing osteoporosis or osteomalacia.
4. Vitamin K is one of the treatments for bleeding events caused by **overdose of the anticoagulant drug warfarin.**
5. Because vitamin K is fat soluble, patients with fat malabsorption, especially in biliary obstruction or hepatic disease, may become deficient; **Menadiol sodium phosphate is a water-soluble synthetic vitamin K derivative** that can be given orally to prevent vitamin K deficiency in malabsorption syndromes.
   - **BUT Menadiol may be toxic by interfering with the function of glutathione.**

3. Multivitamin preparations:

1. There are too many multivitamins combinations found in the market, so choose carefully.
2. It is generally considered **that healthy persons eating a normal balanced diet should have no need for vitamin supplementation**.
3. Supplementation should concentrate **on groups of people at risk of deficiency** such as pregnant and lactating women, who need calcium, folic acid, and iron; and certain groups who need vitamin D; A multivitamin supplement might be considered for some groups such as the elderly and those with reduced calorie intake.

Note 1:

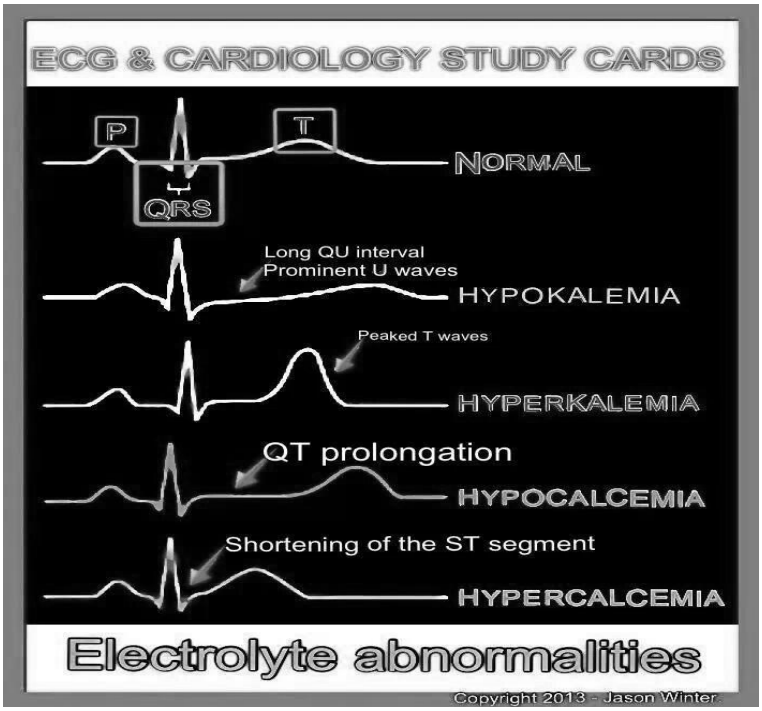
The table below shows the normal range of the common electrolytes, with their causes of elevation and decline:

Normal range	Causes of elevation	Causes of decline
Sodium (Na): 135 – 145 mEq/L	**Hypernatremia:** Excessive loss of water through GI system, lungs, or skin; fluid restriction, certain diuretics, hypertonic IV solutions, tube feeding; hypothalamic lesions, hyperaldosteronism, corticosteroid use, Cushing's syndrome, diabetes insipidus	**Hyponatremia:** Congestive heart failure, cirrhosis, nephrosis, excess fluid intake, syndrome of inappropriate antidiuretic hormone secretion (dilutional hyponatremia); sodium depletion, loss of body fluids without replacement, diuretic therapy, laxatives, nasogastric suctioning, hypoaldosteronism, cerebral salt-wasting disease
Potassium (K): 3.5 – 5.0 mEq/L	**Hyperkalemia:** Aldosterone deficiency, sodium depletion, acidosis, trauma, hemolysis of red blood cells, potassium-sparing diuretics	**Hypokalemia:** Lack of dietary intake of potassium, vomiting, nasogastric suctioning, potassium-depleting diuretics, aldosteronism, salt-wasting kidney disease, major GI surgery, diuretic therapy with inadequate potassium replacement
Calcium (Ca): 8.5 – 10.5 mg/dL	**Hypercalcemia:** Excessive vitamin D, immobility, hyperparathyroidism, potassium-sparing diuretics, ACE inhibitors, malignancy of bone or blood	**Hypocalcemia:** Hypoparathyroidism, malabsorption, insufficient or inactivated vitamin D or inadequate intake of calcium, hypoalbuminemia, diuretic therapy, diarrhea, acute pancreatitis, bone cancer, gastric surgery
Magnesium (Mg): 1.5 – 2.5 mg/dL	**Hypermagnesemia:** Excessive use of magnesium-containing antacids and laxatives, untreated diabetic ketoacidosis, excessive magnesium infusions	**Hypomagnesemia:** Malabsorption related to GI disease, excessive loss of GI fluids, acute alcoholism/cirrhosis, diuretic therapy, hyper- or hypothyroidism, pancreatitis, preeclampsia, nasogastric suctioning, fistula drainage

Note 2: Signs of Nutritional deficiencies:

VITAMIN	DEFICIENCIES
VITAMIN – A	NIGHT BLINDNESS, DRY SKIN
VITAMIN – B1	IMPAIRED GLUCOSE BREAKDOWN, BERI BERI, WERNICKE-KARSAKOFF SYNDROME
VITAMIN – B2	CHEILOSIS, CORNEAL VASCULARIZATION
VITAMIN – B3	PELLAGRA – DIARRHEA, DERMATITIS, DEMENTIA
VITAMIN – B5	DEMATITIS, ENTERITIS, ALOPECIA, ADRENAL INSUFFICIENCY
VITAMIN – B6	CONVULSIONS, HYPERIRRITABILITY, SIDEROBLASTIC ANEMIA, PERIPHERAL NEUROPATHY (INH TREATMENT)
VITAMIN – B12	MEGALOBLASTIC ANEMIA, SUBACUTE COMBINED DEGENERATION OF SPINAL CORD
FOLIC ACID	MEGALOBLASTIC ANEMIA, CONGENITAL DEFECTS
VITAMIN – C	SCURVY – SWOLLEN GUMS, BRUISING, ANEMIA, POOR WOUND HEALING
VITAMIN – D	RICKETS (CHILDERN), OSTEOMALACIA (ADULTS)
VITAMIN – E	HEMOLYTIC ANEMIA, MUSCLE WEAKNESS, NEURODYSFUNCTION
VITAMIN – K	HEMORRAGE – DECREASE SYNTHESIS OF CLOTTING FACTORS II, VII, IX, X, PROTEIN C & PROTEIN S

Note3: ECG and Electrolytes relationship:



Sixth: Medical Dried Milk

There are several types of Milk inside our market, with different signs and symbols, some used for babies and some for adults; below a list that explain their meanings:

No.	Sign	Used for (or meaning)
1	AC	Anti-Colic (for spasm and gases)
2	Cesar	For Cesarean Baby
3	Gentle	Anti-Colic (for spasm and gases)
4	Soya	Allergy form Cow products
5	LF	Lactose Free
6	CT	Constipation Treatment
7	Ensure	Milk for Adults
8	Enure Plus	Food supplement for Adults
9	Pedia Sure	Food Supplement from 1 – 10 years
10	Promil	For Babies from 6 – 12 months
11	Gloserna	For Diabetic Adults
12	IT	Improved Transfer (better absorption)
13	Comfort	Anti-Colic (for spasm and gases)
14	HA	Hypo - Allergic
15	PDF	Post Delivery Formula
16	AR	Anti-Regurgitation (Vomiting)
17	AD	Anti-Diarrhea
18	Aniline	Ca and Vit. D Supplement for Adults
19	HN25	High Nutrition Milk
20	Promise	Food Supplement from 1 – 10 years

Index

(Bold Names indicates a must Know Drug)

1

2

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

β (Beta)