

RAJIV GANDHI UNIVERSITY OF HEALTH SCIENCES
KARNATAKA BANGALORE

PHARMACOTHERAPEUTICS-III

5TH PHARM D

1ST PHARM D (PB)

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DOCTOR OF PHARMACY

Title of the topic

- 1 **Gastrointestinal system:** Peptic ulcer disease, Gastro Esophageal Reflux Disease, Inflammatory bowel disease, Liver disorders - Alcoholic liver disease, Viral hepatitis including jaundice, and Drug induced liver disorders.
- 2 **Haematological system:** Anaemias, Venous thromboembolism, Drug induced blood disorders.
- 3 **Nervous system:** Epilepsy, Parkinsonism, Stroke, Alzheimer's disease,
- 4 **Psychiatry disorders:** Schizophrenia, Affective disorders, Anxiety disorders, Sleep disorders, Obsessive Compulsive disorders
- 5 Pain management including Pain pathways, neuralgias, headaches.
- 6 Evidence Based Medicine

Peptic Ulcer Disease

caused by peptic ulcers

Definition:

- It refers to a group of disorders characterized by the presence of ulcers in any portion of GI tract exposed to acid in sufficient duration and concentration.

Etiology:

- H pylori infection
- NSAIDs
- Severe medical illness
- Hypersecretory states
- Duodenal obstruction

Pathophysiology:

1- Helicobacter pylori:

- pH sensitive, gram -ve organism
- High duodenal acid level promotes colonization.
- Colonization leads to inflammation of the

mucosa promoting more gastric metaplasia.

- This again increase colonization.

- The result of this vicious cycle is that mucosa becomes highly susceptible to ulceration.

- The second proposed mechanism is via an altered immune inflammatory response in which bacteria damage the epithelial cells directly by cell mediated immune mechanisms and indirectly by activation of neutrophils or macrophages that attempt to phagocytose the bacteria.

- Acute *H. pylori* infection is accompanied by transient hypochlorhydria which allows the bacteria to survive in the acidic environment of the stomach.

2. Non-Steroidal anti inflammatory drugs:

- NSAIDs inhibit the synthesis of protective PGs.

- All NSAIDs inhibit both COX-1 and 2 to varying degrees.

□ Signs and Symptoms:

-epigastrium:
مجلس البطن العلوي

- 1- Epigastric pain (most common)
burning sensation
 - occurs 2-3 hours after meals
 - Relieved by food or antacids

2- Nausea

3- Vomiting

4- Heartburn

5- Dyspepsia عسر الهضم

6- Weight loss

□ Diagnosis:

1- Laboratory Studies:

CBCs, liver function tests (LFTs) etc.

2- Radiology and endoscopy

- to differentiate PUD from other acid related GI disorders.

3. Testing for *Helicobacter pylori*:

→ Endoscopic or invasive tests:

① Rapid ureas tests:

- One or more gastric ^{or biopsy} biopsy specimens are placed in the rapid ureas test kit. If *H. pylori* is present, bacterial urease converts urea to ammonia, which changes pH and produces a colour change.

② Histopathology:

Used if the rapid urease test result is -ve and a high suspicion for *H. pylori* persists.

③ Culture

→ Nonendoscopic or noninvasive tests:

① Antibodies to *H. pylori* can be measured in serum, plasma or whole blood.

② Urea breath tests detect active *H. pylori* infection by testing for the enzymatic activity of bacterial urease.

-In the presence of ureas produced by H. pylori, labeled carbon dioxide is produced in the stomach, absorbed into the bloodstream, diffused into the lungs and exhaled.

© Fecal antigen testing: identifies active H. pylori infection by detecting the presence of H. pylori antigens in stools.

4-Special studies:

- A fasting serum gastrin level should be obtained in certain cases to screen for Zollinger-Ellison Syndrome.

□ Treatment:

i-Non pharmacological Treatment:

- a-Surgical care
- b-Avoid spicy, oily food
- c-Maintain hygiene
- d-Stop smoking
- e-Avoid tea, coffee etc.
- f-Increase intake of milk
- g-Avoid alcohol

II. Pharmacological Treatment:

a. Antibiotics:

CHAP A₂B

used in the eradication of H. pylori
تأثير

- Amoxicillin:

MOA:

Interferes with synthesis of cell wall mucopeptides

Dose:

1g PO bid

ADR:

diarrhea

nausea

vomiting

abdominal pain.

Clarithromycin

MOA:

- reversibly binds to P site of 50s ribosomal subunit of susceptible organisms and may inhibit RNA-dependent protein synthesis, causing bacterial growth inhibition.

Dose: 500mg PO bid

b. Proton pump inhibitors:

- Lansoprazole

MOA:

decreases gastric acid secretion by inhibiting parietal cell H^+/K^+ ATP pump

Dose:

15-30 mg PO qd for 4 wk

ADR:

Headache

Diarrhea

- Esomeprazole

Dose: 20-40 mg PO qd for 4-8 wk.

3. Cytoprotectants:

→ induce PG synthesis → cytoprotective effects in the GI tract.

Misoprostol

Dose: 200 mg PO qid

4. H₂ receptor blockers:

- Selectively block H₂-receptors on parietal cells, resulting in diminished acid secretion and ulcer healing.

◦ Cimetidine:

↳ Can be used as primary therapy to heal ulcers not associated with H pylori infection.

Dose:

400 mg PO bid

ADR:

Hypotension

bradyarrhythmias

◦ Ranitidine

Dose: 150 mg PO bid

5. Antacids:

Ex: Magnesium, aluminium, calcium or sodium salts.

MOA:

Reduce the concentration and total load of acid in gastric contents.

ADR:

Diarrhea

Constipation

6. Bismuth compounds:

Eg: colloidal bismuth subcitrate

MOA:

Blocks pepsin activity binds mucos to retard hydrogen back diffusion and suppresses H. pylori.

Dose:

480 mg/day

ADR:

Headache

abdominal pain

diarrhea

rash

Dark stool

7. Gastrointestinal anticholinergics:

Ex:

Atropine

Belladonna leaf

MOA:

Decreased basal and stimulated gastric acid
and pepsin secretion.

ADR:

Dry mouth

constipation

tachycardia

Gastro-Esophageal Reflux Disease (GERD)

✓ reflux of the stomach and duodenal contents
• Definition: into the esophagus.

- Gastro-esophageal reflux disease is the term used to describe any symptomatic clinical condition or histopathological alteration resulting from episodes of reflux of acid, pepsin and occasionally, bile into the esophagus from the stomach.

Epidemiology: occurs in both adults and children.
the prevalence increases in adults older >40 y.

• Etiology:

1. Defective lower esophageal sphincter pressure.
2. Anatomic factors
3. Gastric emptying
4. Composition and volume of the gastric acid, pepsin, bile acids and pancreatic enzymes.

• Pathophysiology:

PATHOPHYSIOLOGY

1. Lower esophageal sphincter pressure

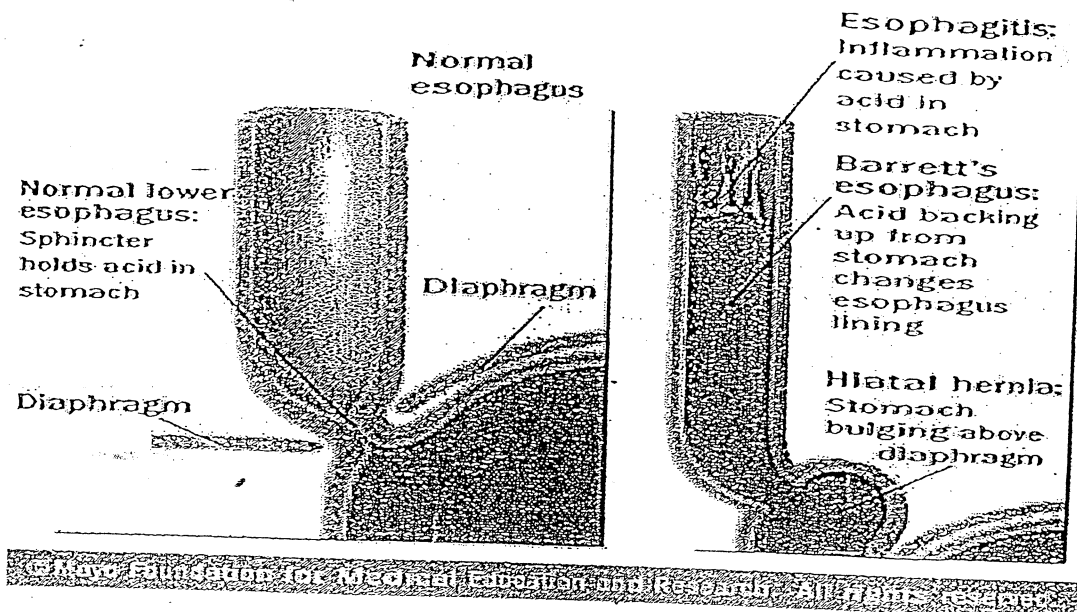
- The sphincter is normally in a tonic state, preventing the reflux of gastric material from the stomach, but relaxes on swallowing to permit the free passage of food into the stomach.
- Patients with more severe gastro esophageal disease have resting lower esophageal sphincter pressures below 5 mm Hg. Transient decreases in the sphincter pressures are responsible for approximately 65% of the reflux episodes in patients with GERD.
- Lower esophageal sphincter pressure depends on numerous factors, including degree of sphincter relaxation, efficacy of esophageal clearance, patient position (more in recumbent position), gastric volume and intra gastric pressure.
- Second, reflux may occur due to increase in intra abdominal pressure (stress reflux) that occurring during straining, bending over, coughing, or eating.
- Third, the lower esophageal sphincter may be atonic, thus permitting free reflux.
- Various foods like spicy foods, orange juice, tomato juice and coffee precipitate symptomatic reflux by direct mucosal irritation.
- Pregnancy, achalasia (condition in which normal muscular activity of the esophagus is disturbed), and scleroderma (persistant hardening and contraction of the body's connective tissue) are conditions in which reflux is common.

2. Anatomic Factors

Patients with hypotensive lower esophageal sphincter pressures and large hiatal hernias are more likely to experience gastro esophageal reflux following abrupt increases in intra abdominal pressure as compared to patients with hypotensive lower esophageal sphincter and no hiatal hernia.

• hernia: بیرون زدگی بخشی از یک عضو یا بافت
از یک منفذ غیر طبیعی

• hiatal hernia: بیرون زدگی هر یک از ساختارهای از سوراخ دیافراگم
به داخل قفسه سینه.



3. Esophageal clearance

- GERD patients with esophagitis have a prolonged acid clearance time from the esophagus. The symptoms and severity of esophageal reflux are partially dependent on the duration of contact between the gastric contents and the esophageal mucosa. The contact time is, in turn, dependent on the rate at which the esophagus clears the noxious material and frequency of reflux.
- The esophagus is cleared by ^①primary peristalsis in response to swallowing, ^②secondary peristalsis in response to esophageal distension, and ^③gravitational effects.
- Swallowing contributes to esophageal clearance by increasing salivary flow. Saliva contains bicarbonate that buffers the residual gastric material on the surface of the esophagus. The production of saliva decreases with increasing age, making it more difficult to maintain a neutral intraesophageal pH. Therefore, esophageal damage due to reflux occurs more often in the elderly.

4. Mucosal resistance

- Within the esophageal mucosa and submucosa there are mucus secreting glands. The mucus secreted by these glands may contribute to the protection of the esophagus. Bicarbonate moving from blood to the lumen can neutralize acidic refluxate in the esophagus.
- When the mucosa is repeatedly exposed to the refluxate in GERD, or if there is any defect in the normal mucosal defenses, hydrogen ions diffuse into the mucosa, leading to the cellular acidification and necrosis that ultimately cause esophagitis.

5. Composition of refluxate

- The composition and volume of refluxate are the most important aggressive factors on determining the consequences of gastro esophageal reflux.
- Acid has two primary effects when it refluxes into the esophagus.
 - ✦ First, if the pH of the refluxate is less than two, esophagitis may develop, secondary to protein denaturation.
 - ✦ In addition, pepsin is activated at this pH and may also cause esophagitis.
- Alkaline esophagitis refers to esophagitis induced by the reflux of bilious and pancreatic fluid.
- An increase in gastric bile concentrations may be caused by duodenogastric reflux because of a generalized motility disorder or slower clearance of the refluxate.
- Bile acids have both a direct irritant effect on the esophageal mucosa and an indirect effect of increasing hydrogen ion permeability of mucosa. symptoms are more often related to acid reflux than to bile reflux.

6. Gastric emptying

- Delayed gastric emptying contributes to gastro esophageal reflux. An increase in gastric volume may increase both the frequency of reflux & amount of gastric fluid available to be refluxed. Gastric volume is related to the volume of material ingested, rate of gastric secretion, rate of gastric emptying, & amount of frequency of duodenal reflux to stomach.
- Factors that increase gastric volume and/or decrease gastric emptying such as smoking and high fatty meals, are associated with gastro esophageal reflux.
- Fatty foods may increase postprandial gastro esophageal reflux by increasing gastric volume, delaying the gastric emptying rate & decreasing the lower esophageal sphincter pressure.

CLINICAL PRESENTATION

Typical symptoms:

- ◇ Heartburn
- ◇ water brash (hypersalivation)
- ◇ Belching
- ◇ Regurgitation

Atypical symptoms:

- ◇ Non allergic asthma
- ◇ Chronic cough
- ◇ Hoarseness
- ◇ Pharyngitis
- ◇ Chest pain that mimics angina

Complicated symptoms:

- ✓ Continual pain
- ✓ Dysphagia
- ✓ Barrett's esophagus (Long-term, recurrent reflux symptoms that are not adequately treated may lead to the replacement of squamous epithelial lining of the esophagus by columnar-type epithelium) which can lead to esophageal adenocarcinoma.
- ✓ Bleeding
- ✓ Weight loss
- ✓ Choking (Acid causing cough, shortness of breath)

DIAGNOSIS

a) Endoscopy and barium radiography

- ⇒ It is a technique for assessing the mucosa for esophagitis & Barrett's esophagus
- ⇒ It enables visualization & biopsy of esophageal mucosa

b) Provocative and pH testing

- ⇒ Continuous pH monitoring can be performed by passing a small electrode pH probe intranasally and placing it approximately 5cm above lower esophageal sphincter.
- ⇒ This test is used to establish a casual relationship between patient symptoms and abnormal acid exposure, especially when esophagitis is not present.

c) Esophageal manometry

- ⇒ It is to evaluate peristaltic function should be performed in any patient who is a candidate for antireflux surgery.
- ⇒ A multilumen tube is passed into the stomach and the pressures are measured as the tube is pulled back across LES, esophagus and pharynx.

c) "Omeprazole test" to diagnose GERD

- ⇒ The empiric use of standard dose or even double dose, omeprazole as a therapeutic trial for diagnosing the presence of GERD.
- ⇒ Sensitivity & specificity of omeprazole (60mg) daily for 7 days as the initial diagnostic tool were similar to that obtained with ambulatory pH monitoring.

TREATMENT

Goals:

- Eliminate the patient's symptoms
- Decrease the frequency or recurrence and duration of gastroesophageal reflux;
- Promote healing of the injured mucosa; and
- Prevent the development of complications.

Non - Pharmacologic Treatment

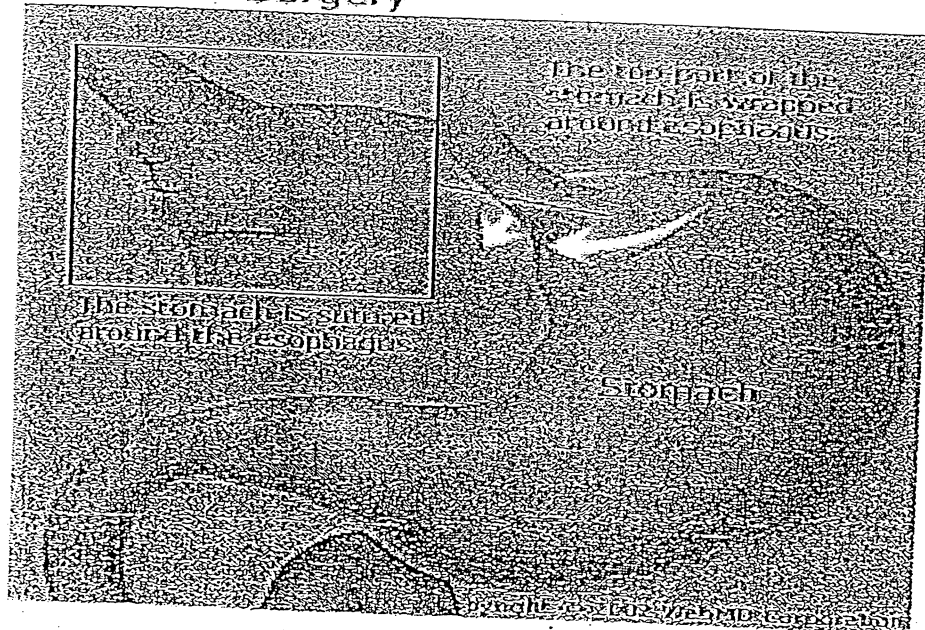
- Elevate the head of the bed (increases esophageal clearance)
- Avoid foods that may decrease lower esophageal sphincter pressure
(Fats, chocolate, alcohol, peppermint & spearmint)
- Avoid foods that have a direct irritant effect on the esophageal mucosa
(Spicy foods, orange juice, tomato juice & coffee)
- Include protein rich meals in diet (augments LESP)
- Eat small meals and avoid eating 2 hours prior to sleeping (decreases gastric volume)
- Weight reduction (reduces symptoms)
- Stop smoking (decreases spontaneous esophageal sphincter relaxation).

- o Avoid alcohol (increases amplitude of LES, peristaltic waves & frequency of contraction)
- o Avoid tight-fitting clothing.
- o Discontinue, if possible, drugs that may promote reflux (CCB, BB, nitrates, theophylline)
- o Take drugs that have direct irritant effect on the esophageal mucosa with plenty of liquid if they cannot be avoided (tetracyclines, quinidine, iron salts, aspirin, NSAIDs).

Surgical Intervention

The goal of anti reflux surgery is to reestablish the anti reflux barrier to position the lower esophageal sphincter within the abdomen where it is under positive pressure and to close any associated hiatal defect.

Antireflux Surgery



It should be considered in patients

- Who fail to respond to pharmacologic treatment.
- Who opt for surgery despite successful treatment because of lifestyle considerations including age, time, or expense of medications.
- Who have complications of GERD (Barrett's esophagus).

- d) Who have atypical symptoms and reflux documented on 24-hr ambulatory pH monitoring.

Pharmacologic Treatment

1. Antacids with antacid-alginic acid products

- ∴ An antacid product combined with alginic acid form a highly viscous solution that floats on the surface of gastric contents.
- ∴ This viscous solution serves as a protective barrier for the esophagus against reflux of gastric contents.
- ∴ It also reduces the frequency of reflux episodes.

Eg: Gaviscon

ADR: Diarrhea or constipation, & alterations in mineral metabolism, and acid-base disturbances

2. Acid suppression with H₂ receptor antagonists

- ∴ For symptomatic relief of mild GERD, low-dose nonprescription H₂-receptor antagonists may be beneficial.

Eg: Cimetidine 800 mg twice daily (Cimetidine)

Famotidine 40 mg twice daily (Famocid)

Nizatidine 150 mg four times daily

Ranitidine 150 mg four times daily (Rantac):

ADR: Diarrhoea, headache, rashes, hepatotoxicity

Drug interactions:

- Cimetidine inhibits the activity of cytochrome P450 and consequently retards oxidative metabolism of some drugs.
- The metabolism of number of benzodiazepine including Diazepam, Flurazepam and Trizolam is impaired and levels are raised.

3. Acid suppression with proton pump inhibitors

- ∴ Proton pump inhibitors block gastric acid secretion by inhibiting gastric H⁺/K⁺-adenosine triphosphatase in gastric parietal cells.
- ∴ This produces a profound, long-lasting antisecretory effect capable of maintaining the gastric pH above 4.

Eg: Omeprazole 20 mg (Omez)
Esomeprazole 20 mg (Nexpro)
Lansoprazole 30 mg (Lancid)
Rabeprazole 20 mg (Rabez)
Pantoprazole 40 mg per day (Pantop)

ADR: Diarrhoea, Headache, Abdominal Pain

Drug Interactions: (DI)

- ☞ Omeprazole can increase the concentration of cyclosporine
- ☞ Clarithrimycin increases esomeprazole concentration.
- ☞ Lansoprazole produces increased plasma concentration of tacrolimus.

4. Prokinetic agents

✓ This is given to the patients who have failed high-dose proton pump inhibitor therapy.

✓ ∴ Prokinetic agents have also been used as adjunctive therapy with an H₂ receptor antagonists.

Eg: Cisapride 5-20mg (Cenz)
Metoclopramide 5-10mg (perinorm)
Bethanecho (50mg) (Colinet)

5. Mucosal Protectants

✓ ∴ It is a nonabsorbable aluminum salt of sucrose octasulfate, has very limited value in the treatment of GERD.

∴ Sucralfate has similar healing rates as H2 receptor antagonists for patients with mild esophagitis.
Eg: Sucralfate (1g/10ml)

ADR: Constipation, nausea, dry mouth, dizziness.

Drug interactions: D

- The use of sucralfate with phenytoin, digoxin, theophylline, quinidine, amitriptyline, warfarin, ketoconazole may reduce their bioavailability. Therefore it should be taken two hours following other medicines

Maintenance Therapy

- ∴ H2-receptor antagonists may be effective maintenance therapy for patients with mild disease.
- ∴ The proton pump inhibitors are the drugs of choice for maintenance treatment of moderate to severe esophagitis.

Elderly Patients with GERD

- ∴ Proton pump inhibitors appear to be the most useful treatment modality because they have superior efficacy and are dosed once daily.

Paediatric patients with GERD

- ∴ H2-receptor antagonists are commonly used.
- ∴ A dose of ranitidine 2 mg/kg twice daily is effective.
- ∴ Lansoprazole a dose of 15 mg once daily is recommended for children weighing ≤ 30 kg, and a dose of 30 mg once daily is recommended for those weighing > 30 kg.

□ Inflammatory Bowel Disease: ^{IBD}

- Inflammation of the gastrointestinal tract that exists in two forms:

1- Crohn's disease:

- Is an inflammation of any part of the gastrointestinal tract in which the inflammation extends from the mucosa through the sub-mucosa, muscularis and serosa.

2. Ulcerative colitis:

- Is an inflammation of the mucosa of the colon and rectum, usually accompanied by rectal bleeding.

- Curiously, cigarette smoking increases the risk of Crohn's disease but decreases the risk of ulcerative colitis.

□ Etiology and risk factors of Crohn's disease:

i. Age:

- Young people are more prone to Crohn's

disease.

biological

ii- Environment:

- The exact environmental factors including life style (Ex: food habit), possible toxic exposure (Ex: pollutants) etc. are responsible for spreading the disease is unclear.

iii- Heredity

iv- Smoking habit

Symptoms:

- Chronic diarrhoea
- Abdominal cramping
- Abdominal pain
- Fever

Etiology of ulcerative colitis:

- The exact etiology of ulcerative colitis

is unknown, but few assumptions are there which are as follows:

1. Genetic factor
2. Smoking
3. Diet
4. Infection due to Bacteria, viruses etc.

Symptoms:

1. Bloody diarrhoea
2. Abdominal pain
3. Constipation problems
4. Presence of visible blood and mucus in the stool.

Pathophysiology:

-The causes of ulcerative colitis and Crohn's disease are not known.

-But A reasonable hypothesis:

As yet unidentified antigens, possibly a mycobacterium, paramyxovirus, or

components of cigarette smoke, activate resting macrophages to release a wide variety of cytokines.

- The most abundant cytokine is interleukin-1 (IL-1), which not only causes diarrhea but also acts as a pyrogen.

- Other cytokines activated in the inflammatory process are IL-6, tumor necrosis factor- α (TNF- α), and the chemokine IL-8.

- Cytokines cause differentiation of lymphocytes to different types of T cells.

- Helper T cells, type 1 (Th1), are associated principally with Crohn's disease, whereas Th2 cells are associated principally with ulcerative colitis.

These cytokines serve to stimulate the immune system and cause an inflammatory reaction, thus producing tissue damage in the intestinal mucosa.

- There is a genetic predisposition for both ulcerative colitis and Crohn's disease.

Diagnosis:

i-Crohn's disease:

- Radiology: abdominal X ray with ultrasound
- CT and MRI
- Haematology: increased ESR

ii-Ulcerative colitis:

- Haematology: increased ESR
- Radiology

Treatment:

Non-pharmacologic treatment:

Nutritional support:

- Proper nutritional support
- Avoidance of milk or supplementation of lactate generally improves patients symptoms.
- Dietary supplementation of fish oil.
- Parenteral nutrition in severe cases.

Surgery:

Surgical procedures involves resection of

segments of intestine that are affected as well as correction of complications or drainage of abscesses.

Pharmacological treatments:

◦ Aminosalicylates

Sulfasalazine

Mesalazine

Olsalazine

◦ Steroids:

Prednisolone

Hydrocortisone

◦ Antibiotics:

Metronidazole

◦ Monoclonal Antibody:

infliximab

◦ Miscellaneous:

Arsenic salts 250mg-1g rectally

lidocaine 200-800_{mg} rectally

1-Aminosalicylates:

Sulfasalazine

MOA:

Act on epithelial cells to moderate the release of lipid mediators, cytokines, and reactive oxygen species.

Dose: 4-8 g orally

1-3 g as suppository

3 g as enema

ADR:

Nausea

Vomiting

Diarrhoea

headache

2. Steroids:

Prednisolone

MOA:

-Direct anti-inflammatory and immunosuppressive

actions which rapidly control symptoms.

Dose: 20-60 mg orally
5-10 mg as suppository

ADR:

Cataract

Glaucoma

obesity

dyspepsia

DI: increased risk of GI bleeding when used with NSAIDs.

3. Antibiotics:

Metronidazole

MOA:

Inhibits phospholipase A, contributing to reduction in damage induced by polymorphonuclear leucocytes.

Dose: 600 mg - 1.2 g orally

ADR:

nausea

Vomiting

diarrhoea or constipation

headache

DI: phenytoin

4- Immunosuppressants:

Azathioprine

MOA:

inhibit purine ribonucleotide which may in turn inhibit lymphocyte function, primarily T cells.

Dose: 25 mg/kg/day

Methotrexate

MOA:

Inhibit dihydro folate reductase, inhibition of cytokine and eicosanoid.

Dose:

15-25 mg orally weekly

15-25 mg IM/SC weekly

ADR:

nausea

vomiting

diarrhoea

Stomatitis

DI: NSAIDs, sulfonamides.

Alcoholic liver Disease

- Alcoholic liver disease is damage to the liver and its function due to alcohol abuse.

Etiology and Risk factors:

- Alcoholic liver disease usually occurs after years of excessive drinking.

Risk factors:

i. Quantity and duration of alcohol use:

- A linear correlation generally exists b/w the amount and duration of alcohol use and development of liver disease.

ii. Gender:

- Women are most susceptible to alcoholic liver disease.

- Risk in women may be increased because they have less "Alcohol dehydrogenase" in

their gastric mucosa and liver, thus, first-pass metabolism (oxidation) of alcohol decreased.

iii- Hepatitis-C

iv- Genetic Factor:

The pt with HLA-B8, is more susceptible to alcoholic hepatitis.

Symptoms:

- Abdominal pain
- Dry mouth
- Nausea
- Mental confusion

- Three distinctive forms of alcoholic liver disease includes:

1. Hepatic steatosis (fatty liver)

- It is characterised initially by small lipid droplets which accumulates within the hepatocytes even on moderate alcohol

consumption.

- Excess consumption results in accumulation of lipid in macrovascular droplets, thereby the nucleus gets displaced.

- The overall effect is enlarged liver with no fibrosis and this condition is reversible.

2. Alcoholic hepatitis:

- It is characterised by necrosis of liver cells specifically in the centrilobular region.

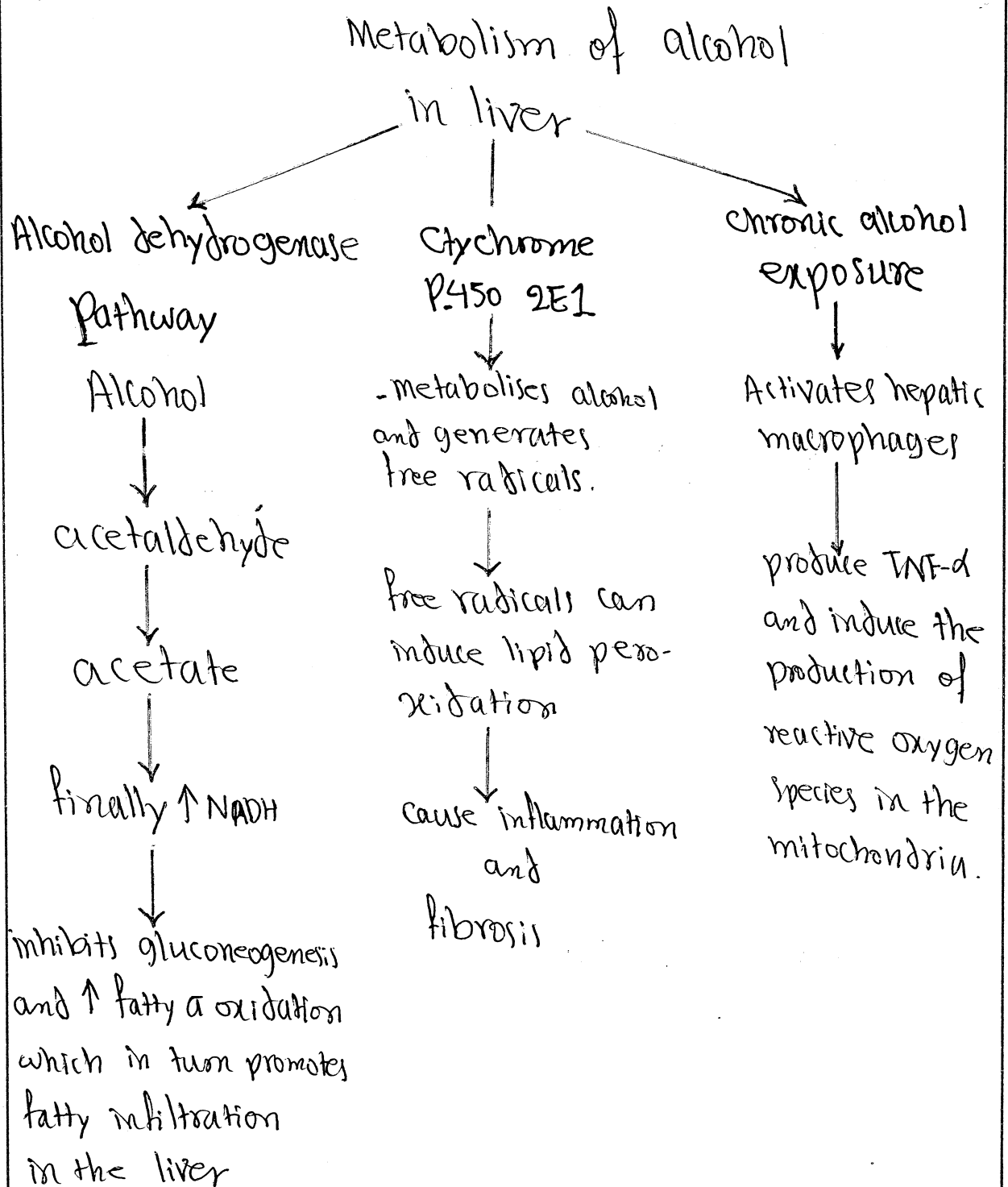
Neutrophilic reaction to degenerating hepatocytes, fibrosis and miliary body formation are some of the features of alcoholic hepatitis.

3. Alcoholic Cirrhosis:

- It is an irreversible and final stage of alcoholic liver disease. The liver acquires brown, ^{as seen} shrunken and non-fatty appearance.

- End stage of alcoholic cirrhosis resembles that of post necrotic cirrhosis.

- Pathogenesis:



□ Diagnosis:

- 1- Blood examination
 - 2- Ultrasound
 - 3- CT scan
 - 4- liver biopsy. → in some cases
- } to assess liver damage.

This minor procedure is done under local anaesthesia, and involves placing a small needle in the liver and obtaining a piece of tissue. The tissue is then sent to the laboratory to be examined under a microscope.

□ Treatment:

1- Abstinence: امتناع

- The first treatment of alcohol-induced liver disease is cessation of alcohol consumption.
- This is the only way to reverse liver damage or prevent liver injury from worsening.

2- Supportive care:

- A nutritional diet and vit supplements

(esp. Vit B) are important during first few days of abstinence.

- Alcohol withdrawal requires use of Benzodiazepines. (e.g. diazepam).

- In pt with advanced alcoholic liver disease, excessive sedation can precipitate hepatic encephalopathy and thus must be avoided.

- Severe acute alcoholic hepatitis commonly requires hospitalization, often in ICU.

3. Specific treatment:

a. Corticosteroids:

e.g. Prednisolone 40mg/d, PO for 4 wks
followed by tapered doses.

MOA:

↓ se inflammation by suppressing migration of PMN leukocytes and reversing ↑ed capillary permeability.

Contraindications:

GI bleeding
renal failure

b-Anticytokines

Ex: pentoxifylline

c-Colchicine to inhibit hepatic fibrosis.

d-Anti-oxidants:

- Alcohol-induced liver damage occurs via generation of oxidants.

↓
Ex: milk thistle

4. liver transplantation:

- Or hepatic transplantation is the replacement of a diseased liver with some or all of a healthy liver from another person.

- When all else fails and liver is severely damaged, the only alternative is a liver transplant.

Disulfiram:

It is a drug used in treatment of alcoholism. It is used to make alcohol consumption an unpleasant experience so that the person gives up drinking.

- It inhibits the enzyme aldehyde dehydrogenase.

Viral Hepatitis

- Hepatitis ^{or} implies injury to the liver characterized by presence of inflammatory cell which is caused by viruses.

Types:

- i- Acute hepatitis: inflammatory necrosis of the liver which ^{persist} persist less than 6 months.
- ii- Chronic hepatitis: prolongation and continuation of hepatic necro-inflammatory process which persist for more than 6 months.

Aetiology:

- Acute Hepatitis

1- Virus

HAV

HEV

herpes simplex etc.

2- Alcohol

3- Pregnancy

4- Drugs

paracetamol

Amoxycillin

□ Chronic Hepatitis:

1- Virus

HBV

HCV

2- Alcohol

3- Autoimmune disease

4- Drugs

methyldopa etc.

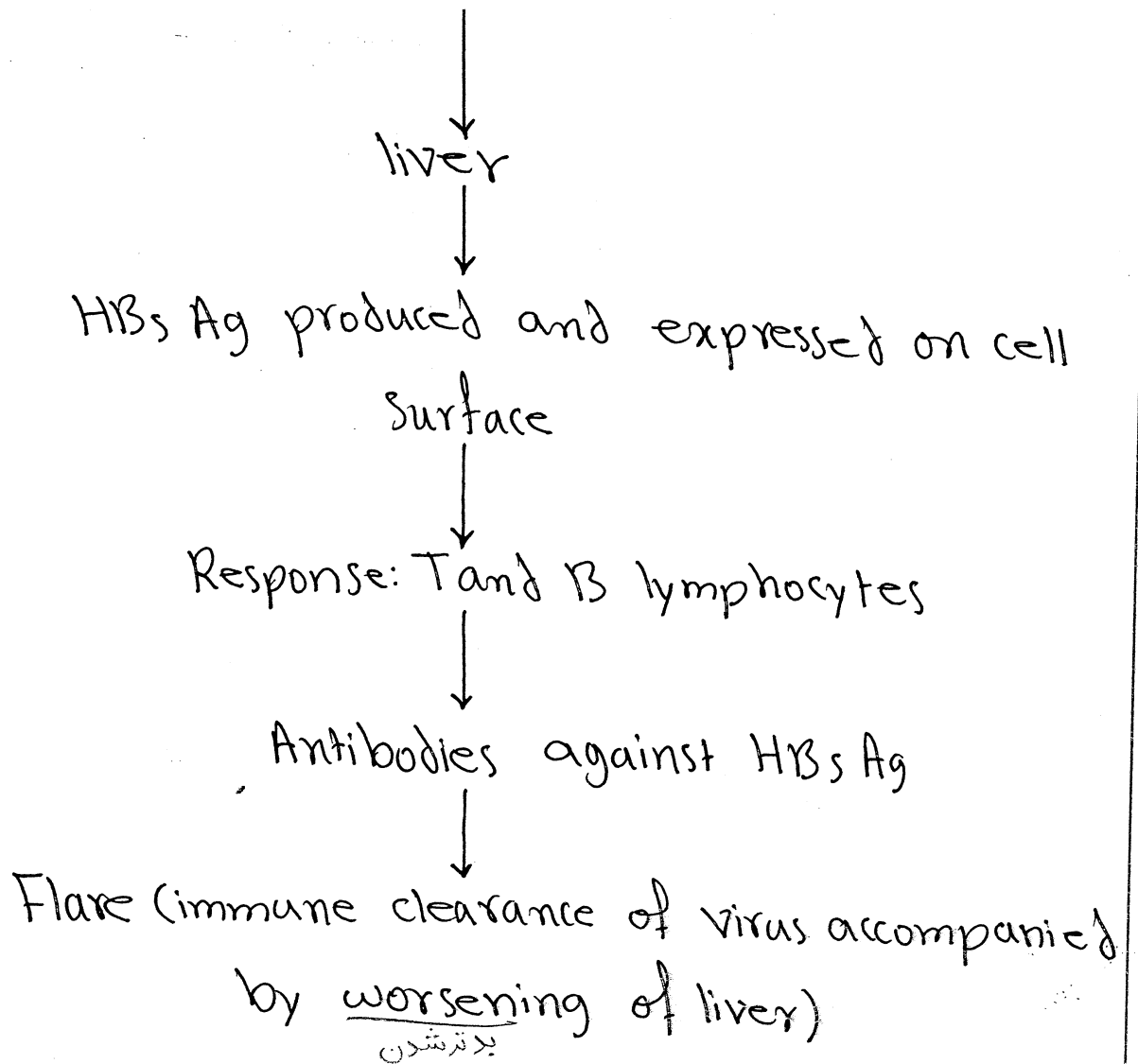
□ Pathophysiology:

□ Hepatitis B:

HBV



Vascular component



- HBV enters the vascular component, it migrates to the liver, where primary replication occurs and interferes with functions of the liver.

HBV replication occurs in liver cells nuclei with HBs Ag produced in the cell cytoplasm and expressed on cell surface.

HBV virions bind to the host cell. During

infection, the host immune responses causes hepatocellular damage and viral clearance. T lymphocytes are important for both the host cellular and humoral responses.

Recovery from acute HBV infection depends on both B and T cell responses.

Signs and Symptoms:

Initial: mild fever, headache, nausea, vomiting, diarrhoea

Other:

Dark urine, pale faeces, enlargement of spleen, weight loss, jaundice

Diagnosis:

1. Blood test:

i- Radioimmunoassay:

a- Test for viral antibodies:

- Specific antibodies against the virus appears

in blood at the onset of symptoms, indicating infection.

Ex:

Antibody to HBV

b-Test for viral genetic material:

Viral genetic materials also appear in the blood.

Ex:

Hepatitis B DNA etc.

II. liver function tests:

-Bilirubin.

Increase in bilirubin level indicates jaundice, hepatocellular damage etc.

DB: 0.1-0.4 mg/dl TB: 0.2-1.1 mg/dl

-Transaminases:

increase in the liver enzymes indicate acute liver damage.

AST: 5-40 U/L

ALT: 7-56 U/L

◦ Serum alkaline phosphatase:

Increase in SAP upto 6 times indicates intrahepatic or extrahepatic cholestasis, metastasis and cholestasis.

35-150 U/L

III. Liver Biopsy:

□ Treatment:

-Goal:

- To decrease morbidity and mortality
- To suppress viral replication
- To prevent and treat symptoms
- To prevent the development of chronic infection

□ Non-pharmacotherapy:

- Sufficient Bed rest
- Avoid hepatotoxic drugs and alcohol
- Frequent meal with low fat, protein and carbohydrates
- Intake of plenty of fluids

PHARMACOTHERAPY:

Hepatitis A :

--99% will recover with out treatment

Drug	Mechanism of action	Doses	Adverse effect	Contraindicati on	Interac
Hepatitis B 1 Interferon	Bind to cell surface receptor & effect viral replication & synthesis of viral mRNA & inhibit translocation	10 million IU 3times/wk	Fatigue, headache, loss of appetite	Hypersensitivity, pregnancy	Theophylline:- increase toxicity decrease the clear

2.Lamivudine	Inhibit DNA polymerase result in chain termination	Adult:- 100mg/day children: 3mg/kg once daily	Fatigue, nausea, vomiting, cough	Hyper sensitivity, lactation	Cotrimoxazole reduce renal excretion drug
Hepatitis C 1 Interferon 2 Ribavarin	It has broad spectrum activity. inhibit GTP & viral RNA synthesis result in viral replication.	Adult :- 1g /day children:- 15mg/kg Daily	Severe anemia, dyspepsia, insomnia	Pregnancy & lactation cardiac disease	Zidovudine: increase effect of drug

Hepatitis D:

--interferone alpha with 9 MU 3 times weekly for at least 12 months.

PREVENTION:

A	HAV vaccine
B	HBV vaccine Don't handle infected person blood, Drug needle Cover don't touch rashes Use 10% solution of household bleach
C	There is no vaccine, Don't handle infected person blood needle vaccine against A & B don't drink alcohol.

HAV	RNA	Faecally spreads
HBV	DNA	Parenterally, sexual contact, blood transfusion
HCV	RNA	Parenterally, needle sharing

Jaundice

Definition:

- Jaundice, or icterus, is a yellowish ^{discoloration} of tissue resulting from the ^{or less} deposition of bilirubin.
- Tissue deposition of bilirubin occurs only in the presence of serum hyperbilirubinemia and is a sign of either liver disease, or less often, a haemolytic disorder.
- The presence of sclera icterus indicates a serum bilirubin of at least $51 \mu\text{mol/L}$ (3.0 mg/dL) (N 0.3-1.0 mg/dL).

Classification:

1. Hemolytic Jaundice (Pre Hepatic)

- This results from excessive red blood cell destruction or due to ineffective erythropoiesis leading to overproduction of bilirubin.

- can be caused due to:

- Intraerythrocytic defects like: sickle cell disease
- Extraerythrocytic defects: cirrhosis, malaria etc

2. Hepato cellular Jaundice (Medical J/ Hepatic)

- Most common type.
- results from inability of the liver to transport bilirubin into bile as a result of liver cell damage, swelling of cells and edema due to inflammation causing mechanical obstruction of intrahepatic biliary tree.
- Concentration of both unconjugated and conjugated bilirubin rises in blood.

- Cause:

Viral hepatitis, Alcoholic hepatitis, drug induced hepatitis like halothane etc.

3. Cholestatic Jaundice (obstructive)

- Cholestasis means failure of bile flow in the liver.

— Intrahepatic cholestasis (small duct obstruction)
: Drugs, Alcohol

— Extrahepatic cholestasis (large duct obstruction)
: Gallstone

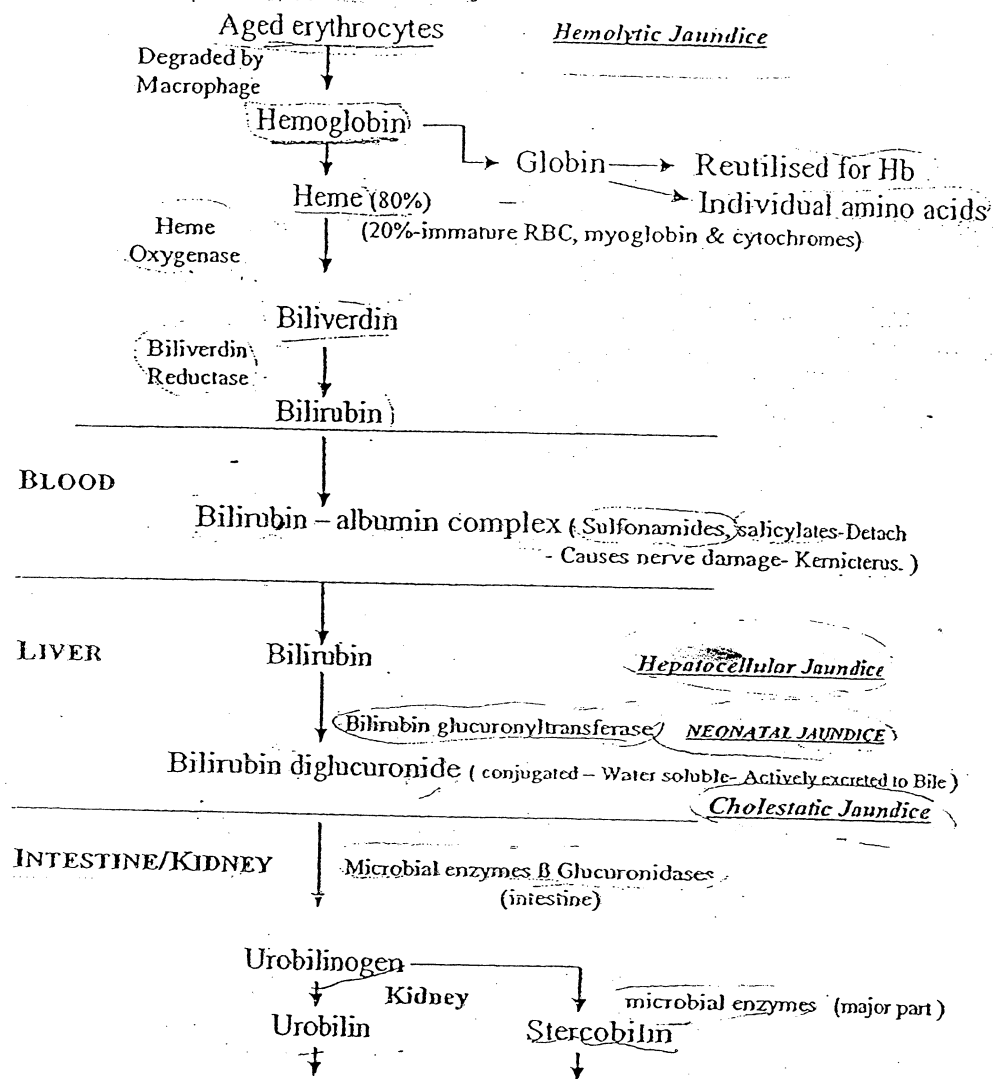
4. Neonatal Jaundice:

- The hepatic machinery for conjugating and excreting bilirubin does not fully mature until about 2 wk of age, hence almost every newborn develops transient and mild unconjugated hyperbilirubemia termed neonatal jaundice.

- Infants are often treated with bili lights, exposing them to high level of coloured lights to break down the bilirubin.

PATHOPHYSIOLOGY:

Summary of bilirubin metabolism:



Both unconjugated bilirubin and bilirubin glucuronides may accumulate systemically and deposit in tissues, giving rise to the yellow discoloration of jaundice.
 The pathophysiologic differences between the 2 forms of bilirubin:-

FEATURE	Unconjugated Bilirubin	Conjugated Bilirubin
Water solubility	Absent	Present
Affinity to lipids	Present	Absent
Normal serum level	More	Less(<0.25mg/dl)
Serum albumin binding	High	Low
Renal excretion	Absent	Present
Affinity to brain tissue	Present (kernicterus)	Absent

- Jaundice occurs when the equilibrium b/w bilirubin production and clearance is disturbed by one or more of the following mechanisms.

1. Excessive production of bilirubin
2. Reduced hepatocyte uptake
3. Impaired conjugation
4. Decreased hepatocellular excretion
5. Impaired bile flow

- The first three mechanisms produce unconjugated hyperbilirubinemia and the latter two predominantly conjugated hyperbilirubinemia.

□ Signs And Symptoms:

◦ Signs:

Xanthomas

Large hard irregular liver

◦ Symptoms:

• Pruritis

• Pale or clay-coloured stools

• Dark urine

• Weight loss

• Bone and Abdominal pain.

Diagnosis:

a. Laboratory studies:

- Elevated serum aspartate and alanine aminotransferase level (AST, ALT).
- Bilirubin raised in serum and present in urine

b. liver biopsy:

c. Imaging:

- By ultra sonography
CT scan
MRI

Treatment:

- If the problem is a disease of liver itself, such as acute viral hepatitis, the jaundice usually gradually disappears as the condition of liver improves.

- In patient with obstruction of bile ducts, therapy is typically directed at mechanical relief

like sphincterotomy, balloon dilation of focal strictures and placement of drains or stents. The alternatives are surgical.

Management of Pruritus:

i-Non-Pharmacological:

use of: emollients
mild fragrance free soaps
less frequent bathing
wearing light clothing.

ii- Pharmacological:

@ Anion exchange resin:

Ex: Cholestyramine
Colestipol

Cholestyramine Resin:

• MDA:

Forms a non-absorbable complex with bile acids in the intestine releasing chloride ions in

the process, inhibits enterohepatic reuptake of intestinal bile salts and thereby increase the fecal loss of bile salt bound low density lipoprotein cholesterol.

ADR:

Constipation

diarrhoea

nausea

Vomiting

Stomach pain

DI:

penicillin

tetracyclin

NSAIDs

digoxin

warfarin

Dose:

Adult oral 4-16g (in two or three divided doses).

⑥ Antihistamines:

Cetirizine } non-sedating antihistamine
loratadine }

MOA:

Competes with histamine for H_1 receptor sites on effector cells in the gastrointestinal tract, blood vessels and respiratory tract.

ADR:

Headache
Drowsiness
Fatigue

DI:

↑ sed toxicity: CNS depressants

DOSE: Adult: oral 5-10mg once daily.

⑦ Phenobarbital and Rifampicin:

induce hepatic microsomal enzymes, which may benefit some pt, possibly by improving bile flow.

-Ritampicin (600mg/day) is effective in the treatment of pruritus.

① Opioid antagonists:

-used to treat pruritus.

-Because it is believed that ^{تولید شده در داخل ارگانیسم} endogenous opioids in the central nervous system are potent mediators of itch.

Ex:

Naloxone

Naltrexone

dose 50mg/day

② Topical preparations:

Calamine lotion

menthol 2% in aqueous cream.

Drug Induced Liver Disorder

- liver is one of the major organ for metabolism.
Almost all of the drugs are metabolised in liver.
Medications have side effects that may harm liver.

-Definition:

- is used to describe abnormalities in liver function following exposure to a drug or non-infectious agent.

□ Classification:

1. Intrinsic Hepatotoxicity:

a) Direct:

Directly destroy the hepatocytes through their toxic effects.

Ex: CCl_4

b-Indirect: induce structural changes in the hepatocytes.

Ex:

Acetaminophen

2. Idiosyncratic:

- This occurs in persons who have inherited specific genes that control the chemical transformation of that specific drug, causing accumulation of the drug or products of their transformation (metabolites) that are injurious to the liver.

Eg:

Halothane

ETIOLOGY:-

Liver disease	Causes (drugs)
Hepatocellular necrosis	Paracetamol, propylthiouracil, salicylates, iron salts, allopurinol, dantrolene, halothane, ketoconazole, isoniazid.
Fatty liver	Amiodarone, tetracyclines, steroids, sodium valproate, L-asparaginase.
Cholestasis	Oral contraceptives, carbimazole, anabolic steroids, ciclosporin.
Cholestasis with hepatitis	Chlorpromazine, tricyclic antidepressants, erythromycin, flucloxacillin, ACE inhibitors, NSAIDS, sulphonylureas, ranitidine, phenytoin.
Granulomatous hepatitis	Phenytoin, clifibrate, hydralazine, sulphonylureas, sulfonamides.
Acute hepatitis	Isoniazid, phenytoin.
Chronic active hepatitis	Methyldopa, nitrofurantoin, isoniazid.
Fibrosis & cirrhosis	Methotrexate, methyldopa, vitamin A (dose related).
Vascular disorders	Azathioprine, dactinomycin.

Pathophysiology:

Pro-toxin $\longrightarrow$ Toxin $\longrightarrow$ Necrosis
(drugs)

The liver often bears the brunt of the toxic action of many drugs because

The liver is the first organ to come in contact with the drug after absorption from the GIT.

The liver expresses high levels of enzymes for the metabolism of various drugs.

Sometimes (pro-toxins) are metabolised to toxic products.

CLINICAL MANIFESTATION:-

Type of liver damage	Signs & symptoms
Hepatocellular necrosis,	Anorexia, malaise, lethargy, abdominal pain, hypoglycemia, metabolic acidosis, bruising & bleeding, hepatic encephalopathy, oliguria & anuria.
Steatosis	Fatigue, nausea, vomiting, hypoglycemia & confusion
Acute hepatitis	Anorexia, dark urine, nausea & vomiting, pale stools and jaundice, weight loss.
Chronic active hepatitis	Tiredness, lethargy, hepatic encephalopathy.
Cholestasis	Severe pruritus, dark urine, jaundice, pale stool, abdominal pain.
Vascular disease	Hepatomegaly, jaundice.
Hepatic tumor	Abdominal pain, weight loss, fatigue, anorexia.

□ Forms:

1. Acute drug induced liver disease:

a- Hepatocellular Injury:

- Necrosis: Acetaminophen, Methyl dopa
- Steatosis: Tetracycline, Ethanol.

b- Cholestatic Injury:·

Chlorpromazine, Oral Hypoglycemic Agents.

c- Mixed Injury:

NSAIDs, Phenytoin

2. Chronic Drug Induced Liver Disease:

a- Chronic Hepatitis:

Anti TB drugs, Aspirin

b- Toxic Cirrhosis: INH

c- Chronic Steatosis:

Glucocorticoids

Ethanol

δ - Fibrosis and Cirrhosis:

Methotrexate

▣ Acute drug induced liver disorder:

- Hepatocellular injury can be either cytotoxic or cytolytic and it result in damage to liver parenchyma.

1- Necrosis:

Drug induced hepatocellular necrosis may primarily involve cells in a centrilobular (zonal) pattern, a diffuse (non zonal pattern) or it may affect significant portion of the entire liver.

2. Steatosis:

This can be macrovesicular or microvesicular
In microvesicular steatosis, the hepatocytes are filled with many tiny droplets of fat that does not displace the nucleus.

-In macrovesicular steatosis, the hepatocytes contains a large fat droplets that displace the nucleus to the periphery.

3. Cholestatic injury:

-These are manifested by:

1. bile stasis without inflammation and with parenchymal injury which is characterized as hepatocanalicular.

2. By cholestasis with inflammation and slight parenchymal injury which is characterized as canalicular.

Chronic drug induced liver disease:

1. Chronic hepatitis:

-All chronic necro inflammatory disease of the liver is now referred to as chronic hepatitis.

Category:

1. The 1st gp:

Consists of drugs that induce liver injury that resembles autoimmune hepatitis.

- Drugs associated with this form of injury are often taken for prolonged periods.

2. Type 2 drug induced chronic hepatitis:
is characterised by antibody formation against Cytochrome P450

3. Type 3:

Drugs such as sulfonamides make up a third form of drug induced chronic hepatitis.

- Patients with type 3 injury often have elevation in their aminotransferases with histologic evidence of chronic hepatitis.

4. Type 4: of drug induced CH produce chronic toxicity rather than the chronic necroinflammatory disease that resembles chronic hepatitis.

Drugs: Acetaminophen, aspirin

2

Classification

A - Based on RBC size

i - microcytic, Hypochromic

- Iron-deficiency anemia
- Thalassemia
- sideroblastic chronic disease

ii - Normocytic, Normochromic

- Hemolytic
- chronic disease

iii - Macrocytic

- Megaloblastic (vit B₁₂ and folate d)
- Non megaloblastic (Aplastic)

B - Nutritional deficiency (iron, vit B₁₂, folate)

C - Hereditary

- Sickle cell a
- Thalassemia
- Aplastic

D - RBC destruction → Hemolytic anemia

□ Anemia

- Anemia is a medical condition in which the red blood cell count or hemoglobin is less than normal.

- For men, anemia is typically defined as hemoglobin level of less than 13.5 gram/100ml and in women as hemoglobin of less than 12.0 gram/100ml.

Types:

1- Aplastic Anemia:

- Anemia due to failure of the bone marrow to produce red and white blood cells as well as platelets.

Causes:

1- Toxic exposure to radiation and chemicals such as benzene

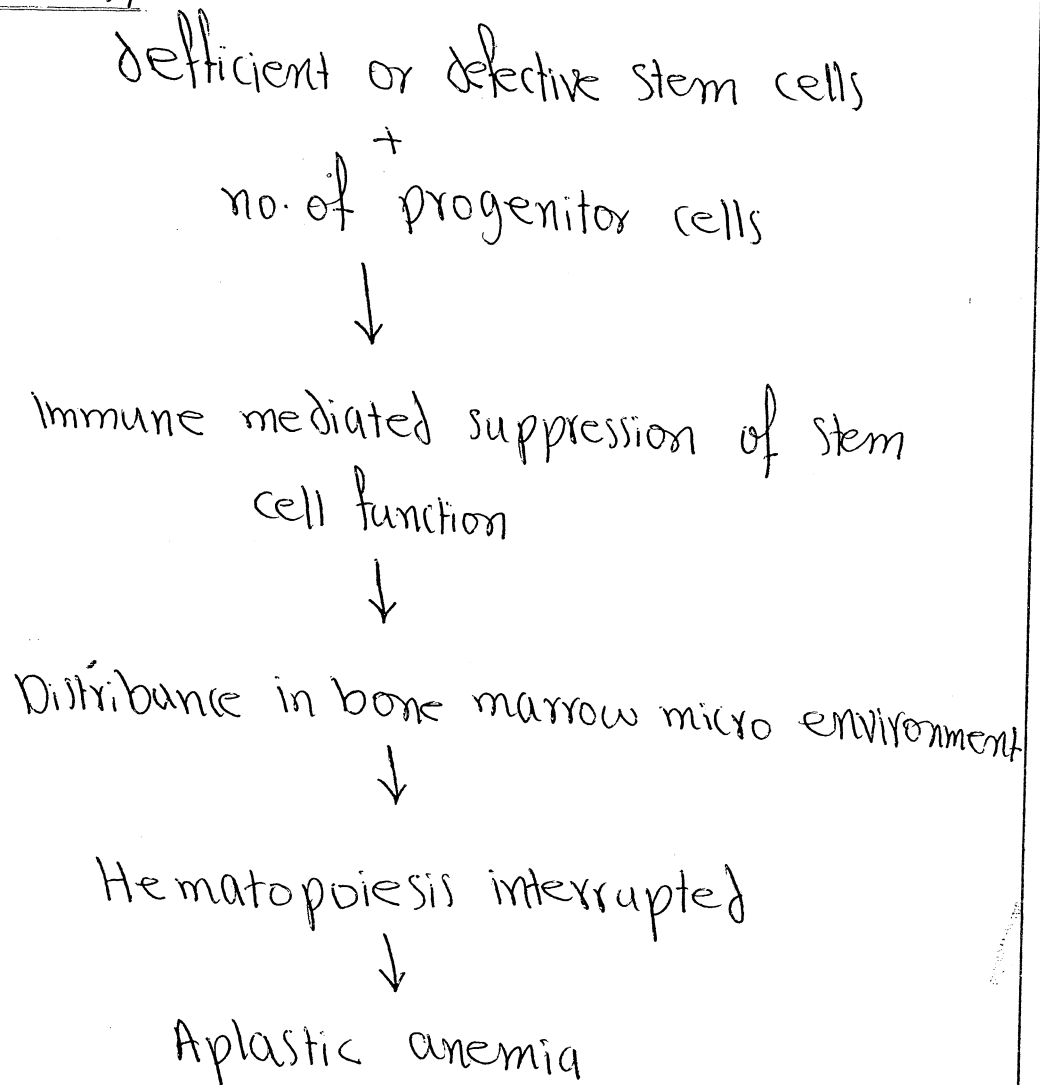
2- Drugs: Chloramphenicol

3- Elements: Gold

4- Pregnancy

5- Infectious causes: HIV, hepatitis viruses

Pathophysiology:



Signs and Symptoms:

Shortness of breath

dizziness

headache

pale skin, gums, and nail beds

chest pain

fever

coldness in your hands or feet

Diagnosis:

Lab Findings:

- ★ Severe pancytopenia with relative lymphocytosis
- ★ Normochromic, normocytic RBCs
- ★ Decreased reticulocyte count
- ★ Bone marrow aspiration and biopsy: Hypocellular/aplastic bone marrow with increased fat spaces

Blood:

- Neutrophils - less than $0.5 \times 10^9/L$
- Platelets - less than $20 \times 10^9/L$
- Reticulocytes - less than 1% corrected (percentage of actual hematocrit [Hct] to normal Hct)

Marrow:

- Severe hypocellularity
- Moderate hypocellularity, with hematopoietic cells representing less than 30% of residual cells.

□ Treatment:

- 1- Transfusion
2. Treatment of infections
3. BMT with an HLA-matched sibling donor
4. Immunosuppressive therapy
5. Options include combination therapy, including ATG, CSA and methyl prednisolone, with or without Cytokine support.

Name of drug	MOA	Dose
Cyclosporine (Sandimmune, Neoral)	Cyclic polypeptide that suppresses some <u>humoral immunity</u> and, to a greater extent, <u>cell-mediated immune reactions</u>	1.5-2 mg/kg IV q12h, adjust to trough level of 500-800 ng/mL
Methylprednisolone (Medrol, Solu-Medrol)	ameliorate the <u>delayed effects of anaphylactoid reactions</u> and may <u>limit biphasic anaphylaxis</u>	5 mg/kg IV on days 1-8; then tapered by using PO 1 mg/kg on days 9-14; further tapering over days 15-29; stop after 1 mo
Cyclophosphamide (Cytosan)	<u>cross-linking of DNA</u> , which may <u>interfere with the growth of normal and neoplastic cells</u>	45 mg/kg/d IV for 4 d

2-Hemolytic anemia:

-is a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over.

-Etiology:

- 1- Hereditary disorders: sickle cell anemia
2. toxic chemical
3. drugs
4. infections
5. immune system attacking the red blood cells
6. destruction of blood cells passing through diseased heart valves.

□ Pathophysiology:

-The pathophysiology of hemolytic anemia involves the destruction of erythrocytes and the subsequent acceleration of erythropoiesis.

□ Signs and symptoms:

- 1- General pallor

2. Tachycardia, tachypnea and hypotension
3. jaundice
4. leg ulcers
5. Splenomegaly

Diagnosis:

- Laboratory Studies
- Complete blood cell (CBC) count
- Peripheral smear and morphologic examination

1. A low mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) are consistent with a microcytic hypochromic anemia, which may occur in chronic intravascular hemolysis (eg. PNH).

"Red blood cell distribution width"

2. An increased RDW is a measure of anisocytosis which is likely in hemolytic anemia.

3. An increased reticulocyte count is a criterion for hemolysis but is not specific for hemolysis.

4. LDH

◦ Although an increase in LDH isozyme 1 and 2 is more specific for red blood cell destruction, these enzymes are also increased in patients with myocardial infarction.

5. Serum haptoglobin:

◦ A low serum haptoglobin level is a criterion for moderate to severe hemolysis.

6. Unconjugated bilirubin is a criterion for hemolysis, but it is not specific because an elevated bilirubin also may indicate Gilbert disease.

- Changes in the LDH and serum haptoglobin levels are the most sensitive general tests because the indirect bilirubin is not always increased.

□ Treatment:

1. Transfusion therapy
2. Discontinuing medications
 - Penicillin
 - Ampicillin
 - Quinine
 - Quinidine
3. Folic acid
2. Corticosteroids
4. Intravenous immunoglobulin G (IVIG)
5. Iron therapy

Name of drug	MOA	Dose
Vitamin- Folic acid (Folvite)	Cofactor for enzymes involved in production of red blood cells. Replenishes depleted folate stores consumed during chronic hemolysis	50 mcg/d PO/IV for 2 d, followed by 2 mg PO twice a wk or 0.5-1 mg/d
Corticosteroid- Prednisone (Deltasone, Orasone)	Inhibits phagocytosis of antibody-covered red blood cells. Indicated in some hemolytic disorders such as AIHA.	1-1.5 mg/kg/d PO maintained for as many as 3-4 wk

3- Sickle Cell Anemia:

A genetic blood disorder caused by the presence of an abnormal form of hemoglobin.

- Normally, your ^{red} blood cells are flexible and round, moving easily through your blood vessels. In sickle cell anemia, the red blood cells become rigid and sticky and are shaped like sickles or crescent moons. These irregularly shaped cells can get stuck in small blood vessels, which can slow or block blood flow and oxygen to parts of the body.

Etiology:

1- is caused by an abnormal type of hemoglobin called hemoglobin S.

- Sickle cell anemia is inherited from both parents.

Pathophysiology:

point mutation in the B-globin
chain of haemoglobin



causing the amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position.



The association of two wild-type α -globin subunits with two mutant β -globin subunits forms haemoglobin S (HbS)



under low-oxygen condition

promotes the non-covalent polymerisation (aggregation) of haemoglobin, which distorts red blood cells into a sickle shape and decreases their elasticity

Signs and Symptoms:

1. Attacks of abdominal pain
2. Bone pain
3. Breathlessness
4. Paleness

5. Fever
6. rapid heart rate
7. Ulcers on the lower legs
8. Chest pain
9. Strokes

Diagnosis:

1. Complete blood count (CBC)
2. Sickle cell test
3. Bilirubin
4. Blood oxygen
5. CT scan or MRI
6. Serum hemoglobin
7. blood in the urin
8. White blood cell count.

Name of drug	MOA	Dose
<u>Codiene</u>	Binds to opiate receptors in CNS, causing <u>inhibition of ascending pain pathways</u> , <u>altering perception and response to pain</u>	15-60 mg PO <u>IV/IM/SC</u> q4-6h not to exceed 120 mg/d
Aspirin (Anacin, A scriptin, Bayer)	Treats mild to moderate pain. <u>Inhibits prostaglandin synthesis</u> , which prevents <u>formation of platelet-aggregating thromboxane A₂</u>	325-600 mg PO <u>q4h</u>

Oxycodone and
acetaminophen
(Percocet, Roxicet)

Drug combination indicated for the relief of moderate to severe pain. DOC for patients who are hypersensitive to aspirin.

(1 tab. PO q4-6h prn)

Name of drug

Dose

Interaction

Cefuroxime (Ceftin)

250 mg PO q12h or 750-1500 mg IV/IM

q8h Disulfiramlike reactions may occur when alcohol is consumed within 72 h

Amoxicillin and clavulanate
(Augmentin)

250-500 mg PO q8h

Coadministration with warfarin or heparin increases risk of bleeding

4-Thalassemia:^{5M}

-Thalassemia is a blood disorder passed down through families (inherited) in which the body makes an abnormal form of hemoglobin, the protein in red blood cells that carries oxygen.

-The disorder results in excessive destruction of red blood cells, which leads to anemia.

◦ Hemoglobin is made of two proteins, Alpha globin and beta globin.

Thalassemia occurs when there is a defect in a gene that helps control production of one of these proteins.

◦ There are two main types of thalassemia.

1: Alpha thalassemia occurs when a gene or genes related to the alpha globin protein are missing or changed (mutated).

2: Beta thalassemia occurs when similar gene defects affect production of the beta globin protein.

- Both alpha and beta thalassemia include the following two forms:

→ thalassemia major

→ thalassemia minor

- You must inherit the defective gene from both parents to develop thalassemia major.

- Thalassemia minor occurs if you receive the defective gene from only one parent. Persons with this form of the disorder are carriers of the disease and usually do not have symptoms.

- Beta thalassemia major is also called Cooley's anemia.

i- Alpha thalassemia:

- Four genes are involved in making the alpha globin part of hemoglobin - two from each parent. Alpha thalassemia occurs when one or more of these genes is variant or missing.

- People with only one gene affected are called silent carriers and have no sign of illness.
- People with two genes affected (called alpha thalassemia minor) have mild anemia and are considered carriers.
- People with three genes affected have moderate to severe anemia, or hemoglobin H disease.
- Babies with all four genes affected (called alpha thalassemia major) usually die before or shortly after birth.

ii. Beta thalassemia:

- Two genes are involved in making the beta globin part of hemoglobin - one from each parent. Beta thalassemia occurs when one or both of the two genes are variant.
- If one gene is affected, a person is a carrier and has mild anemia. (beta thalassemia minor).
- If both genes are variant, a person may have moderate anemia or severe anemia.

□ Signs and symptoms:

1. Fatigue and weakness
2. Pale skin
3. jaundice
4. Dark urine
5. Enlarged spleen and liver
6. poor growth

Diagnosis:

- i - Red blood cells will appear small and abnormally shaped when looked at under a microscope.
- ii - A complete blood count (CBC) reveals anemia.
- iii - Hemoglobin electrophoresis test: shows the presence of an abnormal form of hemoglobin.
- iv - A test called mutational analysis can help detect alpha thalassemia that cannot be seen with hemoglobin electrophoresis.

□ Treatment:

1- Avoid iron supplementation as it contributes to iron overload and does not affect hematologic values or cell morphology.

2. Administer folate supplementation to provide adequate amounts of the vitamin for increased utilization resulting from the hemolytic process and high bone marrow turnover rate.

3. Provide prompt attention to infection, especially in children who have had splenectomy, and administer appropriate vaccines to these individuals.

4. Administer blood transfusions only if necessary.

5. Long term vitamins like folic acid supplements.

6. Regular blood transfusions may be required.

7. Splenectomy - spleen may need to be removed.

8. Bone marrow transplantation

9. Drugs:

Deferoxamine (Desferal)

20-40 mg/kg

Deferasirox

20 mg/kg

5- Sideroblastic Anemia:

- Sideroblastic anemia is a term used to describe a group of rare blood disorders characterized by the bone marrow's inability to manufacture normal red blood cells.

- Abnormal, iron-saturated red cells are present in the blood of people who have this disease.

- Sideroblastic anemia can be inherited but the disease is usually acquired as a result of illness or exposure to toxic substances.

Etiology:

1. Hereditary

2. Acquired:

Toxins: lead or zinc poisoning

Drug-induced: ethanol, isoniazid, cycloserine

Nutritional: copper deficiency

□ Pathophysiology:

1- Defects in the steps of heme biosynthesis

that occur within the mitochondrion produce sideroblastic anemias.

2. The X-linked hereditary sideroblastic anemias result from mutations in the gene encoding ALA-S.

3. Perturbations of the enzymatic activity of delta-amino levulinic acid synthase (ALA-S) produce sideroblastic anemia.

□ Signs and Symptoms:

- 1- Fatigue
2. dizziness
3. Skin paleness
4. enlarged spleen and liver
5. Heart disease.

□ Diagnosis:

- 1- Ringed sideroblasts are seen in the bone marrow.

2. The MCV is decreased (i.e. a microcytic anemia)
3. The RDW is increased with the red blood cell histogram shifted to the left.
4. Serum iron, percentage saturation and ferritin are increased.

Treatment:

1. Transfusion
2. Bone marrow transplantation
3. liver transplantation
4. Antidotes

Name of drug	MOA	Dose
Deferoxamine mesylate (Desferal)	Readily chelates iron from <u>ferritin and hemosiderin</u> but not transferrin. Does not affect iron in cytochromes or hemoglobin. Most effective when provided to the circulation continuously by infusion. Helps prevent damage to the liver and bone marrow from iron deposition.	<u>1 g IM</u> , followed by <u>500 mg</u> 4 and 8 h later
Deferasirox (Exjade)	Oral iron chelation agent demonstrated to <u>reduce liver iron concentration</u> in adults and children who receive repeated RBC transfusions. Binds iron with high affinity in a 2:1 ratio.	Initial: 20 mg/kg qd on empty ston
Folic acid	Required for erythropoiesis	<u>1 mg PO/IM/SC</u> qd
Pyridoxine (Aminoxin)	Necessary for normal metabolism of proteins, carbohydrates, and fats. Also involved in the synthesis of GABA within the CNS	<u>50-600 mg</u>

Venous Thromboembolism

- Presence of ^{is} thrombus in one or more deep veins of the lower limbs with swelling, warmth and erythema, frequently precursor for pulmonary embolism.

- A deep vein thrombus is a thrombus composed of cellular material and fibrin, which can form in any vein in the body.

- Thrombosis is a pathological condition resulting in the formation of haemostatic plug within the vasculature in the absence of bleeding.

Etiology:

VTE occurs due to:

i - Stagnation^{is} of blood flow

ii - Hypercoagulability

→ Stagnation of blood flow related to bedrest surgery or reduced cardiac output (in heart failure).

→ Factors increasing the risk of hypercoagulability includes surgery, pregnancy, oestrogen administration, MI etc.

Risk Factors:

A: Patient factors:

- Age >40 , risk increases exponentially with age.
- Obesity
- Previous history
- Oral contraceptive and hormone replacement therapy

B: Medical conditions:

- MI/heart failure
- Major injuries
- Inflammatory bowel disease

C- Surgical conditions:

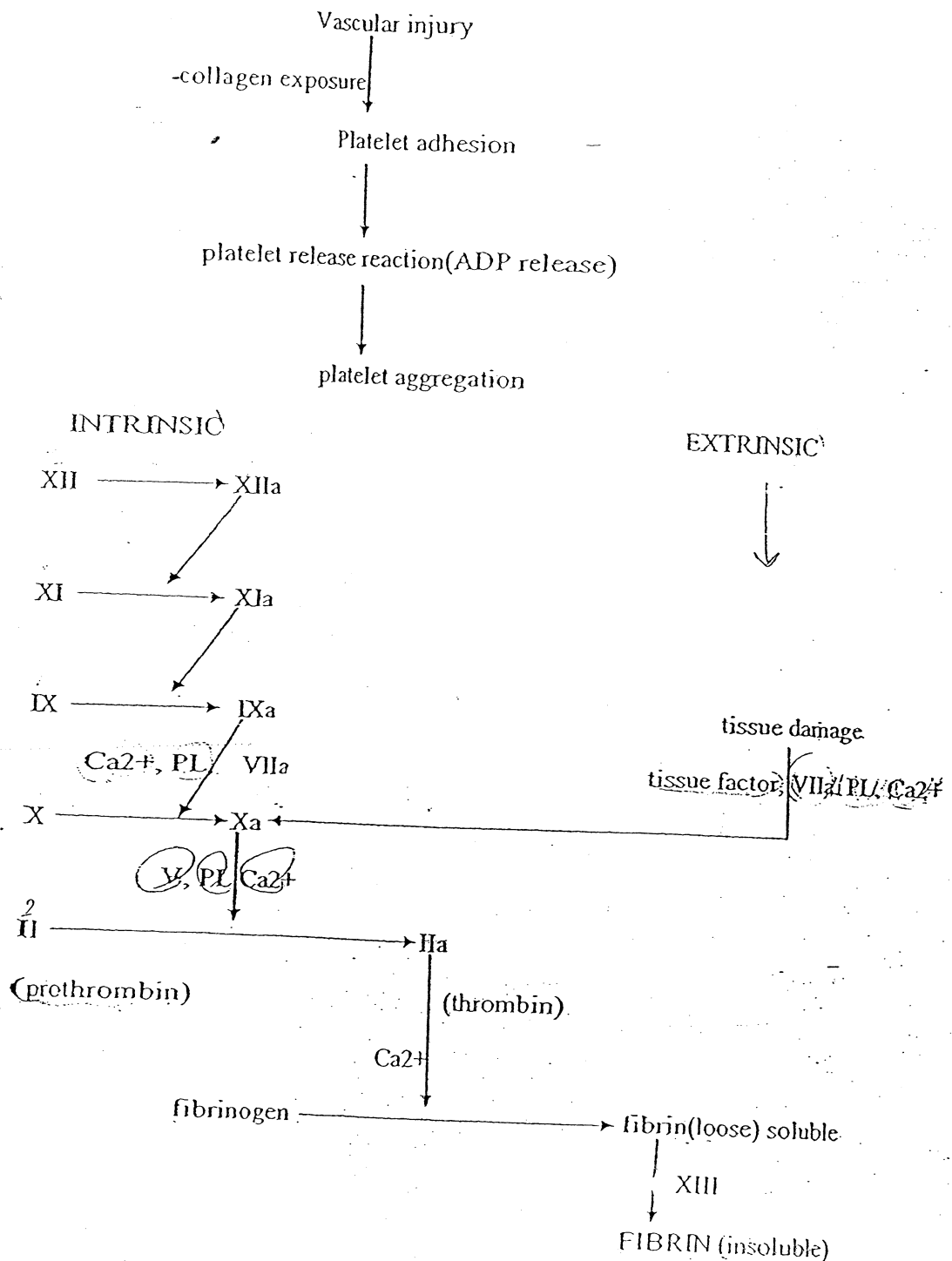
- Surgery for more than half an hour duration
- abdominal, pelvis, orthopaedic surgery to lower limb

D: Anti-coagulant deficiencies:

- Heparin cofactor II
- Antithrombin III

E: Increased clotting factors: Factor XI and VIII

PATHOPHYSIOLOGY



- ⊙ When injury occurs to the vascular endothelium, platelet adheres to the exposed collagen, as well as to other exposed subendothelial tissue.
- ⊙ Following platelet adhesion, release of ADP by the injured platelets leads to platelet aggregation.
- ⊙ Transformation of this temporary platelet plug to a permanent platelet fibrin clot is achieved through activation of the intrinsic or extrinsic blood clotting system.
- ⊙ Each of the clotting factors circulates in the blood as an inactive protein.
- ⊙ Before clotting can occur, each clotting factor must be converted to an active or enzymatic form. -
- ⊙ Exposure of sub endothelial collagen, in addition to interaction with platelets, initiates the intrinsic pathway by stimulating the activation of factor XII.¹²
- ⊙ Activated factor XII then stimulates the conversion of factor XI to the active form, which then stimulates the activation of factor IX.
- ⊙ Activated factor IX, in the presence of Ca^{2+} , phospholipids and factor VIII, stimulates the conversion of factor X to its active form.
- ⊙ Activated factor X in the presence of calcium, phospholipids and factor V, stimulates the conversion of prothrombin to thrombin.
- ⊙ The extrinsic clotting pathway also stimulates the conversion of prothrombin to thrombin.
- ⊙ The release of material that is extrinsic to the blood, such as tissue extract or tissue thromboplastin, activates factor VII, which stimulates the activation of factor X.
- ⊙ Factor X thus occupies a central position at the junction of the extrinsic and intrinsic systems, the pathway at this point becomes the common pathway.
- ⊙ Thrombin which is generated by both pathways, stimulates the conversion of fibrinogen to fibrin in the presence of ionised calcium.
- ⊙ The initial soluble fibrin clot is further converted to an insoluble fibrin polymer when factor XIII is activated by thrombin.

□ Signs And Symptoms:

1. DVT of iliac, femoral or popliteal vein:

Swelling

warmth

erythema: قرمز پوست ناشی از احتقان وریدی

increased tissue turgor
متورم و سفت بودن

2- DVT of calf vein:

Posterior calf tenderness

warmth

modest swelling

mild fever

□ Diagnosis:

A- Clotting properties of blood:

D- Dimer, it is a by product of clotting material.

Measurement gives an indication of hypercoagulability etc.

B- Venography:

Contrast medium is injected into superficial veins of foot and directed towards deep veins by tourniquets. Presence of filling defects or absence of filling of deep veins indicates DVT.

C- Impedence plethysmography:

Use of pneumatic cuffs to detect leg blood volume changes associated with thrombosis.

□ Treatment:

Aims:

- To prevent
- 1) clot becoming larger
 - 2) clot becoming loose
 - 3) new clot formation
 - 4) post thrombotic syndrome

□ Non-pharmacological Treatment:

1. Bed rest: rest decreases oxygen requirement, limit risk of thrombus dislodgment, fibrinolytic breakdown and clot destruction.

-the heparin-antithrombin III complex inhibits activated factor X and thrombin, while LMWH only inhibit factor X and not thrombin.

2. Exercise: Gentle exercise minimize further thrombus formation.
3. Increase fluid intake up to 2L/day
4. Avoid deep palpation
5. Compression stocking to relieve pain and swelling and to prevent post thrombotic syndrome they improve venous flow.

Pharmacological Treatment:

A) ANTICOAGULANTS

1. Injectable anticoagulants

Heparin

MOA: A rapid acting anticoagulant, exerts its antithrombotic effect by accelerating the action of a naturally occurring inhibitor of thrombin, α_2 -globulin, antithrombin III. Antithrombin III inhibits activated clotting factors that have a reactive serine residue at their enzymatically active centre (Heparin by binding at the lysine group of AT III induces to the serine group on the activated clotting factors).

Dose:

IV bolus injection (5000-10000 units every hour)

continuous IV infusion (1000 units/hr)

(SC 3000-5000) followed by 15000-17000U/Kg every 12 hr

ADRs (Hemorrhage, thrombocytopenia, osteoporosis, hypoaldosteronism, hypersensitivity reactions).

LMVH

Eg: enoxaparin, daltaparin, ardeparin, danaperoid

MOA: They have reduced binding to plasma protein, macrophages and endothelial cells, platelets and to osteoblasts. They produce their anticoagulant activity through activating antithrombin.

Use: prophylaxis of DVT

Dose: 1 mg/kg given SC 12 hrs or 1.5 mg/kg SC every 24 hrs

ADR: bleeding, thrombocytopenia, delayed hypersensitivity skin reaction

2. Antithrombin III independent anticoagulants

Heparinoids: eg, danaperoid

MOA: They cause the inhibition of IIa

Use: prophylaxis of DVT

Herudins: eg, lepirudin

MOA: They cause the inhibition of IIa

Use: treatment of type II heparin induced thrombocytopenia

3. Oral anticoagulants

Eg: warfarin

The activation of factor II, VII, IX and X depends upon reduced form of Vit K and enzyme carboxylase...

MOA: inhibit synthesis of vit-k dependent clotting factors such as II (VII, IX and X) warfarin inhibits the effect of vit-k at a post ribosomal step in the hepatic synthesis of the vit-k dependent clotting factors. Vit-k is required in the conversion of non active precursor proteins that lack Ca²⁺ binding capacity to active precursor proteins. This Ca²⁺ binding capacity is needed to hold prothrombin onto phospholipid surfaces during its activation to thrombin.

Use: effective in the primary and secondary prevention of venous thromboembolism as well as in systemic embolism.

Dose: 2-10 mg initially, dose adjusted to prothrombin time.

ADR: Hemorrhage, hepatotoxicity, diarrhoea

DI: Amiodarone, cimetidine, ciprofloxacin and clotrimoxazole inhibits metabolism of warfarin.

NSAID's inhibits platelet function of heparin when taken concurrently with heparin.

B) FIBRINOLYTIC DRUGS:

E.g.: streptokinase, urokinase; alteplase

Urokinase: directly activates plasminogens.

Streptokinase: form a complex with plasminogen which then converts plasminogen to plasmin. Plasmin breaks down clots as well as fibrinogen & other plasma proteins.

Use: pulmonary embolism, anticoagulation treatment failure and in extensive proximal venous thrombosis.

Dose: 100000-250000 units/24-72 hrs.

ADR: hemorrhage, hypertension, allergy, fever, back pain, abdominal pain

Advantages of LMWH over unfractionated heparin

- Increased binding to plasma proteins or endothelium intum leading to,
 - a) Increased bioavailability
 - b) Predictable anticoagulant response
- Affinity for macrophages
- Affinity for platelets
- No monitoring required
- Convenient OD doses
- Decreased incidence of thrombocytopenia

Patient care

- Exercise legs regularly-30 mins brisk walk daily
- Maintain BMI.
- Avoid sitting or lying in the bed for long periods of time without moving legs
- Females >35 yrs should consider risk benefits of OCP's & HRT

For traveller's:

- Exercise legs once/hr during long distance travel, special foot cushions can be used.
- Avoid sleeping pills to prevent immobility.
- Wear loose fitting clothes.
- Keep legs closed.
- Avoid alcohol to prevent dehydration.

Plasminogen

↓ Strep

Plasmin
(activated form)

↓

Fibrin
(clot)

→ Soluble
product

Drug Induced Hematological Disorders

Definition:

The hematological disorders which are induced by the usage of drugs are known as drug induced hematological disorders.

Types of drugs induced Hematological disorders:

1. Aplastic anaemia

Eg: Aspirin, Captopril, Dapsone, Acetazolamide

2. Agranulocytosis:

Eg: Acetaminophen, NSAIDs, Gold salts, β -lactam antibiotics.

3. Megaloblastic anemia:

Eg: Chloramphenicol, metformine, methotrexate, Vinblastine, 5-fluorouracil

4. Thrombocytopenia:

Eg: Quinine, Gold salts

5. Hemolytic anaemia:

Eg: ACE inhibitors, Dapsone, INH

□ Drug-Induced Aplastic Anemia:

Definition:

When a drug causes decrease in all three cell lines accompanied by a hypoplastic bone marrow, the result is termed drug-induced aplastic anaemia.

Symptoms:

- Pallor
- Fatigue
- Weakness
- Fever
- Chills

□ Causes:

The cause of drug induced aplastic anaemia is damage to the pluripotent hematopoietic stem cells, before their differentiation to committed

Stem cells. This damage effectively reduces the normal levels of circulating erythrocytes, neutrophils and platelets.

- Gold salts: Overproduction of cytokines from the activated T-lymphocytes appear to be responsible for hematopoietic failure.

- The nitroso group [of chloramphenicol] may then interact with DNA in the stem cell, causing damage to the chromosome and eventually cell death.

TREATMENT:

- Goals: To improve peripheral blood counts so that patient does not require transfusion and are not at risk for opportunistic infections.
- Steps:
 - o Remove the suspected agent.
 - o Provide adequate supportive care (symptomatic treatment of infections, transfusion support with erythrocyte and platelets)
- Choice of treatment:
 - o Bone marrow transplantation.
 - o Immunosuppressive therapy.
 - o Eg: Antithymocyte globulin, cyclosporine, glucocorticoids etc.

DRUG INDUCED AGRANULOCYTOSIS

DEFINITION:

A drug mediated reduction in the number of mature myeloid cells in the blood (granulocytes and immature granulocytes) to a total count of 500/ μ L or less.

AGENTS ASSOCIATED WITH GRANULOCYTOSIS:

Acetaminophen, acetazolamide, β -lactam antibiotics, captopril, dapsone, furosemide, INH, NSAIDS etc.

SYMPTOMS:

- Symptoms appear within 7-14 days after initiation of therapy.
- Soar throat, fever, malaise, weakness, chills

CLASSIFICATION OF DRUG-INDUCED AGRANULOCYTOSIS

1. TYPE I: The type I reaction is immune-mediated and involves the drug or drug metabolites, antibodies and neutrophils.
2. TYPE II: A type II reaction is associated with accumulated drug toxicity in hypersensitive individuals.
3. TYPE III: Type III results from a combination of both immune and toxic mechanisms.

MECHANISMS:

1. Drug absorption mechanism

The drug adsorbs on the membrane of the blood cell (neutrophil). The drug-membrane complex then acts as a hapten to stimulate antibody formation. The antibodies produced attach to the drug-membrane complex, causing WBC destruction through complement activation.

E.g.: Penicillin derivatives.

2. Innocent bystander phenomenon

The drug induces antibody formation. The antibodies and the drug form a complex in the serum, and the complex nonspecifically adsorbed to the neutrophil membrane, resulting in complement activation. The activated complement then destroys the cell.

3. Protein carrier mechanism

The drug combines with a plasma protein. The complex then attaches to the cell membrane, and antibody formation is stimulated. Antibodies later attach to the complex and activate complement. The cell is lysed by the complement.

4. Spoiled membrane mechanism

The offending drug alters the neutrophil membrane, which induces the formation of autoantibodies (antibodies that attach directly to the neutrophil). Their attachment to the neutrophil causes cellular destruction by the phagocytic system.

TREATMENT

- The primary treatment of drug induced agranulocytosis is the removal of the offending drug.
- Following discontinuation of the drug, most cases of neutropenia resolve over time, and only symptomatic treatment (e.g., antimicrobials for infections) is necessary.
- Sargramostim (GM-CSF) and filgrastim (G-CSF) have been used to shorten the duration of neutropenia.

DRUG-INDUCED MEGALOBLASTIC ANEMIA

DEFINITION:

In the drug-induced megaloblastic anaemia, the development of (RBC precursors) called megaloblasts in the bone marrow is abnormal.

Deficiencies in either B₁₂ or folate are responsible for the impaired proliferation and maturation of hematopoietic cells, resulting in cell arrest and subsequent sequestration ^{in the spleen}.

These megaloblastic changes are due to the direct or indirect effects of the drug on DNA synthesis.

DRUGS ASSOCIATED WITH MEGALOBLASTIC ANEMIA:

Chloramphenicol, 5-fluorouracil, melfonin, methotrexate, phenytoin, vinblastin, oral contraceptives etc.

SYMPTOMS:

Sore and pale throat, altered bowel habit, fever, mild jaundice, clanin skin pigmentation.

MECHANISMS:

- Antimetabolites: E.g. Methotrexate
 - ⇒ Methotrexate an irreversible inhibitor of dihydrofolate reductase causes megaloblastic anemia.
 - ⇒ Dihydrofolate reductase is an enzyme responsible for generating tetrahydrofolate reductase, an essential factor in making deoxythymidine triphosphate, which is necessary for DNA synthesis.
- Phenyton, primidone, and Phenobarbital cause drug-induced megaloblastic anaemia by either inhibiting folate absorption or by increasing folate catabolism.

TREATMENT:

- When drug-induced megaloblastic anemia is related to chemotherapy, no real therapeutic option is available, and the anemia becomes an accepted side effect of therapy.
- If drug-induced megaloblastic anemia results from cotrimoxazole, a trial course of folinic acid 5-10 mg up to four times a day may correct the anemia.
- Folic acid supplementation of 1mg every day often corrects the drug-induced megaloblastic anemia produced by either phenytoin or Phenobarbital.

DRUG-INDUCED HEMOLYTIC ANEMIA

DEFINITION:

Drug can produce hemolysis (destroying RBC's permeability) by causing defects in the RBC's themselves or because of abnormal changes in the intravascular environment.

DRUGS ASSOCIATED WITH HEMOLYTIC ANEMIA:

ACE inhibitors, acetaminophen, acetazolamide, INH, NSAIDs, quinidine, sulfonamides etc.

SYMPTOMS:

Painful fingers and toes with purplish discoloration

CAUSES

1. Immune-- Drug induced immune hemolytic anemia
2. Metabolic-- Drug induced oxidative hemolytic anemia.

Drug-induced immune hemolytic anemia

- a) The adsorption of the drug to the RBC membrane to form a hapten and, subsequently, an antibody. The antibody attaches to the drug without direct interaction with the erythrocyte.

Eg: Penicillins and cephalosporins in high doses, tetracycline, tolbutamide and semi-synthetic penicillins.

- b) Innocent bystander phenomenon—Drugs that induce this reaction form a neoantigen with a specific alloantigen on the RBC. This neoantigen, in turn, forms complexes with drug-specific antibodies (IgG or IgM) that adhere to the RBC membrane. Complement then lyses the RBC membrane.

Eg: Quinidine/phenacetin

Treatment:

- Removal of the offending agent and supportive care
- Glucocorticoids and IV administration of immunoglobulins in severe cases.
- Blood transfusion

Drug-induced oxidative hemolytic anemia:

- It is a hereditary condition.
- Drug-induced oxidative hemolytic anemia most often accompanies a glucose-6-phosphate dehydrogenase enzyme deficiency.
- G6PD is responsible for the production of NADPH in erythrocytes, which in turn keeps glutathione in a reduced state. Reduced glutathione is a substrate for glutathione peroxidase, an enzyme that removes peroxide from erythrocytes, thus protecting them from oxidative stress. Without reduced glutathione, oxidative drugs may oxidize the sulfhydryl groups of hemoglobin, removing them prematurely from the circulation that is causing hemolysis.
- The degree of hemolysis depends on the severity of the enzyme deficiency and the amount of oxidative stress. Any drug that places oxidative stress on the RBC will cause drug-induced oxidative hemolytic anemia.

Eg: Chloroquine, hydroxychloroquine, nalidixic acid, ascorbic acid, primaquine, sulfamethoxazole, sulfapyridine, etc.

Treatment:

- Removal of offending drug is the primary treatment.
- Patients with these enzyme deficiencies should be advised to avoid medication capable of inducing the hemolysis.
- ✓ Blood transfusion.

DRUG-INDUCED THROMBOCYTOPENIA

DEFINITION:

Platelet count below 150,000/ μ L.

SYMPTOMS:

Early symptoms: Increased bruising, petechiae, ecchymoses, and epistaxis.
Bleeding from mucous membranes and severe purpura can appear later in the disorder.

TYPES:

1. Direct toxicity reactions
2. Immune reactions
 - i. Hapten-type immune reactions
 - ii. Innocent bystander type immune reactions.

Direct toxicity reactions

- Direct toxicity reactions, resulting in suppressed thrombopoiesis, produce a decrease in the number of megakaryocytes in the bone marrow.
- Eg: Anti cancer agents, organic solvents, pesticides, amrinone.
⇒ Orally administered Amrinone has been shown to cause thrombocytopenia in up to 18.6% of patients. Amrinone IV is associated with a 2% to 4% incidence of thrombocytopenia, possibly reflecting the short term nature of IV administration compared to oral route.

Immune reactions:

- Immune reactions result in an increased peripheral destruction of platelets and an increased number of megakaryocytes.
- Eg: Quinine, quinidine, gold salts, sulfonamides, heparin.
- The offending agent binds to certain platelet glycoproteins, most commonly Ib/IX/V and IIb/IIIa. Antibodies are generated that bind to these drug-bound glycoprotein epitopes. After the binding of drug-dependent antibodies to the platelet surface, lysis occurs through complement activation or through clearance from the circulation by macrophages.

TREATMENT:

- ✓ Removal of the offending agent and symptomatic treatment of the patient.
- In gold salt-induced thrombocytopenia, prednisone in a dose of 60mg daily is beneficial.
- Abciximab-induced and heparin-induced severe thrombocytopenia can be treated with platelet transfusion, if clinically indicated.

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3

Epilepsy:

- Any of a group of syndromes characterized by paroxysmal transient disturbances of brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, psychic or sensory disturbances, or perturbation of the autonomic nervous system. Symptoms are due to disturbance of the electrical activity of the brain.

• Etiology:

- Seizures are produced by abnormal discharges of neurons that may be caused by any pathological process that affects the brain. For eg:

1. head trauma, intracranial injury during birth.
2. Systemic metabolic disorders (electrolyte imbalance).
3. CNS infections
4. Hormonal changes during pregnancy
5. Alcohol abuse
6. Brain tumour.

Nervous system

Nervous

- A convulsion is a medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body.

◦ Pathophysiology:

- In normal brain inhibitory circuits limits synchronous discharge. GABA is particularly play this role.
- When GABA receptors blocked $\rightarrow$ Rhythmic and repetitive hypersynchronous discharge of neurons $\rightarrow$ seizures.
- Excitatory NT $\rightarrow$ Ach, Aspartate and Glutamate also involved to develop seizures.
- Intracellular recording shows burst of rapid action potential firing with reduction of trans-membrane potential.
- $\downarrow$ inhibitory system + $\uparrow$ excitation $\rightarrow$ genesis of seizures.
- Abnormalities in Ion channel (Na^+ , K^+ , Ca^{2+}) may cause seizures. (Prolongation of depolarization state).

International Classification of Epileptic Seizures

I. Partial seizures (seizures begin locally)

A. Simple (without impairment of consciousness)

1. With motor symptoms
2. With special sensory or somatosensory symptoms
3. With psychic symptoms

B. Complex (with impairment of consciousness)

1. Simple partial onset followed by impairment of consciousness—with or without automatisms
2. Impaired consciousness at onset—with or without automatisms

C. Secondly generalized (partial onset evolving to generalized tonic-clonic seizures)

II. Generalized seizures (bilaterally symmetrical and without local onset)

- A. Absence
- B. Myoclonic
- C. Clonic
- D. Tonic
- E. Tonic-clonic
- F. Atonic
- G. Infantile spasms

III. Unclassified seizures

IV. Status epilepticus

CLINICAL PRESENTATIONS

- Generalised seizures - impairment of consciousness from the onset
 - o Tonic clonic seizures / Grandmal
 - common type

-without warning, patient goes stiff, falls and convulses, laboured breathing and salivation

-cyanosis, incontinence, tongue biting

- convulsion ceases after a few min, followed by drowsiness, confusion, headache and sleep.

o Absence / petitmal

- rare

- childhood and early adolescence

- child goes blank and stares, fluttering of eyelids, flopping of head.

- last only for few seconds and go unrecognised even by the child.

o Atonic seizures

- sudden lose of muscle tone, head drop, dropping of limb, person collapse to ground

- recovery is quick.

- rare form

o Myoclonic seizures

- abrupt, brief involuntary shock like jerks, which may involve whole body, or arms or head.

- usually happen in morning, shortly after waking

- cause the person to fall, but recovery is immediate.

• Partial seizures

o Simple partial seizures

- no loss of consciousness

- localized jerking of limbs or face, stiffness/ twitching, numbness, abnormal sensations

o Complex partial seizures

- altered behavior: plucking clothes, fiddling with other objects, acting in confused manner

- lip smacking/ chewing movements, grimacing, performing aimless activities, wandering around in drunken fashion.

o Secondarily generalized seizures

- convulsive attack with same characteristics as GTC.

- only EEG can demonstrate partial nature of the seizure.

Diagnosis:

1. Careful and accurate patient history.
2. EEG is only examination required and aim to record abnormal neuronal changes.
3. Neuroimaging with MRI
4. Neuropsychological testing: this test can help to pinpoint the location of seizure focus by identifying the areas of decreased brain function.

Seizure type	First line drugs	Alternative drugs
Partial seizures	Carbamazepine Phenytoin Lamotrigine Valproic acid oxycarbazepine	Gabapentin Topiramate Tiagabine Phenobarbitol Primidone

Absence seizures	Valproic acid Ethosuccimide	Lamotrigine
Myoclonic	Valproic acid Clonazepam	Lamotrigine Topiramate Felbamate
Tonic clonic	Phenytoin Carbamazepine Valproic acid	Lamotrigine Topiramate Phenobarbitol Primidone Oxcarbazepine

CLASSIFICATION OF ANTI EPILEPTIC DRUGS

- Barbiturate – phenobarbitone
- Deoxybarbiturate – primidone
- Hydantoin- phenytoin, mephentyoin
- Iminostilbine- carbamazepine
- Succinimide- ethosuximide
- Aliphatic carboxylic acid- valproic acid
- Benzodiazepine – clonazepam, clobazam, diazepam
- Phenyltriazine- lamotrigine
- Cyclic GABA analogue- gabapentine
- Newer drugs- vigabatrin,
topiramate,
tiagabine,
blevetiracetam.

CLONAZAPAM

MOA: Potentiate GABA induced Ca channel influx.

Dose: 0.5 – 5 mg/day

ADR: fatigue, drowsiness, ataxia, rashes, vertigo.

DI: phenobarbitone or phenytoin may accelerate clonazepam metabolism
BN: Clonopam, Petril

PHENOBARBITONE

MOA: potentiate GABAergic inhibition by increasing the lifetime of chloride channel opening induced by GABA.

Dose: 60-180mg/day

ADR: fatigue, depression, poor memory, hypocalcemia, osteomalacia, hepatotoxicity

DI: decreases rifampicin plasma levels

increases sodium valproate plasma levels

BN: Gardinal, Phenbarb

X ADV: Phenobarbital has linear and predictable pharmacokinetics. Multiple dosage forms (e.g., oral solid, oral liquid, IM, and IV) are available, and it is the most inexpensive AED.

X DISADV: These include delayed intellectual development and hyperactivity in children and significant cognitive impairment in adults. It is an enzyme inducer and interacts with many other drugs metabolized by the cytochrome P450 system,

PRIMIDONE

MOA: converted in liver to phenobarbitone.

Dose: 200-500 mg BD

ADR: Anaemia, leucopenia, psychotic reaction, sedation, nystagmus

DI: ethanol increases the metabolism of primidone.

BN: Mysoline

PHENYTOIN

MOA: prolonging the inactivated state of voltage sensitive neuronal Na channel and governs the refractory period of neuron.

Dose: 5mg/kg/day

ADR: ataxia, drowsiness, hirsutism, diplopia, folate deficiency, rash.

DI: increases the plasma levels of isoniazid, chloramphenicol, fluconazole.

Decreases the plasma levels of furosemide and rifampicin.

BN: Eptoin, Dilantin

ADV: It is available as oral solid, oral liquid, and parenteral dosage form, allowing flexibility in dosing and use in emergency situations.

DISADV: displaces Michaelis Menten pharmacokinetics, and the metabolism saturates at doses given clinically. It is associated with multiple side effects.

CARBAMAZEPINE

MOA: prolongation of sodium channel inactivation.

Dose: 400-2400mg/day

ADR: diplopia, blurred vision, ataxia, dizziness, headache, steven johnson syndrome

DI: increases plasma level of cimetidine, erythromycin, sodium valproate.

Decreases the plasma level of phenytoin and phenobarbital.

✗ BN : Carmaz, Zeptol

✓ ADV: Oral immediate- and extended-release solid and liquid dosage forms are available. Compared with other first-generation AEDs, carbamazepine causes minimal cognitive impairment.

✗ DISADV: It induces its own metabolism, which requires careful dosage titration. It also induces the metabolism of other medications, and other drugs may interact with it and/ or the active metabolite. There is no parenteral formulation.

ETHOSUXIMIDE

MOA: Inhibition of T type Ca current

Dose: 500-1500mg/day

ADR: Tiredness, drowsiness, headache, steven johnson syndrome

✗ DI: increases sodium valproate level
decreases carbamazepine level

✗ BN: Zarentin

✗ ADV: This drug is very effective in the treatment of absence seizures. It is generally well tolerated and has few pharmacokinetic interactions.

✗ DISADV: Ethosuximide has a very narrow spectrum of activity

VALPROIC ACID

MOA: prolongation of Na channel inactivation,
facilitation of GABA mediated Cl channel opening and
inhibition of T type Ca current.

Dose: 2-2.5 g/day

ADR: dyspepsia, hair loss, anorexia, anaemia, pancreatitis

DI: increases salicylate plasma levels

BN: Diva, Ipro, Navalin

✓ ADV: Valproic acid is available in multiple dosage formulations. The IV formulation is especially well tolerated. It has a wide therapeutic index.

✓ DISADV: Some patients report significant weight gain with valproic acid, and this can limit compliance. Valproic acid is also associated with other side effects, such as alopecia, tremor, pancreatitis, polycystic ovary disease, and thrombocytopenia.

LAMOTRIGINE

MOA: Prolongation of Na channel inactivation

Dose: 100-500 mg/day

ADR: headache, Diplopia, hepatotoxicity

DI: increases sodium valproate level

Decreases phenytoin and carbamazepine plasma level.

✓ BN: Lamogin, Epitic

✓ ADV: Lamotrigine appears to be generally well tolerated in both children and elderly patients and does not cause weight gain.

✓ DISADV: Lamotrigine is associated with rash, especially in patients who start at a high dose, have rapid dose escalation, and/or are taking concurrent valproic acid. Therefore, the initial doses must be low (lower if the patient is on valproic acid) and escalated slowly in order to maximize patient safety. There is no parenteral dosage form.

VIGABATRIN

MOA: Inhibition of GABA transaminase

Dose: 2-4g/day

ADR: behavioral disturbances, headache, weight gain, depression

ZONISAMIDE

MOA: Exert its antiepileptic effect by inhibition of slow sodium channels, by blockade of T-type Ca^{2+} channels, and possibly by inhibition of glutamate release. It also has a weak carbonic anhydrase inhibitory effect.

Dose:

ADR: Somnolence, dizziness, anorexia, headache, nausea, agitation, word-finding difficulties, and irritability

ADV: It has a very long half-life, which is suitable for once- or twice-daily dosing.

DISADV: Cognitive impairment can occur, especially if dosage is escalated rapidly.

GABAPENTINE

MOA: Gabapentin was designed to be a GABA agonist but does not react at the GABA receptor, alter GABA uptake, or interfere with GABA transaminase. Gabapentin appears to bind to an amino acid carrier protein and appears to act at a unique receptor. Gabapentin inhibits high-voltage activated calcium channels. It elevates human brain GABA levels, possibly via alterations in GABA synthesis or reversal of the neuronal GABA transporter, resulting in nonvesicular release of GABA.)

Dose: 200-400 mg three day

DI: There is a 10% reduction in the clearance of gabapentin in patients taking cimetidine and a 20% reduction in the bioavailability if aluminum antacids are taken simultaneously with gabapentin

ADR: fatigue, somnolence, dizziness, and ataxia

ADV: Gabapentin has multiple mechanisms of action and is mechanistically different from first-generation AEDs. It is not metabolized and is excreted unchanged by the kidney. Gabapentin has the additional advantages of a broad therapeutic index with minimal CNS adverse effects and no drug interactions. Doses can be escalated rapidly.

DISADV: Gabapentin is absorbed by an active process that saturates at higher doses. This may require more frequent daily dosing for patients who need doses greater than 3,600 mg/day. There is no parenteral formulation.

NON PHARMACOLOGIC THERAPY

- Diet high in fats and low in carbohydrates
- Vagal nerve stimulator (VNS) is an implanted device approved for use in epilepsy. It consists of implantable, programmable pulse generator connected to helical head. Generator is implanted in a subcutaneous infraclavicular pocket and is powered by lithium battery. The lead is attached to left vagus nerve and delivers a biphasic current through the skin to the nerve. Patient can use magnet placed over generator to activate it during seizure.
- Surgery: important in patients whose seizures are uncontrollable with medical therapy. It is done to remove epileptic focus or to interrupt nerve pathways through which seizure impulses spread within brain.

PATIENT CARE

- During seizure, patient should be made as comfortable as possible, lying down, cushioning head and loosening any tight clothing.
- Patients should not be moved unless they are in dangerous place.
- No attempt should be made to open patients mouth or force anything between teeth.
- When seizure stops patient should be turned over into recovery position and airway checked for any blockage.
- No drinks should be given after an attack nor should extra AEDs be administered.
- After a seizure, it is important to stay with the patient and offer reassurance until patient has recovered fully.
- If a seizure persists for more than 10 min, if a series of seizures occur or if seizure is severe, then IV or rectal administration of 10-20 mg diazepam for adults; with lower doses being used in children, is advisable.

- o Advised to take the medication as prescribed by the doctor. Never miss the medication and always take it at the same time each day.
- o Patient also advised to have good sleep and balanced diet.
- o Avoid stress, excitement, emotional upset and flashing lights

Parkinson's disease:

- Parkinsonism is disorder caused by the degeneration of the basal ganglia, causing impairment of the motor nerves and disabling motor functions.

- Parkinsonism is caused due to decreased activity of dopamine or an increased activity of acetylcholine in Striatum present in the basal ganglia.

Etiology:

- The decrease in dopamine levels is due to the following reasons:

- 1- Aging
- 2- Genetic factors
3. Poisons
4. Intake of carbon monoxide
5. Production of free radicals such as hydroxyl in the metabolism of neurotransmitters.

-The free radicals damage brain cells and reduce dopamine levels.

□ Types:

→ i- Primary / Idiopathic Parkinsonism:

The cause of the disease is unknown.

Occur in individuals over 60 yrs of ages.

→ ii- Secondary / Drug induced Parkinsonism:

This can be treated by cessation of the pending drug.

Pathophysiology of Parkinson's disease:

-The symptoms of parkinson's disease result from the loss of pigmented dopamine secreting (dopaminergic) cells in the pars compacta region of the substantia nigra.

-These neurons project to the striatum and their loss lead to alterations in the activity of the neural circuits within the basal

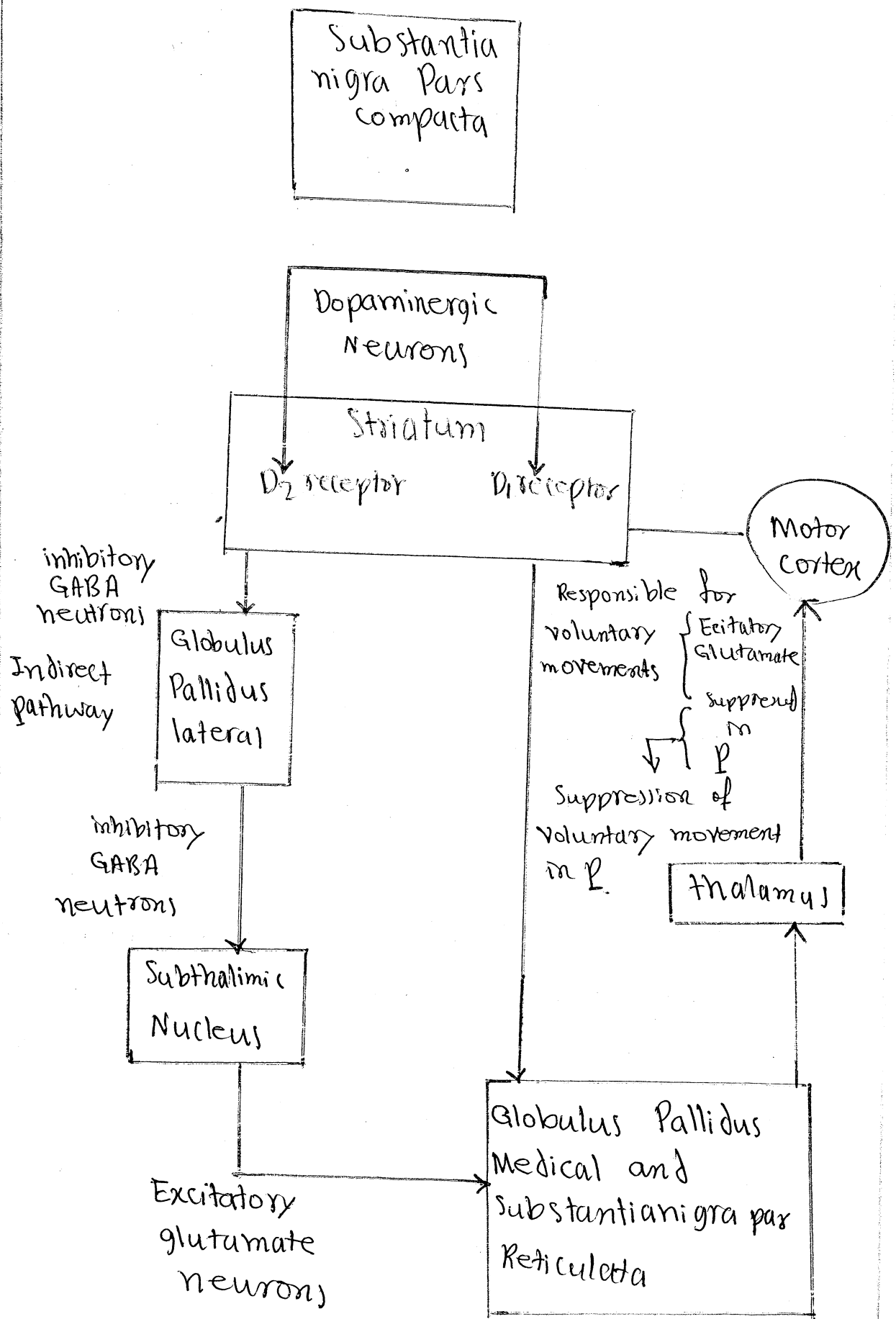
ganglia that regulate movement, the lack of dopamine results in increased inhibition of the ventral anterior nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia.

- The nigrostriatal dopamine pathway in the brain mediates movement and is the most conspicuously affected in early Parkinson's disease.

- The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells.

The death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins b/w two major cellular organelles - the endoplasmic reticulum (ER) and the Golgi apparatus.

- The substantia nigra is a brain structure located in the mesencephalon (midbrain) that plays an important role in movement.



II Sign and Symptoms:

→ i- Motor Symptoms:

- Difficulty and slowness of movements
- nodding of head
- Absence of control over movements of the eye.

→ ii- Non-motor Symptoms:

- Disorders of mood, behavior, thinking and sensation.

Diagnosis:

- Neuroimaging techniques as magnetic resonance imaging, position emission tomography (PET), single proton emission computed tomography (SPECT) are used to detect parkinson's disease.

- Other investigation diagnostic tools; transcranial ultrasound examine deficits in olfaction, detection of oligomeric alpha-synuclein in blood of patient with PD.
- Stages of parkinson disease:

Stage	Characteristic
0	No clinical signs evident
I	<u>Unilateral involvement</u> including the motor features of <u>tremor</u> , <u>rigidity</u> , or <u>bradykinesia</u> ; <u>minimal functional impairment</u> .
II	<u>Bilateral involvement</u> but <u>no postural abnormalities</u> .
III	Mild to moderate bilateral disease, mild postural imbalance, but <u>still ability to function independently</u> .
IV	Bilateral involvement with <u>postural instability</u> ; patient requires substantial assistance.
V	Severe disease; patient restricted to bed or wheel chair unless aided.

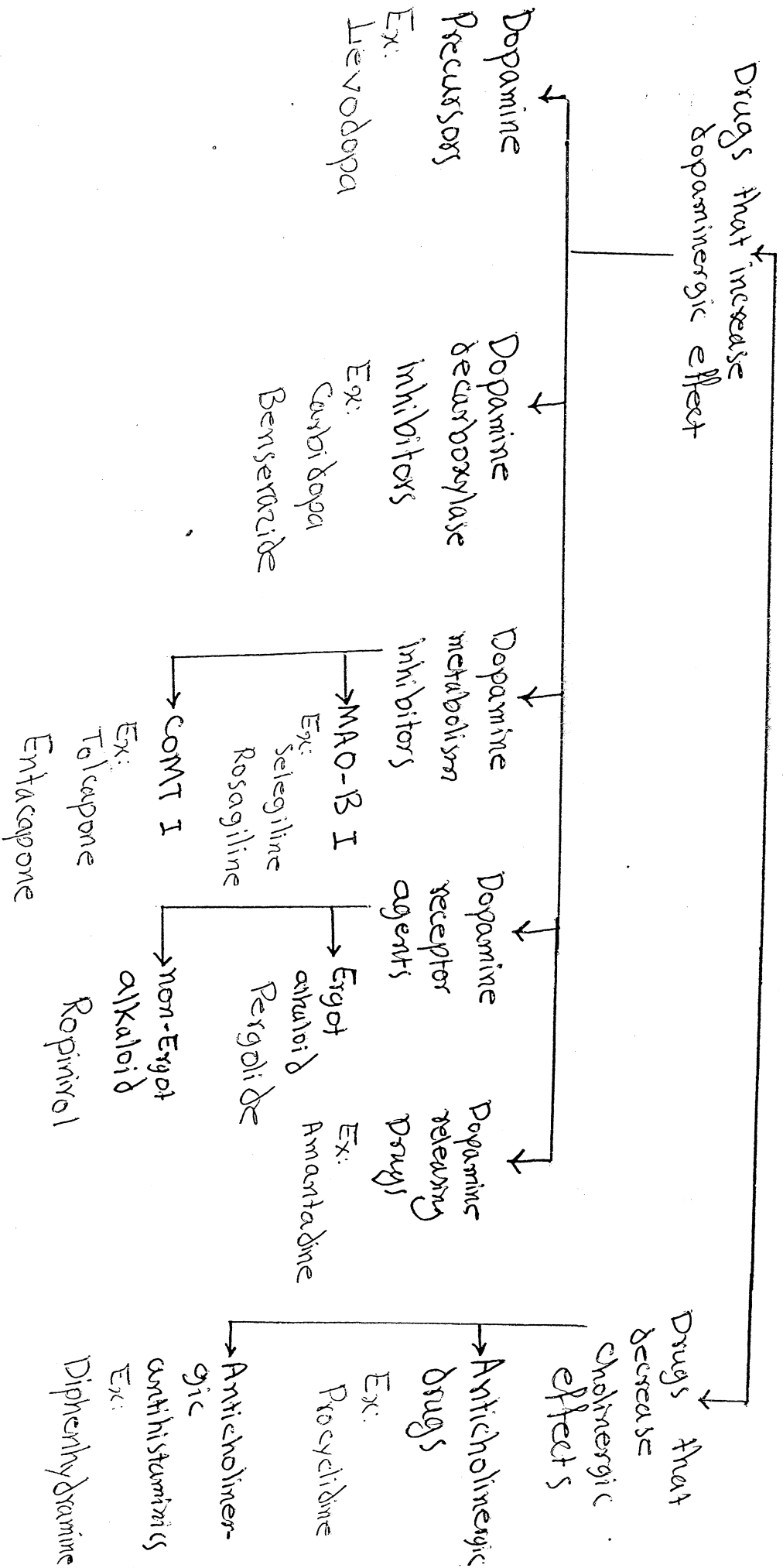
Treatment:

- Non-pharmacological approach:
- Exercise it is an important adjunctive therapy. Regular focused exercise, stretching and strengthening activities can have a positive effect on mobility and mood. It also improves task- performance and functional status of a patient.
- Nutrition: patients with PD are at increased risk of poor nutrition, weight loss, and reduced muscle mass.

→ Sufficient fiber and fluid intake help prevent constipation associated with PD and the medications used to treat disease.

→ Excessive dietary protein in the late stages of PD causes erratic responses to levodopa therapy.

Drugs used in Parkinsonism



- what is a Parkinson disease? classify the drugs used with examples. Describe the pharmacology of Levodopa. [10m, May, 2007]

- Dopamine Precursor:

- Dopamine that is deficient in the nigrostriatal neurons in P. can be restored by dopamine precursors.

- Dopamine does not cross the blood brain barrier, hence the peripherally available dopamine is of no use in P.

Levodopa

- It crosses the BBB.

- Mechanism:

- It crosses the BBB by an active process and gets decarboxylated to dopamine. This dopamine is taken up by the dopaminergic neurons present in the nigrostriatal tract. Much of the levodopa remains in the plasma and get metabolized by dopamine decarboxylase peripherally. As the disease advances, more neurons degenerate which cannot

take up dopamine hence, levodopa becomes less efficient in advanced stages.

Pharmacological Effects:

1. On CNS:

- It improves firstly bradykinesia, and then tremors and rigidity.
- It normalizes excessive sweating and salivation.

2. On C.V.S:

- It cause vasodilation and result in hypotension of the mesenteric and renal vasculature.
- At higher doses, cause vasoconstriction and increased BP.

3. Decreased lactation

4 - on chemoreceptor Trigger Zone:
cause nausea and vomiting

-Pharmacokinetics:

-Levodopa is rapidly absorbed from the small intestine.

-Absorption takes place by active transport, mediated by amino acid carriers.

-Levodopa crosses the blood brain barrier by an active process.

2: Levodopa undergoes decarboxylation by both dopamine decarboxylase and COMT in the gut to give dopamine.

-It also gets degraded as it undergoes first pass metabolism.

3. The metabolites undergo conjugation with glucuronide and sulphate which eventually undergo urinary excretion.

4. Explain Levodopa + carbidopa also.

- Adverse effects:

1- nausea and vomiting.

- can be prevented by taking levodopa after food, taking an anti before food.

2. Postural hypotension, tachycardia, cardiac arrhythmias

3. Headache, hallucinations, dizziness

4. glaucoma.

- Drug interactions:

1- Ferrous salts wgo chelation with L.

2. Pyridoxine (Vit B₆) increases the decarboxylation of L, which reduces bioavailability of levodopa for central effects.

- Contraindications:

1- Acute glaucoma

2. Cardiac arrhythmias

3. Endocrinal disorders

4. Hepatic and renal disorders.

Uses:

1. used for treatment of idiopathic P.
2. It is useful in the treatment of bradykinesia associated with parkinsonism, but tremors and rigidity are not treated completely.

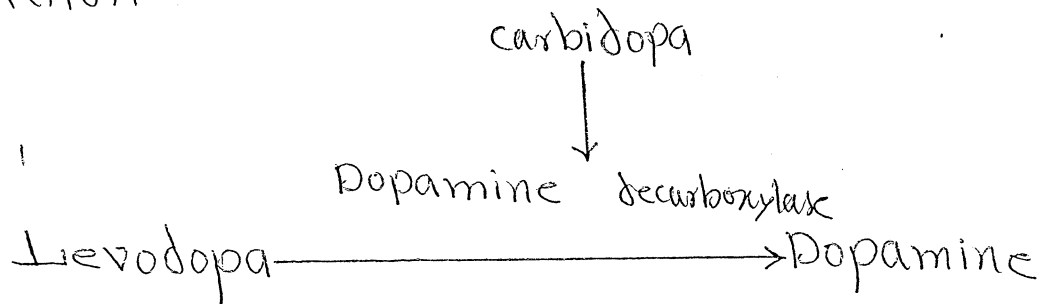
Dopamine Decarboxylase Inhibitors:

- They must be used along with levodopa so that they block the decarboxylation of levodopa peripherally.

Carbidopa:

- Carbidopa causes inhibition of dopamine decarboxylase that converts levodopa to dopamine, thereby increasing the levodopa levels in the plasma. More levodopa is available peripherally that passes through

the BBB and shows higher therapeutic action. Thus, carbidopa increases the bioavailability of levodopa thereby increasing its duration of action.



-Adverse effects:

- 1- nausea, vomiting
2. Cardiac side effects
3. Dyskinesia
4. hallucinations
5. Postural hypotension

-It does not cross the BBB but act peripherally.

- Dopamine metabolism inhibitors:

1. Monoamine oxidase (MAO-B) inhibitors:

- Monoamine oxidase is responsible for the metabolism of adrenaline, noradrenaline, dopamine and serotonin.

a) MAO-A:

- Predominantly in the intestinal mucosa
- responsible for degradation of dopamine peripherally.

b) MAO-B:

- Predominantly in the brain
- responsible for degradation of dopamine centrally.

Selegiline

- Mechanism:

- It is an irreversible MAO-B inhibitor, hence it does not interfere with the peripheral

degradation of dopamine. When administered along with Levodopa, selegiline delays the degradation of dopamine centrally and increases the duration of action of Levodopa.

Adverse effects:

1. Postural hypotension
2. nausea
3. hallucination
4. uncontrolled movements of the body.

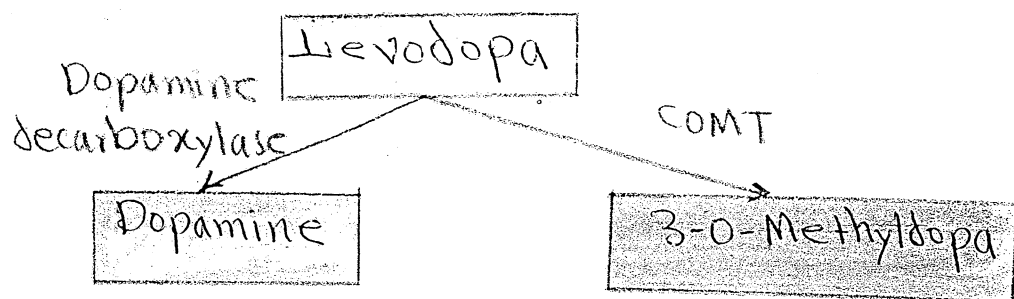
Uses:

1. use along with Levodopa-carbidopa combination in parkinsonism.
2. Improves conditions of sialorrhoea and tremors.
3. Improves defects in walking.

2. COMT inhibitors

-It should be used along with levodopa-carbidopa to prevent their degradation and

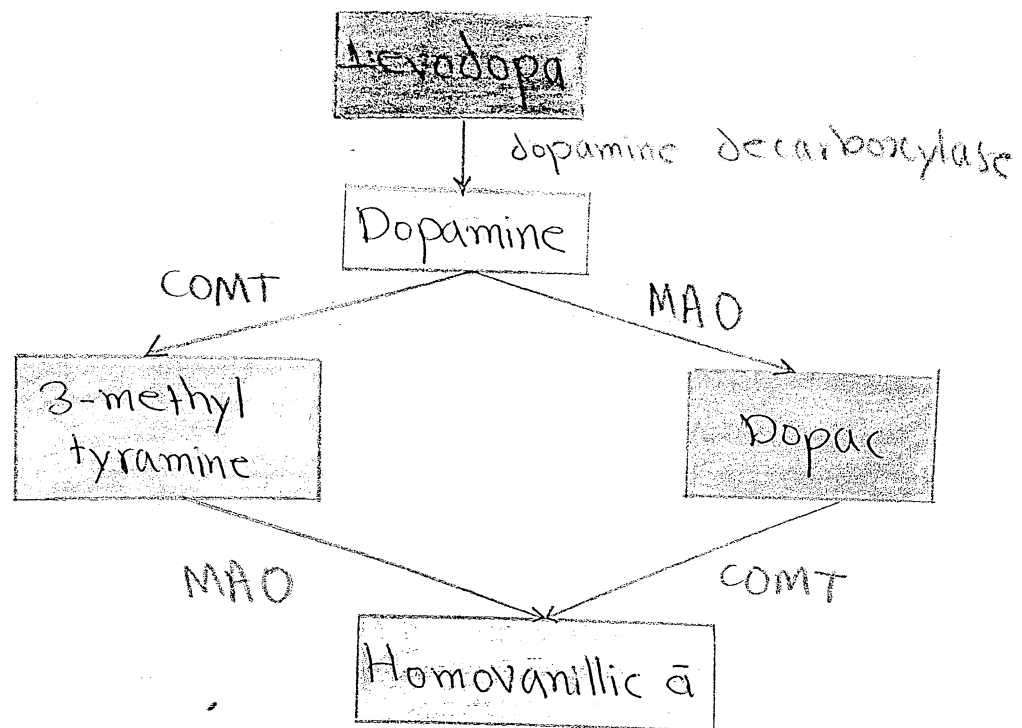
to prolong the half life of Levodopa.



*Fig: Peripheral Metabolism of Levodopa

- When levodopa is administered along with carbidopa peripherally dopamine decarboxylase is inhibited by carbidopa and COMT pathway is still active. Most of levodopa is converted to 3-O-methyldopa. This causes loss of levodopa concentration and increased plasma concentration of 3-O-methyldopa.

- Levodopa and 3-O-methyldopa compete to cross the BBB. Less levodopa crosses the BBB and shows decreased central effects. The COMT inhibitors acting peripherally inhibit the conversion of Levodopa to 3-O-methyldopa and maintain the dopamine levels.



*Fig- Central Metabolism of Levodopa

-The COMT inhibitors act centrally block the COMT pathways and prevent the degradation of dopamine. This maintains, the central levels of dopamine.

Entacapone:

-It acts peripherally, blocks the COMT metabolism and increases dopamine levels.

-Adverse effects:

1. Nausea
2. Diarrhoea
3. Postural hypotension
4. Abdominal pain

-Uses:

1. administered along with Levodopa-carbidopa
2. It shows improvement of dyskinesias.

Tolcapone

- It crosses the BBB.
- It blocks both central and peripheral metabolism of levodopa through COMT pathway.

-Dopamine Receptor Agonists:

-These drugs produce an agonistic effect on the postsynaptic dopaminergic receptor cells without interfering with the metabolism of dopamine from its precursors.

-These drugs cross the BBB.

Bromocriptine

Pergolide

Ropinirole

-Dopamine Releasing Drugs/Dopamine Facilitators:

Amantadine

-Mechanism:

-It causes the release of dopamine from the dopaminergic nerve terminals.

-It also reduces the dopamine reuptake from the synapses.

-Adverse Effects:

- 1- Nausea
- 2- Hallucinations
- 3- Postural hypotension

-Uses:

- 1- reduce levodopa dose in mild pa.
- 2- Reduces dyskinesias

II. Drugs that ~~decrease~~ cholinergic effects:

- Anticholinergic Drugs (Atropine Substitutes):

Trihexyphenidyl HCl

- The drug competes with ACh for binding to muscarinic receptors.

-Adverse effects:

- 1- Dry mouth
- 2- urine retention
- 3- constipation
- 4- loss of memory

Uses:

1. It is used to reduce levodopa dosage
2. It is given in early parkinsonism therapy

Procylidine

- It acts on the muscarinic receptors located centrally. It blocks the cholinergic actions by antagonizing the receptor.

- It also acts as an antispasmodic on smooth muscles.

2. Anticholinergic Antihistaminic / H₁ antagonist:

Diphenhydramine

- It antagonizes histamine H₁ receptors and also has anticholinergic activity useful for the treatment of parkinsonism.

Class	Drug	Mode of action	Adverse drug reactions	Uses	Dosage and route
Dopamine precursor	Levodopa	Levodopa crosses the blood brain barrier and is decarboxylated to dopamine thereby increasing the levels of dopamine in brain.	- Nausea - Vomiting - Cardiac Arrhythmia - Dyskinesia - On-off phenomenon - Wearing off effect. - Insomnia - Hallucinations	- Treatment of idiopathic parkinsonism - Reduces/controls parkinsonian Manifestations - Treatment of akinesia and bradykinesia.	Initial dose of 500-1000 mg per day increased by 750mg to a maximum daily dose of 8gm/day.
Dopamine decarboxylase inhibitors.	Carbidopa, Benserazide	Inhibits dopamine decarboxylase and prevents conversion of levodopa to dopamine peripherally, thereby increases the levodopa concentration crossing the blood brain barrier centrally.	- Dyskinesia - Hallucinations - Delusions - Postural hypotension	- Same improvement is achieved as with lower doses of levodopa - Reduces dopamine induced side effects.	Carbidopa-Levodopa combination of 10 mg/100mg or 25 mg/100 mg administered t.i.d. to get a dose range of 600mg-800mg of levodopa. Levodopa is given along with carbidopa, depending on the patient's response.
Monoamine oxidase (MAO) inhibitors	Selegiline Rasagiline	It inhibits MAO-B irreversibly and delays the degradation of dopamine centrally, thereby increases the duration of action of levodopa. Strong acting when compared to selegiline. Also blocks free radical MPP ⁺ formation.	- Nausea - Vomiting - Hallucinations - Dyskinesia.	- It reduces end-off phenomenon and wearing-off effect. - It improves conditions of sialorrhoea, tremors and defects in walking. - It also has neuroprotective action - It improves motor functions.	5 mg twice daily along with levodopa-carbidopa. After 2-3 days, levodopa dose is reduced by 25%. Maximum dose is 10mg/day Recommended dose: 1 mg/day, once daily combined with levodopa-carbidopa.
COMT - inhibitors	Entacapone	Acts peripherally by blocking COMT metabolism and increasing the dopamine levels.	- Nausea - Diarrhoea - Orange discoloration of urine - Postural hypotension	- Constant levels of dopamine are achieved centrally - It improves dyskinesia	Coadministered with levodopa-carbidopa maximum dosage of 1600 mg/day is given in divided doses 8 times daily.
	Tolcapone	Acts centrally and peripherally and blocks the COMT metabolism	- Levodopa side effects are accentuated	- Prolongs on-phenomenone	Starting with 100 mg tablets b.i.d. or t.i.d. along with levodopa-carbidopa combination. Maximum dosage is 200 mg. t.i.d.
Dopamine receptor agonists 1. Ergot alkaloids	Bromocriptine	It acts as a potent agonist of dopaminergic receptors postsynaptically acts on both D ₁ and D ₂ receptors.	- Nausea and vomiting - Marked hypotension - Peripheral oedema - Erythromelalgia	- It prolongs levodopa failure. - Acts as maintenance drug when dopaminergic neurons have degenerated.	Initial dose of 1.25 mg/day, gradually increased weekly to a dose range of 7.5 - 30 mg/day.

derivatives		receptor agonist and has no affinity to D ₁ receptors.	- e sleep at odd times. - Nausea - Hallucinations	- effects when compared to ergot alkaloids. - Rapid therapeutic response and longer duration of action.	orally 0.25 mg t.i.d. gradually increased upto 1.5 mg/day
Dopamine releasing drugs/dopamine facilitators.	Amantadine	It causes the release of dopamine from dopaminergic nerve terminals and reduces dopamine reuptake from the synapses.	- Anorexia - Nausea - Hallucination - Postural hypotension - Ankle oedema	- Rapidly active but less efficient. - It reduces levodopa dose when co-administered with it. - Reduces dyskinesias.	Adult : 100 mg. h.i.d. or 200mg in daily divided doses. Children (1 - 9 yrs) : Dose should not exceed 150 mg daily.
Anticholinergic drugs (Atropine substitutes)	Trihexyphenidyl HCl, Procyclidine	Acts on cholinergic nerve supply to the neostriatum and as an antagonist to acetylcholine receptors.	- Dry mouth - Blurred vision - Urine retention - Constipation - Loss of memory - Delirium and hallucinations.	- Used to treat drug induced parkinsonism - Used in the treatment of early parkinsonism along with dopamine analogues.	In idiopathic parkinsonism started with 1 mg h.i.d. increased gradually to get a daily dose between 12 - 15 mg. depending on the response. In drug induced parkinsonism, results are seen with 1 mg/day. Dose can be increased further empirically to a daily dose range of 5 - 15 mg.
Anticholinergic antihistaminic/H ₁ antagonist	Diphenhydramine	It possesses both antihistaminic and mild anticholinergic properties.	- Cycloplegia - Glaucoma - Enlargement of prostate gland. - Urine retention - Hallucinations	- Used in the treatment of drug - induced mild parkinsonism.	25 - 50 mg q.i.d. The dose should not exceed a maximum of 300 mg/day.

Clinical Pharmacology:

- Parkinsonism should be treated only when symptoms are bad enough to initiate therapy.

- Selegiline and rasagiline have been shown in some studies to delay the progress of PD.

- Treatment is initiated with selegiline or DA agonists like ropinirole/pramipexole.

- Levodopa is always given with carbidopa and is still the mainstay of treatment in PD.

- All drugs are started with a low dose and gradually titrated.

- Drugs holidays: when adverse effects become seriously troublesome or when the response to drug is inadequate, a drug holiday for a short period (3-21 days) may be tried.

- Levodopa is contraindicated in pregnancy and lactation.

-with drawal of drugs:

- a) Antimuscarinics.
- b) Dopamine inhibitor.
- c) Dopamine releasing Agent.
- d) DA receptor agonist.
- e) Levodopa.

-Diet and exercise:-

- 1) Constipation should be prevented by intake of food rich in fibres along with high amount of H₂O.
- 2) Levodopa should not be administered along with protein rich diet as both compete for the same receptors.
- 3) Diet rich in fat should not be taken as it lowers the rate of digestion and interferes with the drug absorption.
- 4) Exercise is helpful in improvement of motor activities.

#Stroke:

- A Stroke, or cerebrovascular accident (CVA), is the rapid loss of brain function(s) due to disturbance in the blood supply to the brain. As a result, the affected area of the brain is unable to function.

o Etiology:

- thrombus (blood clot)
- cardiac arrest
- Arrhythmias
- MI
- pulmonary embolism
- bleeding
- Hypertensive disease
- Vasoconstriction.

o Classification:

1. Ischemic Stroke are those that are due to interruption of blood supply.

2. Hemorrhagic stroke that are due to rupture of the blood vessels or an abnormal vascular structure.

□ Risk factors:

1. Cigarette smoking.
2. Age
3. Gender
4. Heredity
5. HTN
6. Myocardial disease
7. Diabetes
8. Alcohol

□ Pathophysiology:

I. Cerebrovascular Disease:

Cerebral ischemia

Atherothrombotic disease

etc.

II- Cerebral Embolism:

@ Atherothrombotic disease:

Fatty streak on Blood vessels



yellow fatty fibrous plate



formation of lesions



ulceration n calcification



plaque formation



Enhances platelet aggregation n
clot formation



narrowing of arteries



aorta cranial stenosis



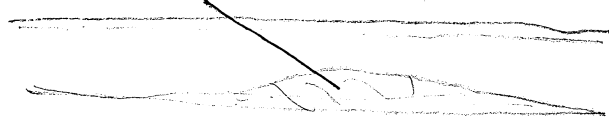
Stroke

etc.

Ruptured Aneurysm

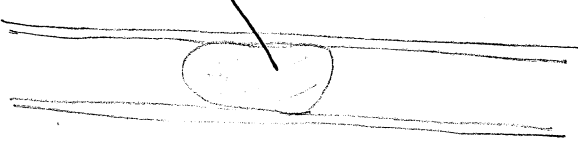


Thrombus



مسدود شدن ناگهانی یک
شریان بزرگ ریه (فتل یا جسم
خارجی که به ورید جریان
خون به محل مربوط آورده
شده است.

Embolism (blockage)



Symptoms:

- Sudden numbness or weakness of the face, arm or leg (especially on one side of the body)
- Sudden confusion, trouble speaking or understanding speech.
- loss of balance
- Sudden severe headache with no known cause.
- Vertigo

#Diagnosis:

- Evaluation of clinical presentations and laboratory findings.
- Cerebral arteriography
- CT scan
- MRI
- ECG
- X-ray of head.

#Pharmacotherapy:

1. Anticoagulant therapy:

Heparin
warfarin

2. Antiplatelet therapy:

Aspirin
clopidogrel
Ticlopidine

3. Thrombolytic therapy:

- Streptokinase
Alteplase

Thrombolytic Agents:

Streptokinase + plasminogen



Activator complex



plasminogen → plasmin

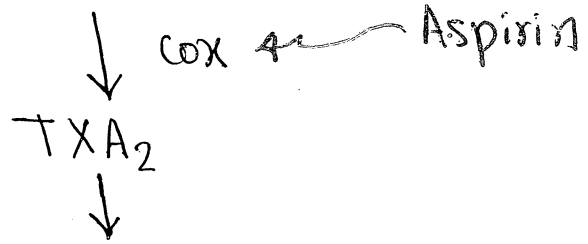


Hydrolyzes fibrin
fibrinogen, factor V, VIII

Drug	Dose	Contraindication	ADR
Streptokinase	1.5 million IV/infusion	Internal bleeding Allergy Pregnancy Peptic ulcer Surgery	Bleeding Stroke Asthma

Antiplatelet Therapy:

Arachidonic Acid



inhibit platelet shape change
inhibit platelet aggregation
inhibit platelet release

Drug	Dose	CI	ADR
Aspirin	50-325 mg/day	Bleeding Hypersensitivity	GI irritation Bleeding Dyspepsia

Alzheimer's disease

- It is a slowly progressive disease of the brain that is characterized by impairment of memory and ^{عاقبة بالغة} eventually by disturbances in reasoning, planning, language and ^{معرفة بالحواس} perception.

Many scientists believe that Alzheimer's disease results from an increase in the production or accumulation of a specific protein (beta amyloid protein) in the brain that leads to nerve cell death.

Etiology:

1- Genetics:

2. Environmental and other Factors:

- A number of environmental factors have been associated with an increased risk of AD, including stroke, alcohol abuse, small head circumference, repeated or severe head trauma.

Pathophysiology:

• Structural Changes:

-AD destroys neurons in the cortex and limbic structures of the brain

-these areas are responsible for higher learning, memory, reasoning, behaviour, and emotional control
Anatomically, four major alterations in brain structure are seen:

- 1- Cortical atrophy
2. degeneration of cholinergic and other neurons
3. presence of neurofibrillary tangles (NFTs)
4. accumulation of neuritic plaques.

-Inflammatory mediators and other immune sys. constituents are present near areas of plaque formation, suggesting that the immune system plays an active role in the pathogenesis of AD.

-The elevated cholesterol levels in brain neurons may alter membrane functioning and result in the cascade leading to plaque formation and AD.

Clinical Presentation:

Alzheimer's Symptoms into two basic categories: Cognitive symptoms

and noncognitive (behavioral) symptoms

→ Cognitive: Memory loss, aphasia, disorientation.

→ Noncognitive: Depression, Hallucination and delusions, behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness)

→ Functional:

Inability to care for self (dressing, bathing, toileting and eating).

Diagnosis:

Laboratory Tests:

Rule out vitamin B₁₂ and Folate deficiency

Rule out hypothyroidism with thyroid function tests

CT or MRI scans may aid diagnosis

- Ask questions about overall health, past

medical problems, ability to carry out daily activities, and changes in behavior and personality.

- Conduct tests of memory, problem solving, attention, counting and language.

Treatment:

Non-pharmacologic Therapy:

1. Communication between the patient and family members essential in order to minimize stress on everyone.
2. Non-medication based treatments include maximizing patient's opportunities for social interaction and participating in activities such as walking, singing dancing that they can still enjoy.
3. The components of a Mediterranean diet which include fruit and vegetable, bread, wheat and other olive oil, fish and red wine, may all individually

or together reduce the risk and course of Alzheimer's disease.

Pharmacologic Therapy:

1. Pharmacotherapy For Cognitive Symptoms:

- The cholinesterase inhibitors are indicated for treatment of mild to moderate AD.

→ Acetylcholinesterase inhibitors are employed to reduce the rate at which ACh is broken down, thereby increasing the concentration of ACh in the brain and combating the loss of ACh caused by the death of cholinergic neurons.

→ Additionally, Vit E should be used adjunctively with the cholinesterase inhibitors throughout treatment.

Rivastigmine 3-6 mg twice a day

Galantamine 8-12 mg twice a day

ADR:

Nausea, vomiting, dizziness, insomnia, muscle cramps, brady cardia.

Other Agents

Memantine (By and Admenta)

Memantine, an NMDA-antagonist, is a novel agent for treating AD. By blocking NMDA receptor excitotoxic reactions, which ultimately lead to cell death, may be prevented.

(Memantine is likely to be used as monotherapy and also in combination with cholinesterase inhibitors, particularly in patients with moderate to severe AD. Memantine should be initiated at 5 mg once a day and increased weekly by 5 mg a day to the effective dose of 10 mg twice daily.)

The most frequent adverse events associated with memantine include constipation, confusion, dizziness, headache, coughing, and hypertension.

Vitamin E

Based on pathophysiologic theories involving free radicals, significant interest has evolved regarding the use of antioxidants in the treatment of AD.

(Vitamin E is often recommended as adjunctive treatment for AD patients, and should be titrated to a maintenance dose of 1000 international units twice a day.)

Estrogen

Interest in estrogen use has increased over the last decade. Most, but not all, epidemiologic studies show a lower incidence of AD in women who took estrogen replacement therapy postmenopausally.

Showed increased risk in coronary heart disease, breast cancer, stroke, and pulmonary embolism. Benefits included reduced risk of colorectal cancer and hip fracture.

(The effect of estrogen in AD as a treatment of cognition has not been established, and other health risks are also of concern; therefore, estrogen should only be used in those patients who have another medical reason for estrogen replacement therapy.)

Anti-Inflammatory Agents

(Long-term usage of non-steroidal anti-inflammatory drug (NSAIDs) is associated with a reduced likelihood of developing AD.)

NSAIDs can reduce inflammation related to amyloid plaques

Epidemiologic studies have also suggested a protective effect against AD in patients who have taken nonsteroidal anti-inflammatory drugs (NSAIDs). Treatment for less than 2 years has been associated with a lower relative risk of AD; however, longer treatment duration lowered this risk further.

Lipid-Lowering Agents

Interest in the potential protective effects in AD patients of lipid-lowering agents, particularly the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, is growing based on recent epidemiologic studies.

Studies suggested that the incidence of AD is lower in patients who have taken either a statin or another lipid-lowering agent, but not in patients who were taking other cardiovascular medications.

Interestingly, pravastatin and lovastatin, but not simvastatin, were associated with a lower prevalence of AD.

For now these agents should be reserved for patients who have other indications for their use.

Ginkgo Biloba

(Egb 761) is an extract of ginkgo biloba, is claimed to improve memory. Although it is thought to be an antioxidant and to affect inflammation and neuromodulation, the mechanisms of the multiple compounds in Egb have not been elucidated.)

Standardized doses of ginkgo ranged from 120 to 240 mg/day.)

No significant adverse events were reported; however, some case reports have shown an association with hemorrhaging.)

Until these products are better standardized and their manufacturing and stability better assured, it is recommended that they be used with caution.

2. PHARMACOTHERAPY OF NONCOGNITIVE (BEHAVIOURAL) SYMPTOMS

The majority of patients with AD manifest noncognitive symptoms at some point in the illness. These symptoms can be roughly divided into three categories: psychotic symptoms, inappropriate or disruptive behavior, and depression.)

Effective management of these problems is important because behavioral symptoms are distressing to both the patient and the caregiver, necessitate increased caregiver supervision and patience, and are a leading reason for nursing home placement.

Strategies for treatment of psychotic or behavioral symptoms should include both environmental and pharmacologic interventions (e.g., antipsychotics, antidepressants, mood stabilizers, and anxiolytics.)

Drugs	Suggested Dosage	Indications
<u>in Dementia (mg/day)</u>		
<u>Antipsychotics</u>		
Haloperidol	0.5-4 mg	Psychosis: hallucinations, delusions, suspiciousness
Olanzapine	2.5-10 mg	Disruptive behaviors (agitation, aggression)
Quetiapine	12.5-200 mg	
Risperidone	0.25-2 mg	
<u>Antidepressants Depression:</u>		
Citalopram	10-20 mg	poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, agitation
Fluoxetine	5-20 mg	
Mirtazapine	15-45 mg	
Paroxetine	10-40 mg	
Sertraline	50-200 mg	
Trazodone	75-400 mg	
Venlafaxine	37.5-150 mg	
<u>Anticonvulsants</u>		
Carbamazepine	100-1,000 mg	Agitation or aggression
<u>Others</u>		
Bupropion	10-45 mg	Disruptive behaviors
Oxazepam	10-60 mg	Disruptive behaviours
Selegiline	10 mg	Disruptive behaviors, agitation, anxiety, depression

Antipsychotics

Antipsychotic medications have traditionally been used to treat (disruptive behaviors) and psychosis in AD patients. Symptoms responding to antipsychotics include assaultiveness, extreme agitation, hyperexcitability, hallucinations, delusions, suspiciousness, hostility, and uncooperativeness; whereas withdrawal, apathy, cognitive deficits, wandering, and incontinence are not responsive.

Antidepressants

These medications are used since, actual prevalence rates of major depression in AD are probably 5% to 15% in community-based patients.

Depression may be more common in the early stages of AD as the patient attempts to adjust to limitations associated with cognitive loss.

Miscellaneous Therapies

Because antipsychotic therapy has shown only modest efficacy and poses a substantial risk of undesirable side effects, medications traditionally used to treat disruptive behaviors and aggression in other psychiatric and neurologic disorders have been suggested as potential alternatives.

These alternatives include benzodiazepines, buspirone, carbamazepine, selegiline, and SSRIs.

In addition to antipsychotics, citalopram (10 to 20 mg/day) and carbamazepine (mean dose of 300 mg/day) have been shown to decrease psychosis and behavioral disturbances of dementia.

Benzodiazepines, particularly oxazepam, have been used to treat anxiety, agitation, and aggression, but they generally show inferior efficacy when compared to antipsychotics. Because benzodiazepines impair cognition, can result in disinhibition, and may increase the risk of falls in AD patients, their routine use is not advised.

Conversely, the 5-HT_{1A} partial agonist buspirone has shown benefit in treating agitation and aggression in a limited number of patients with minimal adverse effects.

Selegiline decreases anxiety, depression, and agitation.

<https://www.facebook.com/Pharmacy-Notes-1593423834279694/>

4

□ Schizophrenia:

- Schizophrenia is a severe brain disorder in which people interpret ^{عاشيا} reality abnormally.
- Schizophrenia may result in some combination of hallucinations, delusions, and extremely disordered thinking and behavior.
- The word "schizophrenia" does mean "split mind".

Etiology:

- 1- Genetic
- 2- Brain damage
- 3- Viral attack
- 4- Imbalance of neurotransmitters in brain develops schizophrenia.
 - a- Dopamine levels increase
 - b- Serotonin receptors also increases.

□ Symptoms:

- 1- Emotional disorder

Psychiatry disorders

2. Delusions and hallucinations
3. Agitation
4. Abnormal behaviours
5. Social withdrawal
6. depression

Pathogenesis:

- Dopamine (DA) and serotonin (5-HT) play an important role in schizophrenia. The imbalance in these two neurotransmitter develop schizophrenia.
- Both levels of DA and 5-HT increases during schizophrenia which leads to hallucinations and delusions.
- Dopamine and 5-HT act as inhibitory neurotransmitter in brain.

TYPES OF SCHIZOPHRENIA

- ❖ Paranoid schizophrenia
- ❖ Hebephrenic schizophrenia
- ❖ Catatonic schizophrenia
- ❖ Undifferentiated schizophrenia
- ❖ Residual schizophrenia

Paranoid Schizophrenia

- Paranoid schizophrenia is characterized mainly by delusions, feelings of passive or active control, feelings of intrusion, and often by megalomaniac tendencies also. The delusions are not usually systemized too much, without tight logical connections and are often combined with hallucinations of different senses, mostly with hearing voices.
- Disturbances of affect, volition and speech, and catatonic symptoms, are either absent or relatively inconspicuous.

Hebephrenic Schizophrenia

- Hebephrenic schizophrenia is characterized by disorganized thinking with blunted and inappropriate emotions. It begins mostly in adolescent age, the behavior is often bizarre. There could appear mannerisms, grimacing, inappropriate laugh and joking. There is a tendency to social isolation.
- Usually the prognosis is poor because of the rapid development of "negative" symptoms, particularly flattening of affect and loss of volition. Hebephrenia should normally be diagnosed only in adolescents or young adults.
- Denoted also as disorganized schizophrenia

Catatonic Schizophrenia

- Catatonic schizophrenia is characterized mainly by motoric activity, which might be strongly increased (hyperkinesia) or decreased (stupor), or automatic obedience and negativism.
- We recognize two forms:

- productive form — which shows catatonic excitement, extreme and often aggressive activity. Treatment by neuroleptics or by electroconvulsive therapy.
- stuporose form — characterized by general inhibition of patient's behavior or at least by retardation and slowness, followed often by mutism, negativism, flexibilitas cerea or by stupor. The consciousness is not absent.

- **Undifferentiated Schizophrenia**

- Psychotic conditions meeting the general diagnostic criteria for schizophrenia but not conforming to any of the subtypes of paranoid/catatonic schizophrenia or exhibiting the features of more than one of them without a clear predominance of a particular set of diagnostic characteristics.

- This subgroup represents also the former diagnosis of atypical schizophrenia.

- **Residual Schizophrenia**

- A chronic stage in the development of schizophrenia with clear succession from the initial stage with one or more episodes characterized by general criteria of schizophrenia to the late stage with long-lasting negative symptoms and deterioration (not necessarily irreversible).

- **DIAGNOSIS**

- ❖ The Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM-IV-TR), specifies the following criteria for the diagnosis of schizophrenia:

- ❖ Persistent dysfunction lasting longer than 6 months
- ❖ Two or more symptoms (present for at least 1 month) including hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms
- ❖ Significantly impaired functioning (work, interpersonal, or self-care)

Diagnostic issues - Subtypes

- ❖ Paranoid – 35-40%. Disorganized – 10%. Catatonic – 10%. Undifferentiated – 20%. Residual – 20%.

TREATMENT:

NONPHARMACOLOGICAL TREATMENT:

- PSYCHOSOCIAL TREATMENTS
- REHABILITATION
- COGNITIVE BEHAVIORAL
- PSYCHOTHERAPY
- FAMILY EDUCATION
- SELF-HELP GROUPS
- COMMUNITY AND SOCIAL SUPPORT

❖ PSYCHOSOCIAL TREATMENTS

- Psychosocial treatments help to solve most with psychological, social, and occupational problems.
- Useful for patients with less severe symptoms or for patients whose psychotic symptoms are under control.
- Focus on improving the patient's social functioning.

❖ REHABILITATION

- Includes a wide range of non-medical interventions.
- Social and vocational training helps patients overcome difficulties.
- Vocational counseling, problem-solving skills.
- Provided by Partial Hospital or Day Treatment Programs (4 to 6 hrs per day, several days per week).

❖ COGNITIVE BEHAVIORAL PSYCHOTHERAPY

- More effective than other types of psychotherapy in treating depression and panic attacks.
- Cognitive treatment helps treat distorted perceptions of the world, including self, and disordered or disorganized thinking.
- Behavior therapy teaches the social skills never learned, and helps understand when to apply those skills to problems in the world.
- Examples of training: Stress Management Training, Assertiveness Training, Communication Skills Training, Problem Solving Skills.

❖ FAMILY EDUCATION

- It is important for family members to learn all they can about schizophrenia when they have to take care of a family member who has been discharged from the hospital.
- Family psycho education includes teaching various coping strategies and problem-solving skills. It is a cognitive-behavioral treatment approach to family therapy.
- This approach helps families to deal more effectively with their ill relative and to contribute to an improved outcome for the patient.

❖ SELF-HELP GROUPS

- Members provide continuing mutual support as well as comfort in knowing that they are not alone in the problems they face.
- Families working together can more effectively serve as supporters for needed research and hospital and community treatment programs.
- Patients acting as a group rather than individually may be better able to dismiss dishonor and draw public attention to such abuses as discrimination against the mentally ill.
- Groups are very active and provide useful information and assistance for patients and families of patients with schizophrenia.

❖ COMMUNITY AND SOCIAL SUPPORT

- Patients with schizophrenia may need help from people in their family or community.
- Ensuring that a person with schizophrenia continues to get treatment after hospitalization is important.
- Encouraging the patient to continue treatment and assisting him or her in the treatment process can positively influence recovery.
- A positive approach may be helpful and perhaps more effective in the long run than criticism.

• Pharmacological treatment

Classification of antipsychotic drugs:

1) First generation or typical classical antipsychotics:

ex: chlorpromazine flupentixol
haloperidol clopenthixol
fluphenazine

2) Second generation or atypical antipsychotics:

ex: clozapine amisulpride
risperidone aripiprazole
sertindole zotepine,
quetiapine ziprasidone

اضطرابات Anxiety Disorders

Definitions:

1. Generalized anxiety disorder (GAD) is characterized by excessive, almost daily anxiety and worry for ≥ 6 mo about many activities or events.

- The cause is unknown, although it commonly coexists in people who have alcohol abuse, major depression, or panic disorder.

2. A panic attack is a sudden ^{عاصه} episode of intense ^{بسيار زياد} fear that triggers severe physical reactions when there is no real danger or apparent cause.

3. Social anxiety disorder (SAD)

- Also called social phobia, is an anxiety disorder in which a person has an excessive and unreasonable fear of social situations.

- A person with social anxiety disorder is afraid that he or she will make mistakes, look bad,

and be embarrassed or humiliated in front of others.

4. Obsessive-compulsive disorder (OCD)

OCD is characterized by unreasonable thoughts and fears (obsessions) that lead you to do repetitive behaviors (compulsions).

- It's also possible to have only obsessions or only compulsions and still have OCD.

□ Etiology:

- Changes in the brain
 - environmental stress
 - certain drug
 - Genetic
 - Patients with SAD commonly report having overprotective parents.
 - Common Medical illnesses associated with anxiety
- Symptoms: Angina, congestive heart failure, migraine, Asthma, Anemias

- Drugs associated with Anxiety Symptoms:

Antibiotics: isoniazid

Bronchodilators: theophylline

Corticosteroids: prednisone

Dopa agonists: levodopa

Pathophysiology:

Data from biochemical and neuroimaging studies indicate that the modulation of normal and pathologic anxiety states is associated with multiple regions of the brain and abnormal function in several neurotransmitter systems, including NE, γ -aminobutyric acid (GABA), serotonin (5-HT), corticotrophin-releasing factor.

Clinical Presentation:

Presentation of Generalized Anxiety disorder

- worries that are difficult to control
- Poor concentration
- restlessness

- Fatigue
- Sleep disturbance
- Shortness of breath
- Nausea
- Dry mouth
- Heart palpitations
- Dizziness
- Feelings of panic, fear

A. Generalized Anxiety Disorder:

- Nonpharmacologic therapy:

- include:

psychoeducation, short-term counseling, stress management,

- Psychoeducation includes information on the etiology and management of GAD. Anxious patients should be instructed to avoid caffeine, and excessive use of alcohol.

□ Most patients with GAD require psychologic

therapy, alone or in combination with anti anxiety drugs, to overcome fears and to learn to manage their anxiety and worry.

Cognitive behavioral therapy (CBT) is the most effective psychologic therapy in GAD patients.

□ Pharmacologic therapy: BAB

~~I-Benzodiazepine Therapy~~

MOA:

-Benzodiazepins ameliorate anxiety through potentiation of the inhibitory activity of GABA.

-Benzodiazepins bind on the GABA receptor at the α_1 , α_2 , α_3 and α_5 subunits in combination with a β subunit and the γ_2 subunit. The anxiolytic effects of benzodiazepines are mediated at the α_2 site while sedative effects result from binding at the α_1 subunit.

ADR:

CNS depression

-confusion

Sedation

<u>Ex:</u>	Dose (mg/day)
chl or diazepam	25-100
Clonazepam	1-4
Diazepam	2-40
Lorazepam	0.5-10

2. Antidepressant Therapy

Antidepressants are considered first-line agents in the management of GAD.

MOA:

- Research indicates that antidepressants modulate receptor activation of neuronal signal transduction pathways connected to the neurotransmitters 5-HT, DA, and NE. As a result these cascades modify the expression of certain genes and the proteins that are produced.

ADR:

nausea

- decreased libido

abdominal ejaculation

dry mouth

Drugs:

Duloxetine

30 or 60mg/day

Paroxetine

50mg/day

3. Buspirone Therapy:

□ Buspirone is a nonbenzodiazepine anxiolytic that lacks anticonvulsant, muscle relaxant, hypnotic, motor impairment, and dependence properties.

- It is considered to be a second line agent for GAD.

MOA:

Buspirone's anxiolytic mechanism of action is unknown. It is thought to exert its anxiolytic effect through 5HT_{1A} partial agonist activity at the presynaptic 5-HT receptors by reducing the firing of 5-HT neurons.

ADR:

dizziness

nausea

headaches

B. Panic Disorder treatment:

Nonpharmacologic Therapy:

- Patients should be educated to avoid substances that can precipitate panic attacks, including caffeine, drugs of abuse and nonprescription stimulants.
- CBT
- Bibliotherapy (the use of selfhelp books)
- exercise

Pharmacologic Therapy: SBTM

i- Selective Serotonin reuptake inhibitors:

	Starting dose	range
Fluoxetine	5mg/day	10-30
Fluvoxamine	25 mg/day	100-300

MOA:

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity.

ADR:

insomnia

restlessness

agitation

ii- Serotonin Norepinephrine reuptake inhibitors:

drugs:

Benzodiazepines

Alprazolam	0.25 mg three times a day	4-10
Clonazepam	0.25 mg once or twice per day	1-4
Diazepam	2-5 mg three times a day	5-20
Lorazepam	0.5-1 mg three times a day	2-8

ADR:

nausea

sweating

abnormal sexual functioning

iii - Tricyclic Antidepressants:

Imipramine 10mg per day 75-250

MOA:

TCA's are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. At therapeutic concentrations, they do not block dopamine transporters. By blocking the major route of neurotransmitter removal, the TCAs cause increased concentrations of monoamines in the synaptic cleft, ultimately resulting in antidepressant effects.

- TCAs also block serotonergic, adrenergic, histaminic and muscarinic receptors.

ADR:

- Dry mouth
- Constipation
- Urinary retention
- increased body temperature
- Sexual dysfunction
- memory impairment
- anxiety
- changes in appetite and weight

iv - Monoamine oxidase inhibitor:

Phenelzine

C. Social Anxiety Disorder treatment:

Nonpharmacologic Therapy:

o Patients should be educated about SAD and effective therapeutic options.

Support groups are helpful for some patients.

- Self-help group programs that focus on effective communication can benefit people with public speaking phobia. CBT for SAD consists of exposure therapy, cognitive restructuring, relaxation training techniques, and social skills training:

SMBB

pharmacologic Therapy:

1. Selective serotonin reuptake inhibitors

Fluvoxamine	50mg/day	150-300
Paroxetine	10mg/day	10-60

2. Serotonin-norepinephrine reuptake inhibitor

clonazepam	0.25mg per day	1-4
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3. Monoamine oxidase inhibitor

Phenelzine	15mg at bed time	60-90
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4-Alternative agents:

Buspirone

10 mg twice
per day

45-60

D. Obsessive - Compulsive Disorder:

Non-pharmacologic Treatment:

- CBT:

In the management of OCD, CBT involves exposure plus response prevention combined with cognitive therapy.

- Exposure involves having the patient perform actions that were formerly avoided.

Pharmacological Treatment:

SSRIs and TCA are effective.

□ Sleep disorders:

◦ Sleep cycle:

→ There are five stages of sleep that cycle over and over again during a single night's rest: Stages 1, 2, 3, 4 and REM (rapid eye movement).

→ Stages 1 through 4 are also known as non-rapid eye movement sleep (NREM).

→ Stage 1 is light sleep during which the muscles begin to relax and a person can be easily awakened.

→ During Stage 2, brain activity slows down and eye movement stops.

→ Stages 3 and 4 comprise deep sleep, during which all eye and muscle movement ceases. It can be difficult to wake a person during deep sleep.

→ REM: increase in eye movement, heart rate, Bp breathing and temperature.

Classification of sleep disorders

A: Primary sleep disorders

1. Dyssomnias

- I. Primary insomnia
- II. Primary hypersomnia
- III. Breathing-related sleep disorder
- IV. Narcolepsy
- V. Circadian rhythm sleep disorder

2. Parasomnias:

- Nightmare disorder
- Sleep terror disorder
- Sleepwalking disorder

3. Sleep disorders related to another Mental Disorder:

- Insomnia related to another mental disorder

4. Other:

- Substance-induced sleep disorder

-Insomnia:

-is the inability to obtain an adequate amount or quality of sleep.

The difficulty can be in falling asleep, remaining sleep, or both.

Etiology:

- caffeine
- alcohol
- nicotine
- anxiety disorder
- Stress
- Shift work
- chronic pain
- panic disorder
- Diuretics
- SSRI

-Diagnosis:

-The diagnosis of insomnia is made by a physician based on the patient's reported signs and symptoms.

It can be useful for the patient to keep a daily record for two weeks of sleep patterns, food intake, use of alcohol etc and any other

information recommended by the physician.

-If the patient has a bed partner, information can be obtained about whether the patient snores or is restless during sleep.

This, together with a medical history and physical examination, can help confirm the doctor's assessment.

□ Treatment:

◦ Nonpharmacologic Therapy

1. Stimulus control therapy
2. relaxation therapy
3. Cognitive therapy
4. Sleep hygiene
5. Sleep restriction

◦ Pharmacologic:

Nonbenzodiazepine Hypnotic Agents:

Zolpidem

MOA:

Acts selectively at the BZ1 receptor.

Dose: 10mg

ADR:

Headache

Amnesia

Dizziness

Zaleplon

MOA:

Binds selectively at the BZ1 receptor

Dose: 5-20mg

ADR: Headache, Somnolence, Dizziness

Valerian:

MOA:

Inhibition of the enzyme that break down GABA

Dose:

2-3g given one to several times a day.

ADR: Amnesia, Drowsiness, Headach, Dizziness

DRUG	MECHANISM	DOSE	ADVERSE EFFECTS
Zolpidem	Acts selectively at the BZ ₁ receptor	usual dose is 10 mg, but 5 mg in elderly patient and those with hepatic impairment	Drowsiness Amnesia → (rare) Dizziness Headache

2-Sleep Apnea:

- Sleep apnea is a sleep disorder characterized by pauses in breathing during sleep.

Classification:

1. Obstructive Sleep Apnea (OSA)
2. Central Sleep Apnea (CSA)
3. Mixed Apnea

□ Obstructive Sleep Apnea:

- is a potentially serious sleep disorder in which breathing repeatedly stops and starts during sleep.

□ Causes:

Occlusion of the upper airway due to:

Obesity

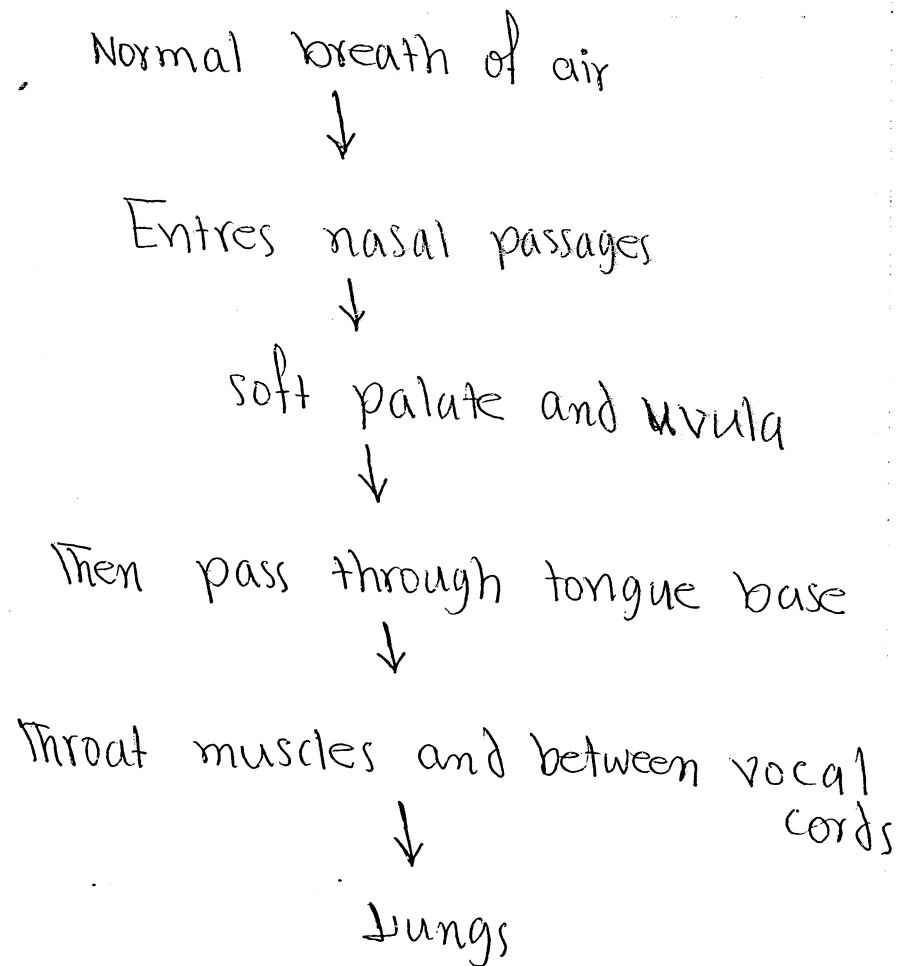
Polyps

Enlarged tonsils, adenoid or tongue

□ Symptoms:

Somnolence
morning headache
poor memory
irritability

□ Pathogenesis:



→ Any obstruction to the flow of air at these levels may lead to apnea.

DIAGNOSIS:

Epworth sleepiness scale can be used. Risk of dozing can be ranked from the following chart:

- ☐ 0---- unlikely to fall asleep
- ☐ 1---- slight risk of falling asleep
- ☐ 2---- moderate risk of falling asleep
- ☐ 3---- highly likelihood of falling asleep

NON PHARMACOLOGICAL TREATMENT:

- ☐ Weight loss
- ☐ Tonsillectomy
- ☐ Nasal/continuous positive airway pressure (CPAP): elevates the pressure in the oropharyngeal space to maintain positive airway pressure during the respiratory cycle
- ☐ Uvulopalatopharyngoplasty: surgical procedure to enlarge the pharyngeal airspace that reduces apnea.

PHARMACOTHERAPY:

- ☐ The single most important pharmacological intervention is avoidance of all CNS depressants (alcohol), anxiolytics, hypnotics, narcotics, zolpidem)
- ☐ Protryptiline 10-30 mg/d
 - decreases the REM sleep
- ☐ Fluoxetine 20 mg/d
- ☐ Respiratory stimulants like theophylline and clonidine

Central Sleep Apnea:

Central sleep apnea is a disorder in which your breathing repeatedly stops and starts during sleep.

- Central sleep apnea occurs because your brain doesn't send proper signals to the muscles that control your breathing.

Symptoms:

- being very tired during the day
- waking up often during the night
- having headaches in the early morning
- poor memory
- mood problems

Causes:

Nasal obstruction

Autonomic system lesions

Myasthenia gravis

CHF

Treatment:

If central sleep apnea is associated with some other condition, such as congestive heart failure that condition is treated, if possible.

- Losing weight if necessary, and then maintaining a healthy weight.
- Avoiding the use of alcohol and sleeping pills, as these items make the airway more likely to collapse during sleep.
- Using nasal sprays or breathing strips to keep air flowing if you have sinus problems or nasal congestion.
- Oxygen therapy
- CPAP (continuous positive airway pressure)

□ Narcolepsy:

- A medical condition in which someone suddenly falls into a deep sleep while talking, working etc.

Symptoms:

Fatigue

Impaired performance

disturbed night time sleep

- Cataplexy → A condition characterized by sudden, brief attacks of muscle weakness
- Sleep paralysis sometimes causing the body to fall helplessly, that is usually triggered by strong emotion

□ Diagnosis:

Tests:

- 1- Polysomnogram: you usually stay overnight at a sleep center for a PSG. The test records brain activity, eye movements, heart

rate, and blood pressure

2. Multiple sleep latency test

- A technician checks your brain activity during daytime. He/she notes how quickly you fall asleep and how long it takes you to reach various stages of sleep.

- It's often done the day after a PSG.

Excessive day time somnolence	Dose	MOA	ADR
✓ Dextroamphetamine	5-60 mg	They enhance the nor epinephrine release from presynaptic neurons and thus promotes wakefulness	Abuse, tolerance, Headache, insomnia, nervousness, agitation, confusion, tremor, anxiety,
Methamphetamine	5-15 mg		hypertension, palpitation, tachycardia, mania
Methylphenidate	30-80 mg bid		
✓ Modafinil (non amphetamine stimulant)	200-400 mg morning and after noon		
Pemoline	18.75-112.5mg		

Cataplexy, sleep paralysis	Dose.	MOA	ADR
Imipramine	50-250 mg	Blocks nor epinephrine and serotonin reuptake and reduces cataplexy and sleep paralysis	Dry mouth, blurred vision
Protriptyline	5-30 mg		constipation,
Nortriptyline	50-200 mg		urinary hesitancy,
Selegeline	20-40 mg		tachycardia,
Gamma hydroxy butyrate (GHB)	60 mg/kg at night		postural hypotension

Circadian Rhythm Disorders

- Circadian rhythm disorders occurs due to the mismatch between an individuals biological clock and external time cause of the environment

① Jet lag occurs due to rapid travel over multiple time zones and results in degrees and durations of sleep-onset or maintenance insomnia complaints and day time sleepiness.

- When traveling across a number of time zones, the body clock will be out of synchronization with the destination time.

Symptoms:

Headache

Fatigue

irregular sleep patterns

Insomnia

Irritability

mild depression

constipation or diarrhea

Treatment:

1. Stay less than 7 days in a new time zone by adhering to the normal sleep/wake schedule.
2. Arising 1-2 hrs later several days before the trip.
3. Avoid ingestion of alcohol
4. Short acting BZD can be used (alprazolam, triazolam).

② Shift work sleep problems:

- working at night causes a misalignment in the sleep/wake cycle and circadian rhythm associated with a decrease in alertness, performance and quality of day time sleep.

On non working nights many night shift workers experience insomnia.

Treatment:

1. Recommending a day time job.
2. Extending the day time sleep by sleeping in the afternoon.

3. Scheduled exposure to bright lights at night and darkness during the day time improves psychological and behavioral adaptation to night work and day time sleep.

4. Melatonin can be used.

Dyssomnias not otherwise specified

Dyssomnias that is not primary due to general medical condition, or substance induced is categorized as not otherwise specified.

1. Idiopathic restless leg syndrome
2. Nocturnal myoclonus (periodic limb movements)

Restless legs Syndrome:

◦ RLS, also known as EKBOM's Syndrome, is a discomfort, not pain, verbalized as pins and needles, a crawling sensation, or cramping mainly in the calves, thighs or arms.

- Iron deficiency, pregnancy and renal failure are associated with RLS.
- Caffeine, stress or fatigue may worsen the symptoms.
- It is generally bilateral in nature and occurs during rest and inactivity.
- It is relieved quickly by walking or moving the legs.
- This mainly occurs when the person resumes sleep and thus resulting in insomnia.

Treatment:

i- BZDs 1st line agents for less severe cases.

□ Clonazepam - 0.5-2mg

□ Lorazepam - 5-10mg

ii- Opiates:

□ Methadone 5-20mg

□ Codeine 30-120mg

□ Oxycodone 2.5mg

iii - Other agents:

Amantadine

Tramadol

Clonidine

Carbamazepine

□ Patient should take the agent early enough prior to bedtime to allow time for drug absorption.

→ Dorland's: sleepwalking, rising out of bed and walking about or performing other complex motor behavior during an apparent state of sleep.

□ Somnambulism:

• Sleepwalkers arise from the slow wave sleep stage in a state of low consciousness and perform activities that are usually performed during the day.

• These activities can be as benign

1. As sitting up in bed
2. Walking to the bathroom and cleaning
3. Cooking
4. Driving etc.

Causes:

- Delay in maturation
- An immaturity in the CNS
- the use of some neuroleptics or hypnotics

Treatment:

the treatment consists of protection from injury by:

- Putting safety latches on doors and windows
- removing hazardous objects from bedroom
- Covering glass doors with heavy curtains
- theorectically sleep walking may be prevented by suppressing delta sleep.
- BZDs suppress delta sleep.
- SSRIs and TCAs can also be used

In severe cases:

□ Levodopa 200mg + Carbidopa 50mg

It should be taken 30 mins before bed time.

Periodic Limb Movements:

• PLMs are described as stereotypic, repetitive, periodic movements of the legs that occur every 20-40 secs and lasts 10 mins to several hrs.

• The movement generally involve the big toe, ankle, knee and hip.

• It occurs during sleep.

• Renal failure is a predisposing condition.

• BZD withdrawal and TCAs precipitates the condition.

• Most patients with RLS also have PLs.

• Treatment is similar to RLS.

→ A category of sleep disorders in which abnormal events occur during sleep, such as sleepwalking, or talking, due to inappropriately timed activation of physiological systems.

Parasomnias:

→ Parasomnias refer to a group of acute, episodic physical phenomena, that occur either exclusively during sleep or are exaggerated by sleep.

1. Sleep walking disorder (somnambulism)
2. Sleep terror disorder
3. Nightmares disorder

Sleep Terror:

- Sleep terror disorder is defined as repeated temporary arousal from sleep, during which the affected person appears and acts extremely frightened.
- Sleep terror disorder is also referred to as pavor nocturnus when it occurs in children, and incubus when it occurs in adults.
- Sleep terrors are also sometimes called night terrors.

Symptoms:

- rapid heartbeat
- sweating
- rapid breathing
- Sitting up suddenly in bed
- Crying

□ Treatment:

includes psychotherapy and diazepam.

!وړځ = a terrifying dream

○ Nightmares (dream anxiety disorder)

- They are REM phenomenon associated with frequent elaborate recall of frightening dream content.

Eg:

Dreams of physical attacks and death

- The victim is always awakened by these threatening and frightening dreams.

- Causes:

Stress

Anxiety

Post-traumatic stress disorder

Side effects of the drug Amphetamines, antidepressants and stimulants like cocaine can cause nightmares.

Blood pressure medication
levodopa and medications for Parkinson's
disease.

Treatment:

- consist of psychological intervention
- Cyproheptadine (with frequent)

Obsessive - Compulsive Disorder (OCD)

- Obsessive - compulsive disorder (OCD) is characterized by obsessive thoughts and compulsive behaviours that impair everyday functioning.

- Fears of contamination and germs are common, as are hand washing, counting behaviours, and having to check and recheck such actions as whether a door is locked.

Aetiology:

1. Genetic factor
2. Infections [ex: streptococcus]
3. It is likely that abnormalities in several areas of brain functioning interact to cause these chronic anxiety disorders.

Pathophysiology:

- Although OCD occasionally begins following a brain injury, especially involving the basal ganglia, there is usually no neurologic precipitant.

-The neurotransmitter 5-HT appears to play an important role in the pathogenesis of OCD.

Neurochemical theories:

- Both 5-HT and DA are implicated in the pathogenesis of OCD.
- DA dysregulation may contribute to some forms of OCD.

Neuroimaging studies

- individuals with OCD show hyperactivity in the ventral prefrontal cortex (VPFC) of the brain.

Clinical presentation:

Patients can present in a seemingly incongruous manner to nonpsychiatrists for other complaints- dermatologists for eczema or chapped skin because of severe dermatitis from excessive washing, paediatricians for parental concerns over a child's compulsive hand washing,

neurologists for tics, or dentists for gum lesions from compulsive teeth brushing.

Presentation of obsessions or compulsions

A. Either obsessions or compulsions

Obsessions as defined as:

- i- Recurrent and persistent thoughts, impulses or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress.
- ii- Attempts are made to ignore or suppress the thoughts, impulses, or images or to eliminate them.
- iii- It is recognised that the obsessional thoughts, impulses, or images are a product of the person's own mind (not imposed from without).

Compulsions as defined by:

- i- Repetitive behaviours (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting) that the person feels driven to

perform in response to an obsession, or according to certain rules.

B. The person has recognised that the obsessions or compulsions are excessive or unreasonable.

C. The obsessions or compulsions cause marked distress, are time consuming, or significantly interfere with the person's normal routine

- Patients with OCP often have comorbid depression, anxiety disorders, and alcohol abuse or dependence.

Diagnosis:

Only trained therapists can diagnose OCP.

Therapists will look for 3 things:

- The person has obsessions
- He or she does compulsive behaviors
- The obsessions and compulsions take a lot of time and get the way of important activities

the person values, such as working, going to school etc.

□ Treatment:

Goals:

- Reduction in the frequency of obsessive thoughts and in the time spent performing compulsive acts and reduction in the degree of anxiety.
- To provide the patient with an optimal level of psychosocial and occupational functioning and an overall improved QOL.
- To minimize adverse drug events and prevent drug interactions.

Nonpharmacologic Therapy:

i. Cognitive-behavioral therapy (CBT) is the treatment of choice for mild OCD in both adolescents and adults. In the management of OCD, CBT involves exposure plus response prevention combined with cognitive therapy. Exposure involves having the

patient perform actions that were formerly avoided.

ii- Techniques such as teaching patients to prevent relapse through self-exposure and self-imposed ritual prevention are suggested to foster optimal nonpharmacologic therapy.

iii- Exposure with response prevention is particularly helpful for contamination or other fears etc.

iv- Cognitive therapy is beneficial for scrupulosity, moral guilt, and pathologic doubt.

Pharmacologic therapy:

i- The SSRIs (e.g. Fluoxetine, Fluvoxamine etc) are considered to be the drugs of choice in the treatment of OCD.

ii- Anti-depressants may be combined with CBT or used alone in adults with moderate to severe symptoms.

iii- An SSRI should be added when there has been no response or partial response to CBT alone. Generally, an SSRI is selected before clomipramine, and whenever anticholinergic, cardiovascular, sexual, sedative or weight gain adverse effects are a major concern.

iv- If one SSRI is ineffective, then another SSRI should be tried.

v- Clomipramine may be selected after two to three failed SSRI trials.

MOA:

5-HT is important for the antiobsessional effects of medication. The SSRIs inhibit 5-HT reuptake into the presynaptic neuron.

- Inhibiting reuptake of 5-HT makes more 5-HT available to post synaptic receptors and reduces the formation of 5-HT metabolite.

Comorbid Conditions:

- OCD in pregnant patient is treated with CBT alone.
- OCD in patients with cardiac or renal disease may be treated with a CBT alone or CBT plus an SSRI.

Side effects:

Drugs	Clomipramine	Fluoxetine	Fluvoxamine
	Dry mouth	Nausea	Insomnia
	Dizziness	Headache	Nausea
	Fatigue	Anxiety	Somnolence
	Nausea	Sedation	Fatigue
	sexual dysfunction	Insomnia	Dry mouth
	weight gain	Diarrhea	decreased libido
	Somnolence	Sexual dysfunction	

Dosing

- ? If there is inadequate response to an average dose, then it should be incrementally increased to the maximum dose within 4 to 9 weeks from the start of treatment.
- ? If there is an inadequate response after 4 to 6 weeks at the maximum dose, then another SSRI should be tried.
- ? Eight to thirteen weeks is considered an adequate trial before changing to another drug or augmenting with another agent.

Dosing of Selective Serotonin Reuptake Inhibitors in Treatment of OCD

Generic Name	Usual Initial Daily Dose (mg)	Usual Daily Dosage Range (mg)	Average Target Daily Dose (mg)
✓ Citalopram	20	20-60	40
✓ Clomipramine	10	→ 100-250	150-200
✓ Fluoxetine	20	→ 20-80	40-60
✓ Fluvoxamine	50	100-300	200
✓ Paroxetine	20	→ 20-60	40
✓ Sertraline	50	75-200	150

Maintenance

- ? After patients have responded to the acute phase of treatment, treatment gains are maintained with maintenance-phase strategies.
- ? Monthly follow-up visits are recommended for at least 3 to 6 months, and a medication taper can be considered after 1 to 2 years of treatment.
- ? Medication should not be rapidly discontinued, and booster CBT sessions may reduce the risk of relapse when medication is withdrawn.
- ? The drug dosage can be decreased by 25%, and then 2 months should lapse before again decreasing the dose, depending on response.
- ? Long-term or lifelong prophylaxis with pharmacotherapy is recommended after two to four severe relapses or three to four mild to moderate relapses.

Affective Disorders (mood disorders)

Definition:

Affective disorders - mental illnesses characterized by pathological changes in mood (not thought - compare with schizophrenia)

i - Unipolar disorders

◦ Depression - is characterized by feelings of extreme sadness and hopelessness.

- If you have depression, you may experience episodes that last for several days or even weeks.

◦ Mania -

mental illness in which a person becomes very emotional or excited.

ii - Bipolar disorder:

- Bipolar disorder means having periods of depression and periods of mania.

□ Classification of mood disorders:

- 1- F30 Manic episode
- 2- F31 Bipolar affective disorder.
- 3- F32 Depressive episode
- 4- F33 Recurrent depressive disorder
- 5- F34 Persistent mood (affective) disorders
- 6- F38 Other mood (affective) disorders
- 7- F39 Unspecified mood (affective) disorder

Etiology:

- Neurotransmitters
- Endocrine system
- Genetic factors
- Sleep dysfunction
- Stressful life events
- Behavioral factors $\left\{ \begin{array}{l} \text{cognitive factors} \\ \text{Psychodynamic} \end{array} \right.$

□ Depression:

◦ Major Depressive Episode Criteria / Core Symptoms:

□ Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

- depressed mood most of the day
- markedly diminished interest or pleasure
- significant weight loss/gain
- insomnia or hypersomnia
- feelings of worthlessness or excessive or inappropriate guilt

Neurobiological theory of depression:

□ Monoamine (catecholamine) theory = the underlying biological or neuroanatomical basis for depression is a deficiency of central noradrenergic and/or serotonergic transmission in the CNS.

Supported by:

- Pharmacological effect of antidepressants (TCA, MAOI)

□ In the past, medication of hypertension with reserpine induced depression.

Contraindication:

- Several drugs (e.g. cocaine) increase the amount of these neurotransmitters in the CNS but are unable to treat depression.

Receptor theory = the problem is in up-regulation of post-synaptic receptors and alterations in their sensitivity.

- The antidepressant treatment increases the amount of monoamines in CNS and thereby gradually normalize the density/sensitivity of their receptors.

Bipolar disorder:

- unusual and chronic mood swings
- during depression, symptoms similar to those for major depressive disorder
- during mania, less sleep and feelings of

exaggerated self-confidence, irritability, aggression, self-importance or in severe cases delusions or hallucinations.

□ Persistent Mood (Affective) Disorders:

• Persistent mood disorders are persistent and usually fluctuating disorders of mood in which individual episodes are not sufficiently severe to warrant being described as hypomanic or even mild depressive episodes.

Persistent mood (affective) disorders:

i- Cyclothymia

ii- Dysthymia

iii- Other persistent mood disorders

□ Cyclothymia:

- Or cyclothymic disorder, is a mild form of bipolar disorder (manic depression)

- In cyclothymic disorder, moods swing between short periods of mild depression and hypomania, an elevated mood. The low and high mood swings never reach the severity of major depression or full mania.

□ Dysthymia:

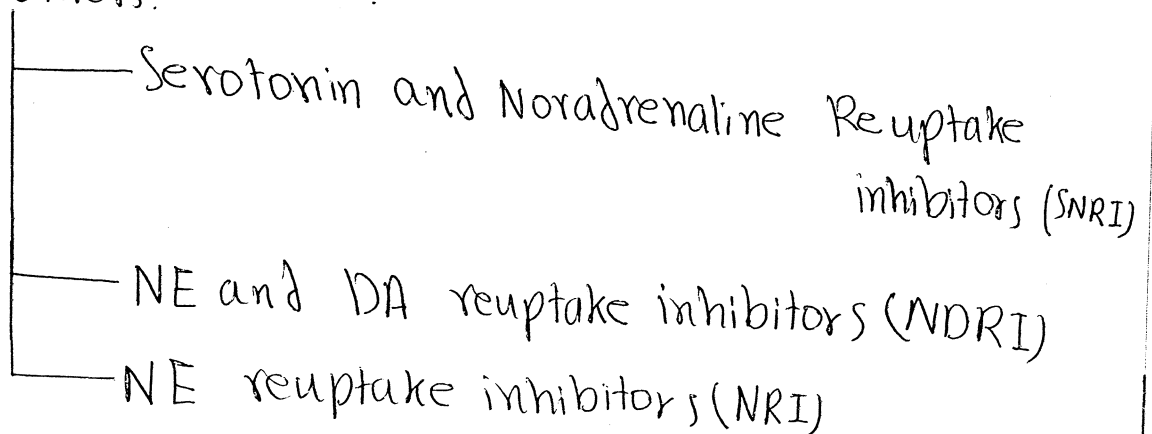
- is a mild but long-term (chronic) form of depression.

- Symptoms usually last for at least two years, and often for much longer than that.

□ Therapy of depression: ^{MOST}

Pharmacotherapy:

- 1- Tricyclic antidepressants (TCA)
- 2- Monoamine oxidase inhibitors (MAOI)
3. SSRI
4. Others:



Non-pharmacological treatment:

- Psychotherapy
- Cognitive therapy
- Electroconvulsive therapy (ECT)

□ Tricyclic Antidepressants (TCAs):

MOA:

Blockade of re-uptake of monoamine neurotransmitters NA and 5-HT by competition for binding site of the carrier protein.

- Imipramine
- Desimipramine

Adverse effects:

- | | |
|---------------------|-------------------------------|
| - Dry mouth | - sedation |
| - blurred vision | - difficulty in concentration |
| - constipation | - sexual dysfunction |
| - urinary retention | |
| - tachycardia | |

□ Monoamine oxidase inhibitors (MAOI)

MOA:

inhibition of intracellular enzyme MAO in CNS neurons, thus preventing the breakdown of monoamine neurotransmitters and thereby increasing their availability.

- There are two isoforms of monoamine oxidase, MAO-A and MAO-B.

- MAO-A preferentially deaminates serotonin, melatonin, epinephrine, and norepinephrine.

- MAO-B preferentially deaminates phenethylamine and trace amines.

- Dopamine is equally deaminated by both types.

□ MAOI drugs:

i. Irreversible non-selective inhibitors (hydrazides)

- phenelzine

- tranylcypromine

- ii - Reversible Inhibitors of MAO-A (RIMA)
- Moclobemide: 150mg, 300mg

Great difference in adverse reactions between these groups.

Note: Reversible inhibitors of MAO-B (e.g. selegiline) are used in the treatment of parkinson's disease.

□ Adverse reactions:

- Hypertension
- Postural hypotension
- Insomnia
- weight gain
- Hepatotoxicity (rare)

□ ~~Selective Serotonin Re-uptake Inhibitors (SSRI)~~

MOA:

- SSRI's inhibit the reuptake of serotonin. As a result, the serotonin stays in the synaptic gap

longer than it normally would, and may repeatedly stimulate the receptors of the recipient cell. In the short run this leads to an increase in signalling across synapses in which serotonin serves as the primary neurotransmitter.

Drugs:

- Fluoxetine: 10mg, 20mg, 40mg, 60mg, 90mg
- Fluvoxamine: 50mg, 100mg, 300mg
- Paroxetine: 10mg, 20mg, 30mg

Adverse effects:

- nausea, vomiting, diarrhea
- Headache
- Sexual dysfunctions
- Insomnia and fatigue

Other:

i- SNRI:

Venlafaxine

ii- NDRI: bupropion

III - Noradrenaline reuptake inhibitors (NARI)
Reboxetine

Therapy of bipolar disorder:

Main aim:

to eliminate mood episodes, maximize adherence to therapy, improve functioning of the patients and eliminate adverse effects.

Mood Stabilizers: ^{CLAY}

- Lithium (0.6-1.2 mEq/L)
- Valproate (50-125 mg/L)
- Carbamazepine (6-12 mg/L)
- Lamotrigine
- Adjunctive agents (antidepressants and benzodiazepines)

Lithium

MOA:

1- lithium might help to regulate mood include the alteration of gene expression.

ii-Lithium may also increase the release of serotonin by neurons in the brain.

iii-The excitatory neurotransmitter glutamate could be involved in the effect of lithium as other mood stabilizers, such as valproate and lamotrigine, exert influence over glutamate.

□ Research suggests these different mechanisms which may or may not together to deliver the mood-stabilizing effects of this ion.

□ Adverse effects:

Vomiting

profuse diarrhea

confusion

coma

arrhythmias

hypotension

-renal toxicity (long-term therapy)

Treatment: Cognitive therapy

Aim:

to change the habitual errors in thinking which will lead to mood change

Method:

Clients are taught to examine their thought processes and link these to emotions.

- Together the therapist and client uncover and change faulty thinking patterns and underlying schemas.

Treatment: Psycho dynamic therapy:

- A type of psychotherapy that draws on psychoanalytic theory to help people understand the roots of emotional distress, often by exploring unconscious motives, needs and defenses.

Treatment: Electroconvulsive therapy:

ECT is a procedure in which electric currents

are passed through the brain, intentionally triggering a brief seizure. ECT seems to cause changes in brain chemistry that can quickly reverse symptoms of certain mental illness.

- It often works when other treatments are unsuccessful.

5

- Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

#Types of pain:

i- Acute Pain:

It results from noxious stimulation such as an injury to the body and it can be managed by analgesic drugs and is often self-limiting.

ii- Chronic Pain:

Chronic pain is pain which lasts for 6 months or more.

The origin of chronic pain may be neurogenic, nociceptive, psychiatric or idiopathic.

- Chronic pain is subdivided into pain associated with malignancy and nonmalignancy.

ii-a: Chronic Malignant pain:

The pain is associated with cancer, which may arise from many different sources and has the characteristics of both acute and chronic pain.

ii-b: chronic non-malignant pain:

Pain not associated with a malignant disease and lasting for 6 months or more or beyond the healing periods is considered to be chronic non-malignant pain.

Pathophysiology:

Pathophysiology can be understood in terms of stimulation, transmission, perception and modulation.

1- Stimulation:

→ First step leading to sensation of pain is stimulation of free nerve ending known as nociceptors.

→ These receptors are found in somatic (skin, bone, joint) and visceral structures (intestine, pancreas).

They are activated by mechanical, thermal and chemical impulses which release bradykinins, PGs,

histamine, serotonin and substance P which activates nociceptors.

- Receptor activation leads to action potential that is transmitted along afferent nerve fibres to the spinal cord.

2. Transmission:

→ Nociceptive transmission takes place in A-delta and C afferent fibres.

→ Stimulation of large diameter sparsely myelinated A-delta fibre evokes sharp well localized pain whereas stimulation of unmyelinated small diameter C fibers produce dull aching and poorly localized pain.

→ Afferent C fibres and A-delta fibres transmit pain signals to an area known as the substantia gelatinosa, located in the dorsal horn of the spinal cord.

→ Cells within the dorsal horn collect and interpret these signals and send them to

transmission cells with terminals projecting to distant sites outside of dorsal horn -

→ Some of the C fibres and the A-delta fibres terminate in the dorsal root horn, whereas others form complex known as the lateral spinothalamic tract.

→ Pain impulse travel upward along this tract to the thalamus and from there to the cerebral cortex of the brain.

3. Pain perception:

→ At this point transmission of pain is thought to be a conscious experience which takes place in higher cortical structure.

→ The brain may accommodate a limited number of pain signals thus cognitive and behavioral functions can modify pain.

4. Modulation:

- Body modulates pain through a number of

complex processes, one known as endogenous opiate system which consists of neurotransmitters eg enkephalins, dynorphins and Bendorphins and receptors (μ , δ , κ) found throughout CNS.

→ like exogenous opioids, endogenous opioids binds to opioid receptors sites and inhibit the transmission of pain impulses.

→ The CNS also contains a highly organized descending system for control of pain transmission at the dorsal horn.

Signs and Symptoms:

→ Acute pain may be accompanied by signs of autonomic nervous system activity (tachycardia, HTN, diaphoresis, mydriasis and pallor that mimic those of anxiety, which often co-exists with acute pain.

→ Superficial pain is associated with local throbbing, burning or pricking.

- Visceral pain presents as diffuse, dull aching pain and is poorly localized.
- Somatic pain is dull and aching in nature and can be localized in nature.

#Diagnosis:

- Pain is the subjective phenomenon and quantitative assessment is very difficult.
- The most commonly used instruments are visual analogue scale and verbal rating scale.
- Visual analogue scales are 10cm long lines labeled with two extremes at two ends, usually "no pain at all" and "worst pain imaginable".
- Patient is asked to mark the severity of pain b/w the two extremities.
- Verbal rating scale uses adjectival descriptors such as none, mild, moderate and extruclating.

Treatment:

◦ Goals of treatment:

- decrease subjective intensity and duration of the pain complaint.
- Decrease the potential for conversion of acute pain to chronic persistent pain.
- Decrease suffering and disability associated with pain.
- Optimize drug therapy to take advantage of synergy and to avoid drug-drug interactions.
- Improve patient's quality of life and optimize ability to perform activities of daily living.

◦ Non pharmacological treatment:

- Exercise, yoga, meditation.
- Hydrotherapy, music
- Physical therapy
- Stimulation therapy, TENS, these machines are portable battery powered devices that generate a small current to electrodes applied to the skin and the current is increased until para-

esthesia is felt at the site of skin.

Pharmacological treatment:

- NSAID'S (non-pioid analgesics)
- Weak opioids
- Strong opioids

1) NSAID's

MOA: inhibition of cyclooxygenase enzyme which is required for the conversion of arachidonic acid to PG's.

Non selective COX inhibitors

a) Salicylates aspirin, sodium salicylate

Dose: 10-15mg/kg dose every 4-6 hours.

CI: bleeding disorders, asthma.

ADR: hemorrhage, fatigue, insomnia

DI: Concurrent use of aspirin & heparin increases the risk of bleeding.

Aspirin reduces the effect of ACE inhibitors.

b) Para-aminophenol derivatives paracetamol, phenacetin.

Dose: 0.5-1gm 4-6 hourly

CI: Renal or hepatic impairment

ADR: skin rashes, acute renal tubular necrosis, nausea.

DI: reduces the absorption of cholestyramine

c) Indoles and related drugs indomethacin, sulindac

Dose: 25-30mg dose 2-3 times/day

CI: Renal impairment, hypersensitivity

ADR: rashes, dizziness, headache, nausea.

DI: decreases the activity of β blockers and captopril

d) Heterocyclic aryl acetic acid derivative diclofenac

Dose: 50mg 3 times/day

CI: decreased Renal and hepatic function, hypersensitivity to diclofenac

ADR: rashes, abdominal cramp, heart burn

DI: decreases the effect of thiazide, furosemide.

e) Propionic acid derivative: ibuprofen, fenoprofen

Dose: 4-10mg/kg/dose 3-4 times/day

CI: hypersensitivity to NSAID

ADR: rashes, dizziness, fatigue

DI: increases serum concentration of digoxin, methotrexate

f) Oxicams: piroxicam

Dose: 10-20mg/day

CI: hypersensitivity to NSAID

ADR: indigestion, abdominal cramp, nausea

DI: decreases the effect of diuretics, β blockers

Selective COX 2 inhibitors

Rofecoxib, celecoxib

Dose: 100-200mg bid

CI: severe hepatic and renal impairment, severe heart failure, peptic ulcer

ADR: abdominal cramp, nausea, edema, headache, insomnia, rashes

DI: increased risk of bleeding when co-administered with corticosteroids, anticoagulants or alcohol

2) Weak opioids:

Codeine, dihydrocodiene and dextropropoxyphene

MOA: these mimic the actions of enkephalins, β -endorphins and other exogenous ligands and inhibit the release of ACh, NE and substance P.

Dose: adult - 15-60 mg every 4-6 hours as needed Children - 1 year and older - 0.5 mg/kg/dose every 4-6 hours as needed (MAX 60mg/dose)

CI: premature infants, hypersensitivity

ADR: hypotension, respiratory depression

DI: alprazolam additive respiratory depression.

3) Strong opioids or narcotic analgesics:

Morphine, pethidine, tramadol

MOA: Morphine Sulphate is a μ opioid agonist, selective to the μ receptor, with primary action in the brain through transitory stimulation prior to depression. In the CNS, it promotes analgesia and respiratory depression by decreasing brain stem respiratory centre response.

Dose: 5-20 mg IM every 4-6 hours for the treatment of mild to moderate pain

CF: Asthma, Circulatory Shock, may cause vasodilation and exacerbate hypotension and hypo perfusion.

ADR: anaphylaxis, cardiac arrest, dyspnea, hypotension, respiratory depression, shock

Analgesic ladder:

This forms the basis of many approaches to use analgesic drugs.

Step 1 (mild)	Step 2 (moderate)	Step 3 (severe)
NSAID's, aspirin, paracetamol ± adjuvants	Codeine, oxycodone, dihydrocodeine, tramadol ± adjuvants	Morphine, hydromorphone, methadone, fentanyl ± adjuvants

Adjuvant drugs used in treatment of pain

Drug class	Type of pain	example
Anticonvulsants	Neuropathic pain, cluster headache, migraine	Carbamazepine, gabapentin, sodium valproate
Antidepressants	Neuropathic pain, musculoskeletal pain	Amitriptyline, imipramine
i.v. anaesthetic agents	Neuropathic pain, burn pain, cancer pain	Ketamine
Skeletal muscle relaxants	Muscle spasm spasticity	Baclofen, dantrolene
Steroids	Raised intracranial pressure, nerve compression	Dexamethasone, prednisolone
Antibiotics	Infection	As indicated by culture and sensitivity
Antispasmodics	Colic smooth muscle spasm	Hyoscine, loperamide
Hormones / hormonal analogues	Malignant bone pain, spinal stenosis, intestinal obstruction	Calcitonin, octreotide
Bisphosphonates	Bone pain	Alendronate, resdronate

References:

- Text book of therapeutics by Herfindal
- Pharmacotherapy by Dipiro
- Clinical pharmacy and therapeutics - Roger walker
- Harrison's principles of internal medicine

HEADACHE

- ♦ A headache (medically known as cephalgia) is a condition of mild to severe pain in the head; sometimes upper back or neck pain may also be interpreted as a headache.

EPIDEMIOLOGY

- ♦ 90% of individuals have atleast one headache/yr.
- ♦ prevalence peaks between the ages of 20 and 50 years.
- ♦ 40% of individuals suffer from severe disabling headache annually.
- ♦ Headaches account for >8 million doctor visits/yr.
- ♦ Women are affected 3 times more prone than men.

CLASSIFICATION

♦ INTERNATIONAL HEADACHE SOCIETY

♦ PRIMARY HEADACHE

1. Migraine Headache.
2. Tension Type Headache.
3. Cluster Headache.
4. Miscellaneous Headache Unassociated With Structural Lesions.

♦ SECONDARY HEADACHE

1. Headache associated with head trauma.
2. Headache associated with vascular disorders.
3. Headache associated with nonvascular intracranial disorder.
4. Headache associated with substance or their withdrawals.
5. Headache associated with noncephalic infections.
6. Headache associated with metabolic disorder.
7. Headache or facial pain associated with disorder of facial or cranial structures.
8. Cranial neuralgias, nerve trunk pain, and deafferentation pain.
9. Headache not classifiable.

• Migraine: a symptom complex of periodic headaches, usually temporal and unilateral, often with irritability, nausea, vomiting, constipation or diarrhea, and photophobia, preceded by constriction of the cranial arteries.

Migraine headache

- ♦ Migraine is a neurological syndrome characterized by altered bodily experiences, painful headaches and nausea.
- ♦ The typical migraine headache is one-sided and pulsating, lasting 4 to 72 hrs.
- ♦ Accompanied complaints are nausea, vomiting, heightened sensitivity to bright lights (photophobia) and noise (hyperacusis).

Migraine without aura:

- ♦ Most commonly seen form on migraine.
- ♦ Attacks lasting 4-72 hours.
- ♦ Typical characteristics – unilateral location, pulsating quality and moderate or severe intensity.
- ♦ Aggravated by physical activity.
- ♦ Associated with nausea and/or photophobia and phonophobia.

Migraine with aura:

- ♦ Second most commonly seen type
- ♦ Characteristics:
 - 1) One or more fully reversible aura symptom indicating focal cerebral cortical and/or brainstem dysfunction.
 - 2) At least one aura symptom develops gradually over more than four minutes.
 - 3) No aura symptom lasts for more than 60 minutes.

Pathophysiology of Migraine

Vascular theory:

- ♦ Intracranial vasoconstriction is responsible for the aura of migraine and that the subsequent rebound vasodilatation and activation of perivascular nociceptive nerves resulted in headache.
- ♦ This theory was based on the observations that (1) extracranial vessels become distended and pulsatile during a migraine attack

- (2) stimulation of intracranial vessels in an awake person induces headache;
and
(3) vasoconstrictors (eg, ergots) improve the headache, whereas vasodilators (eg, nitroglycerin) provoke an attack.

Neural theory:

- ♦ When certain nerves or an area in the brainstem is irritated, migraine begins.
- ♦ In response to the irritation, body releases chemicals which cause inflammation of blood vessels.
- ♦ These cause further irritation of nerves and blood vessels and results in pain.
- ♦ Substance P is one of the substance released with first irritation.
- ♦ Pain then increases because substance P aids in sending pain signals to the brain.

Serotonin theory:

- ♦ Serotonin is a type of neurotransmitter or a "communication chemical" which passes messages between nerve cells.
- ♦ It helps to control mood, pain sensation, sexual behaviour, sleep, as well as dilation and constriction of the blood vessels
- ♦ Serotonin level in the brain may lead to a process of constriction and dilation of blood vessels which trigger a migraine.

Magnesium Deficiency:

- ♦ Another theory proposes that deficiency of magnesium in the brain triggers a chain of events, starting with platelet aggregation and glutamate release and finally resulting in the release of 5-hydroxytryptamine, which is a vasoconstrictor.

Triggoring factors:

- ♦ Allergic reaction.
- ♦ Bright lights, loud noises, certain odours of perfumes.
- ♦ Physical or emotional stress.
- ♦ Change in the sleep patterns.
- ♦ Smoking or exposure to smoke.
- ♦ Skipping meals.
- ♦ Alcohol.

- ♦ Foods containing tyramine(smoked fish) and nitrates(hot dogs).

Tension-type Headaches

- ♦ Most common type of primary headaches.
- ♦ The pain can radiate from the neck, back, eyes or other muscle groups in the body.
- ♦ Accounts for almost 90% of all headaches.
- ♦ Tension type HA can be episodic or chronic
- ♦ Episodic tension type HA are defined as tension type HA occurring fewer than 15 days a month.
- ♦ Chronic tension type HA occur 15 days or more a month for at least 6 months.

Tension type headache Pathophysiology

- 1 ♦ Physical or psychological stress or nonphysiological working condition may trigger TTH.
- 2 ♦ TTH may also be precipitated by menstruation.
- 3 ♦ Reduced CNS 5-HT levels may be responsible for abnormal pain modulation producing the decreased pain thresholds which is observed in most patients with chronic TTH.

CLUSTER HEADACHE

- ♦ Cluster headache is neurological disease that involves immense degree of pain.
- ♦ 'CLUSTER' refers to the tendency of these headaches to occur periodically.
- ♦ The duration of attack is 15 minutes to three hours.
- ♦ Onset is rapid and most often without preliminary signs.

Pathophysiology

- ♦ The intense pain is caused by the dilation of blood vessels which creates pressure on the trigeminal nerve.
- ♦ This process is immediate cause of the pain, the etiology is not fully known.

Diagnosis:

- ♦ A high erythrocyte sedimentation rate in a patient older than 50 years with new headache onset suggests temporal arteritis. This diagnosis must be confirmed by temporal artery biopsy.
- ♦ Scans can be performed to exclude intracranial causes of headache or to rule out lesions that cause neurologic or visual abnormalities associated with headache.
- ♦ Computed tomography scanning of the paranasal sinuses is useful in evaluating the role of acute or chronic sinus infection as a cause of the headache.
- ♦ Magnetic resonance imaging is currently the best scan for viewing the posterior fossa and occipital areas of the brain.

Treatment

- ♦ Drugs used for acute headache treatment include:
 - 1) Analgesics (alone or in combinations with caffeine or barbiturates): Aspirin, Acetaminophen. First line agents for mild to moderate migraine.
 - 2) Opioids (alone or in combination with some drugs): methadone, butorphanol.
 - 3) Selective serotonin agonists (triptans) sumatriptan, zolmitriptan, Rizatriptan, almotriptan.
 - 4) Ergotamine derivatives: Dihydroergotamine, Ergotamine tartrate.
 - 5) Corticosteroids: prednisone, dexamethasone.
 - 6) Neuroleptics: chlorpromazine, haloperidol.
- ♦ Drugs used for preventive measures include:
 - 1) β -blockers: Atenolol, Metoprolol, Propranolol, Timolol.
 - 2) Anti-depressants: Amitriptyline, Nortriptyline, Fluoxetine, Sertraline.
 - 3) Calcium channel blockers: Amlodipine, Diltiazem, Verapamil.
 - 4) Serotonin antagonist: Cyproheptadine, methylsergide.
 - 5) Anticonvulsants: valproic acid, topiramate.
 - 6) Lithium carbonate.

Non Pharmacological Therapy:

- ♦ Behavioural modification which include normalizing the patients routine so that he or she minimizes variability in sleeping, eating, activities of daily living, and exercise time.
- ♦ Other behavioural modification include biofeedback training, relaxation training and cognitive-behavioural therapy (stress management)
- ♦ Physical therapy helps patient relieve stress and muscle tension via massage stretching exercises, aerobic exercises and hot or cold therapy.
- ♦ Cold compresses to the affected area provided relief in 65% to 75% of TTH patients.

Patient Education:

- ♦ Patient should be educated about their headaches, their medications, and how to monitor their progress.
- ♦ They should be reassured that headaches are not life threatening and that headache frequency may be controlled but headaches may not completely disappear with treatment.

References:

- ♦ Pharmacotherapy by Dipiro
- ♦ Harrison's principles of internal medicine, volume I, 16th edition.
- ♦ Text book of therapeutics - Herfindal
- ♦ <http://en.wikipedia.org/wiki/migraine>.

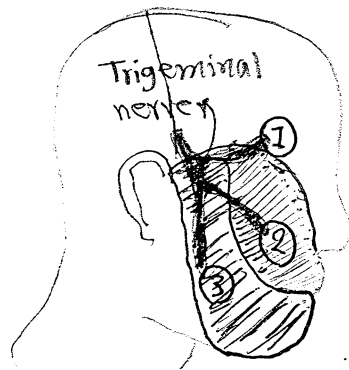
Neuralgias:

→ Neuralgia means burning, numbness, and pain that extends along one or more nerves.

→ Neuralgia may occur in any nerve.

-Types:

i- Trigeminal neuralgia is the most common form of neuralgia. It affects the main sensory nerve of the face, the trigeminal nerve (trigeminal literally means "three origins", referring to the division of the nerve into three branches).



- This condition involves sudden and short attacks of severe pain on one side of the face, along one of the areas supplied by the trigeminal nerve.

The pain attacks may be severe enough to cause a facial grimace, which is classically referred to as a painful tic.

2. Postherpetic neuralgia:

Occurs after certain infections such as shingles, which is caused by the varicella-zoster virus, a type of herpes virus.

This can produce a constant burning pain after shingles rash has healed. The pain is worsened by movement or contact with the affected area.

3. Glossopharyngeal neuralgia:

-Pain from the glossopharyngeal nerve, which is in the throat, is not very common. This type of neuralgia produces pain in the neck and throat.

• Etiology:

1. chemicals
2. inflammation

3. Trauma

4. Compression by adjacent structure (tumors or inflamed tissues).

5. Infections

6. Diabetes.

Diabetes damages the tiny arteries that supply circulation to the nerve, resulting in nerve fibre malfunction and sometimes nerve loss.

Pathophysiology:

i. Trigeminal neuralgia:

The leading explanation of pathophysiology is that a blood vessel is likely to be compressing the trigeminal nerve near its connection with pons. Such a compression can injure the nerve's protective myelin sheath and cause erratic and hyperactive functioning of the nerve. This leads to the pain attacks at the slightest stimulation of any area served by the nerve as well as hinder the nerve's ability to shut off the pain signals after the stimulation ends.

This type of injury also may be caused by an aneurism, by a tumor, by an arachnoid cyst in the cerebellopontine angle, by trauma or even tongue piercing or multiple sclerosis. When there is no structural cause, the syndrome is called idiopathic, post herpetic neuralgia may cause similar symptoms if the trigeminal nerve is affected.

ii-Post herpetic neuralgia:

PHN is a painful condition caused by the varicella-zoster virus in a dermatomal distribution after an attack of herpes-zoster.

During the primary infection the virus gains entry into the sensory dorsal root ganglia.

The damaged fibres cannot send electrical signals from the skin to the brain as they normally do and may be erratic or exaggerated causing chronic pain that persist or recur for months or even years in the area where shingles first occurred.

iii. Glossopharyngeal neuralgia:

- Any sort of compression or irritation to the glossopharyngeal nerve can result in neural hyper-excitability and neuralgia.

- The most common cause of secondary neuralgia is Eagle's Syndrome characterized by the glossopharyngeal nerve hyper excitability caused by compression of the nerve against an elongated or fractured styloid process or a calcified stylo-hyoid ligament.

- Other causes of secondary glossopharyngeal neuralgia include post tonsillectomy, local infection etc.

□ Signs and Symptoms:

- Pain
- Impaired function of affected body part due to pain or muscle weakness
- Increased sensitivity of the skin or numbness of the affected skin area.
- Movement may be painful.

Diagnosis:

- No tests are specific for neuralgia.
- Your doctor or nurse will examine you and ask questions about your medical history and symptoms, including:
 - When did the pain start? etc.

The exam may show:

- Abnormal sensation in the skin
- Reflex problems
- Loss of muscle mass
- Lack of sweating (sweating is controlled by nerves)
- Tenderness along a nerve

There are no specific tests for neuralgia, but the following tests may be done to find the cause of the pain:

- i - Blood test to check blood sugar, kidney function, etc.
- ii - MRI
- iii - Spinal tap
- iv - Nerve conduction study with electromyography

Management:

Goals:

- i - To reverse or controll the cause of the nerve problem if it is identified.
- ii - To provide pain relief.

Non-pharmacological:

i - Surgical:

For both trigeminal and glosso-pharyngeal neuralgias a procedure called microvascular decompression, can result in symptom improvement.

This surgical procedure consists in removing any possible compression exerted by neighbouring blood vessels over the affected nerve. surgical removal of tumours etc.

- Surgical praedures to decrease sensitivity of the nerve. Some procedures involve the ablation (surgical destruction) of the affected nerve using different methods, such as local radiofrequency, heat (thermocoagulation), balloon compression, and injection of chemicals.

- Another strategy sometimes used for resilient cases of neuralgia is called motor cortex stimulation (MCS), which consists of surgically placing an electrode over the sensory cortex of the brain. The electrode is hooked to a pulse generator pocketed under the skin.

ii - Physiotherapy:

- Physical therapy may be helpful for some types of neuralgia, especially postherpetic neuralgia.

Treatment of shingles with antiviral medication may decrease the incidence of postherpetic neuralgia.

- A rhizotomy procedure involves sectioning of the glossopharyngeal nerve and upper rootlets of the vagus nerve. This effectively relieves the pain for the majority of sufferers, but may however, cause swallowing problems due to the nerve injury.

□ Pharmacological:

1. Analgesics:

a. Aspirin

b. NSAIDs

c. Opioid analgesics

→ Analgesics such as aspirin, acetaminophen or ibuprofen may be helpful for mild pain.

→ Narcotic analgesics such as codeine may be needed for a short time to control severe pain.

2. Antidepressants:

Tricyclic antidepressants

Mech.

They block the reuptake of serotonin and NE thus enhancing the pain inhibition they also acts as inhibitory action pre synaptically thereby increasing the release of NE post synaptically.

Ex:

Mipramine

clomipramine

trimipramine

lofepramine

ii- Selective Serotonin reuptake inhibitors:

MOA:

They block the reuptake of serotonin selectively and thereby enhancing the pain inhibition.

Ex:

Fluoxetine

Fluvoxamine

Paroxetine

3. Anti convulsants:

MOA:

They decrease the neuronal excitability and thereby reduce the pain conduction.

Eg:

Carbamazepine, phenytoin, Valproate

4. Topical application:

- The topical (local) application of creams

containing capsaicin also may help to control the pain.

MOA:

they deplete nerves of substance P.

5. local anaesthetic agents:

Eg:

lidocaine, prilocaine

- For postherpetic neuralgia, injections of anaesthetics and steroids in the subarachnoid space through a spinal tap may provide pain relief.

Treatment for postherpetic neuralgia depends on the type and characteristics of pain experienced by the patient. Possible options include:

i. Lidocaine skin patches:

- The patches must be applied directly to painful skin to deliver relief for 4 to 12 hours.

ii. Analgesics:

• Topical analgesics Aspirin mixed into an appropriate solvent such as diethyl ether may reduce pain.

iii- Opioids

Tramadol or fentanyl

iv- Antidepressants:

Amitriptyline,

v- Anticonvulsants:

- These agents are used to manage severe muscle spasms and provide sedation in neuralgia. They have central effects on pain modulation.

Ex:

phenytoin, used to treat seizures, also can lessen the pain associated with postherpetic neuralgia.

• Carbamazepine:

vi- Corticosteroids:

- These agents have anti-inflammatory properties.

- Methyl prednisolone

vii- Antiviral agents:

FamCiclovir

Penciclovir

Prevention:

-Treatment of associated disorders such as diabetes and renal insufficiency may prevent development of some neuralgias.

-If shingles could be prevented, postherpetic neuralgia could be completely avoided.

Vaccine: Zostavax

Secondary prevention:

-Treatment of zoster at the time of rash with antiviral agents such as acyclovir can reduce the chance of postherpetic neuralgia.

Palliative Care ^{مرافقہ کی نگاہ سے}

- Palliative care also known as comfort care is primarily directed at providing relief to a person having incurable illness through symptom management and pain management the goal is not to cure but to provide comfort and maintain the highest possible quality of life for as long as life remains.

- Thus palliative care:

- 1- provides relief pain and other distressing symptoms
2. Offers a support system to help patients live as actively as possible until death.
3. Offers a support system to help the family during the patient illness.
4. Will enhance the quality of life.
5. Uses a team approach to address the needs of patients and their families, including counseling if indicated.

#WHO defines palliative care as the active total care of patients whose disease is not responsive ^{جوابگو}

to curative treatment.

Control of pain of other symptoms and of psychological, social and spiritual problem is paramount.

The goal of palliative care is achievement of the best quality of life for patients and their families.

6

Evidence Based Medicine

-Definition:

EBM is an approach to medical practice that uses the results of patients care research and other available objective evidence as a component of clinical decision making.

How do we do it?

1. Form an answerable question
2. Obtain current best evidence
3. Critically ^{3. Critical} appraise the evidence
4. ^{4. Applying the evidence} Integrate appraised evidence with clinical expertise and patient values
5. Evaluate our successes and failures
5. Evaluating performance

1. Form an answerable question:It should contain:

- Intervention ^{تدخل} you are interested in
- Pt or population you are interested in
- Outcomes you are interested in

□ The acronym PICO can be helpful to remember the elements of a well-balanced question:

P = patient

I = intervention

C = comparison ^{المقارنة}

O = outcome

2. Finding the evidence:

2. Obtain current best evidence:

- Once you have formulated your clinical question, the next ^{الخطوة التالية} step is to seek relevant evidence that will help you answer the question.

- There are several sources of information that may be of help.

i. Traditional sources of information:

textbooks, Journals

ii. Secondary sources

May help provide quick evidence based answers to specific clinical questions.

a. Clinical Evidence (<http://www.clinicalevidence.com/ceweb/conditions/index.jsp>).

b. BestBets (<http://www.bestbets.org/index.html>)

3. Critical appraisal:

□ Consider the following concepts:

- Internal validity
- External validity
- Bias

□ Internal validity:

Concerns whether the results of a study are true in the context of what was set out to be studied.

- For internal validity to exist a prospectively defined question must be answered in a precise and accurate manner.

□ External validity:

- Concerns whether the results of a study are true in the context of the wider world.

- A measure of external validity is the extent to which results can be generalised to different clinical situations or populations.

^{مطلوب}
- To demonstrate external validity a study should be applicable to a range of populations, settings, treatment variables, and measurement variables.

- Determining external validity can require judging many characteristics of a study, but at very least requires an assessment of applicability based on the characteristics of the study's participants.

^{تعريف}
□ Bias is the systemic introduction of error into a study that can distort the results in a non-random way.

- It is almost impossible to eliminate all sources of bias even in the most carefully designed study, as such it is the job of the person appraising a study to assess the importance and potential effects of bias on the results of the study.

→ Applying the evidence:

4. Apply the results to patient situations to best assist clinical decision making:

- Several patient-specific factors must be considered in the final analysis:

1. Compare the patient with those in the study (similar disease state and stage, similar baseline characteristics).

2. Consider the patient's baseline risk for the outcome of interest and other potential risks associated with the therapy.

3. Consider the patient's value, beliefs, concerns, and readiness for the intervention.

□ Limitations:

1. Ethics:

- In some cases, such as in open-heart surgery, conducting randomized, placebo-controlled trials is commonly considered to be unethical.

although observational studies may address these problems to some degree.

2. Cost:

- The types of trials considered "gold standard" (i.e. large randomized double-blind placebo-controlled trials) are expensive, so that funding sources play a role in what gets investigated.
- For ex, public authorities may tend to fund preventive medicine studies to improve public health, while pharmaceutical companies fund studies intended to demonstrate the efficacy and safety of particular drugs.

3. Generalizability:

- Furthermore, evidence-based guidelines do not remove the problem of extrapolation to different populations or longer time frames.
- Even if several top-quality studies are available, questions always remain about

how far, and to which populations, their results are "generalizable".

4. Publication bias:

- It is recognized that not all evidence is made accessible, that this can limit the effectiveness of any approach, and that efforts to reduce publication bias and retrieval bias is required.

- Failure to publish negative trials is the most obvious gap.

Or 4. Applying the evidence:

- When we decide after critical appraisal that a piece of evidence is valid and important, we then have to decide whether that evidence can be applied to our individual patient or population.

- In deciding this we have to take into account the patient's own personal values and circumstances.

-The evidence regarding both efficacy and risks should be fully discussed with the patient or parents, or both, in order to allow them to make an informed decision.

-This approach allows a "therapeutic alliance" to be formed with the patient and the parents and is consistent with the fundamental principle of EBM: the integration of good evidence with clinical expertise and patient values.

-The decision to apply evidence should also take account of costs and the availability of that particular treatment in your hospital or practice

Step 5. Evaluating performance:

-As we incorporate EBM into routine clinical practice, we need to evaluate our approach at frequent intervals and to decide whether we need to improve on any of the four steps discussed above.

Conclusions:

- EBM aims to improve quality of care through the integration of best research evidence with clinical expertise and patient's and parent's preferences.

Advantages:

- It improves clinicians understanding of research and its methods.
- It improves computer literacy and data searching skills.
- It allows better communication with the patient about the rationale behind treatment.
- EBM opens decision making processes to patients.
- Juniors can contribute as well as seniors.
- It allows group problem solving and teaching.

^{dis}
Disadvantages:

- It takes time to learn the methods and to put them into practice.
- There is the financial cost of buying and maintaining equipment.
- Medline and other electronic databases are not always comprehensive
- Authoritarian practitioners may find these methods threatening.

