• In anesthetics: in local anesthetics to increase the duration of the local anesthesia and to prevent systemic toxicity (by vasoconstriction).

4. Pharmacokinetics
• Rapid onset but brief duration of action.
• In emergency situations, epi is given IV for the most rapid onset of action.
• It may also be given SC, by endotracheal tube, by inhalation, or topically to the eye.
• Oral administration is ineffective, because epi and the other catecholamines are inactivated by intestinal enzymes.

5. Adverse effects
• CNS disturbances: anxiety, fear, tension, headache and tremor
• Hemorrhage: cerebral hemorrhage as a result of marked elevation in blood pressure
• Cardiac arrythmias: particularly if patient is receiving digitalis
• Epinephrine increases coronary blood flow as a result of increased cardiac workload; it may precipitate angina in patients with coronary insufficiency.
• Pulmonary edema

6. Interactions
• Hyperthyroidism: the dose of epi must be reduced because of the possible enhanced CV actions in these patients.
• Cocaine: epi produces exaggerated CV actions. This is due to the ability of cocaine to prevent reuptake of catecholamines into the adrenergic neuron.
• TCA block catecholamine reuptake and may potentiate the effects of NE and epi.
• Some halogenated anesthetic agents and digitalis may sensitize the heart to beta receptor stimulants, resulting in ventricular arrhythmias.

B. Norepinephrine
• When the drug is given in therapeutic doses to humans, the alpha adrenergic receptor is most affected.

1. CV actions
• Vasoconstriction: NE causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (alpha1). Both systolic and diastolic blood pressure increase.
• NE causes greater vasoconstriction than does epi because it does not induce compensatory vasodilation via beta2 receptors of blood vessels supplying skeletal muscles.
• The weak beta2 activity of NE also explains why it is not useful in the treatment of asthma.
• Baroreceptor reflex: in isolated cardiac tissue, NE stimulates cardiac contractility, however, in vivo, it is not noted. This is due to the increased blood pressure that induces a reflex rise in vagal activity by stimulating the baroreceptors. This bradycardia is sufficient to counteract the local actions of NE on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug.
• Effect of atropine pre-treatment: if atropine, which blocks the transmission of vagal effects, is given before NE, then the stimulation of the heart is evident as tachycardia.

2. Therapeutic uses
• NE is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure.
• However, metaraminol is favored, because it does not reduce blood flow to the kidney, as does NE.
• Other actions of NE are not considered to be clinically significant.

C. Isoproterenol
• Predominantly stimulates both beta1 and beta2 receptors.
• Its nonselectively is one of its drawbacks.
• Its action on alpha receptors is insignificant.

1. Actions
• CV:
• Intense stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output. It is therefore useful in the treatment of atrioventricular block and cardiac arrest.
• It also dilates the arterioles of skeletal muscle (beta2), resulting in a decreased peripheral resistance.
• Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure.
• Pulmonary:
• A profound and rapid bronchodilation is produced by the drug (beta2). Isoproterenol is as active as epi and rapidly alleviates an acute attack of asthma when taken by inhalation. The action lasts about one hour.

2. Therapeutic uses
• Now rarely used as a bronchodilator in asthma. It can be employed to stimulate the heart in emergency situations.

3. Pharmacokinetics
• Can be absorbed systemically by the sublingual mucosa but is more reliably absorbed when given parenterally or as an inhaled aerosol.
• The efficacy of many antiarrhythmic agents remains unproven.
• Adverse effects of all antiarrhythmic drugs: proarrhythmic effect, decreased inotropic effect (except amiodarone) → promote symptoms of heart failure; GI problems (all drugs given PO), CNS symptoms, hypersensitivity
• Risk of torsade de pointes: Quinidine, Procainamide, Sotalol

Class I antiarrhythmic drugs
• Class I antiarrhythmics act by blocking voltage-sensitive sodium channels via the same mechanism as local anesthetics.
• The decreased rate of entry of sodium slows the rate of rise of phase 0 of the action potential → ↑ ERP, ↑ threshold of excitability
• The use of sodium channel blockers has been declining continuously due to their possible proarrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.
• Class IA: slow the rate of rise of the action potential, ↑ APD (action potential duration), ↑ ERP, slow conduction
• They have an intermediate speed of association with sodium channels.
• Class IB: decrease the duration of the action potential by shortening phase 3 repolarization. They decreased the ERP, but relatively increase the ERP.
• They rapidly interact with sodium channels.
• Class IC: markedly depress the rate of rise of the membrane action potential. Therefore, they cause marked conduction slowing but have little effect on the duration of the membrane potential or the ventricular ERP.
• They bind slowly to sodium channels. The least safe of the class I drugs → not much used.

A. Use-dependence
• Class I drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarized following recovery from the previous depolarization cycle.
• Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing (for example, during tachycardia, when the sodium channels open often).
• This property is called use-dependence, and it enables these drugs to block cells that are discharging at an abnormally high frequency without interfering with the normal, low-frequency beating of the heart.

B. Quinidine
• The prototype class IA drug.
• Slows the rapid upstroke during phase 0 and also decreases the slope of phase 4 spontaneous depolarization.
• Cardiac effects: ↓ automaticity, ↓ conduction, ↓ myocardial contractility, ↑ effective refractory period
• Prolongation of QT interval → possible for Torsade de pointes
• Extracardiac effect: alpha adrenergic blocking, anticholinergic effect
• Quinidine inhibits ectopic arrhythmias and ventricular arrhythmias caused by increased normal automaticity. Quinidine also prevents reentry arrhythmias by producing a bidirectional block.
• The drug has little effect on normal automaticity.
• Quinidine can induce tachycardia in normal individuals because of its atropine-like (anticholinergic) effect.
• Quinidine is used in the treatment of a wide variety of arrhythmias, including atrial, AV-junctional, and ventricular tachyarrhythmias.
• PO

1. Adverse effects
• CV: heart failure (due to negative inotropic effect), hypotension, quinidine syncope (associated with a prolonged QT interval).
• At high doses, it can actually precipitate arrhythmias, which can lead to fatal ventricular fibrillation.
• A potential side effect of quinidine (or of any antiarrhythmic drug) is an exacerbation of the arrhythmia. At toxic levels, the drug may induce ventricular tachycardia. Cardiotoxic effects are exacerbated by hyperkalemia.
• Nausea, vomiting and diarrhea are commonly observed.
• Large doses of quinidine may induce the symptoms of cinchonism (blurred vision, tinnitus, headache, disorientation, and psychosis).
• The drug has a mild alpha-adrenergic blocking action as well as an atropine-like effect.
• Bone marrow suppression may occur.
• Drug interactions: increases digoxin levels and the risk of digitalis toxicity.

C. Procainamide
• A derivative of the local anesthetic procaine.
• Class IA
• PO
• T ½: 2-3 hours
• Procainamide is acetylated in the liver to NAPA, which has little effect on the maximum polarization of Purkinje fibers but prolongs the duration of the action potential. Thus, NAPA has properties of a class III drug.

1. Adverse effects
• With chronic use, procainamide causes a high incidence of side effects, including a reversible lupus-like syndrome that develops in 25 to 30 %.
• Toxic concentrations of procainamide may cause asystole or induction of ventricular arrhythmias.
• CNS side effects include depression, hallucination, and psychosis.
• GI intolerance is less frequent than with quinidine.

D. Disopyramide
• Class IA
• Disopyramide produces a negative inotropic effect that is greater than the weak effect exerted by quinidine and procainamide, and unlike the latter drugs, disopyramide causes peripheral vasoconstriction.
• Disopyramide is used in the treatment of ventricular arrhythmias as an alternative to procainamide or quinidine.
• PO

1. Adverse effects
• Disopyramide shows effects of anticholinergic activity (for example, dry mouth, urinary retention, blurred vision and constipation)
• CI in patients with heart failure.

E. Lidocaine
• Class IB
• The class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of class IB agents are manifested when the cardiac cell is depolarized or firing rapidly.
• Class IB drugs are particularly useful in treating ventricular arrhythmias.
• Lidocaine is the drug of choice for emergency treatment of cardiac arrhythmias.
• Lidocaine, a local anesthetic, shortens phase 3 repolarization and decreases the duration of the action potential.
• Increases effective refractory period, and that is why it can be used to treat arrhythmias even though the action potential is decreased.
• Unlike quinidine, which suppresses arrhythmias caused by increased normal automaticity, lidocaine suppresses arrhythmias caused by abnormal automaticity.
• Lidocaine, like quinidine, affects A-V junction.
• Lidocaine is useful in treating ventricular arrhythmias arising during myocardial ischemia, such as that experienced during MI.
• Lidocaine does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias.
• IV, due to extensive first pass metabolism
• SE: it shows little impairment of left ventricular function and has no negative inotropic effect.
• CNS effects are the most common and include drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions.
• Cardiac arrhythmias may also occur.

F. Mexiletine and Tocainide
• Class IB
• Mexiletine is used for chronic treatment of ventricular arrhythmias associated with previous MI.
• Tocainide is used for treatment of ventricular tachyarrhythmias. This drug has pulmonary toxicity, which may lead to pulmonary fibrosis.

G. Phenytoin
• Given PO
• Has been used in acute and chronic arrhythmias, especially in digitalis intoxication.

H. Flecainide
• Class IC
• These drugs slowly dissociate from resting sodium channels, and show prominent effects even at normal heart rates.
• They are approved only for refractory ventricular arrhythmias.
• Suppresses phase 0 upstroke in Purkinje and myocardial fibers. This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness.
• Flecainide has a negative inotropic effect and can aggravate congestive heart failure.
• PO
• SE: can cause dizziness, blurred vision, headache and nausea.
• Digoxin
• Phenytoin
• Tolbutamide
• Warfarin

E. P450 enzyme inducers
• CYP 1A2: cigarette smoke, omeprazole, phenobarbitone
• CYP2E1: ethanol, isoniazide
• CYP3A4: carbamazepine, ethosuximide, glucocorticoids, phenobarbitone, rifampicin, sulfadimidine, nevirapine, sulfipyrazone

F. P450 enzyme inhibitors
• CYP1A2: cimetidine, fluvoxamine, FQs
• CYP2C9: amiodarone, chloramphenicol, cimetidine, fluconazole, isoniazide, omeprazole, sertraline, sulfaphenazole, sulfapyrazole
• CYP2E1: cimetidine, disulfiram
• CYP3A4: amiodarone, cannabinoids, cimetidine, clarithromycin, clotrimazole, delavirdine, diltiazem, erythromycin, fluxetine, fluvoxamine, grapefruit juice,itraconazole, ketoconazole, metronidazole, miconazole, nefazodone, paroxetine, protease inhibitors (indinavir, nelfinavir, ritonavir)
• Effective sedative and hypnotic that induces sleep in about 30 minutes and lasts about 6 hours.
• Used in institutionalized patients. It displaces warfarin from plasma proteins.
• SE: epigastric distress, unpleasant taste sensation

B. Antihistamines
• Diphenhydramine and doxylamine are effective in treating mild types of insomnia.
• Synergistic action with ethanol.

C. Ethanol (See also Pharmacology of alcohol)
• Ethanol has anxiolytic and sedative effects, but its toxic potential outweighs its benefit.
• Ethanol has a shallow dose-response curve; therefore, sedation occurs over a wide dosage range.
• Ethanol is metabolized primarily in the liver, first to acetaldehyde by alcohol dehydrogenase and then to acetate by aldehyde dehydrogenase.
• The treatment of choice for alcohol withdrawal is the benzodiazepines. Carbamazepine is effective in treating convulsive episodes during withdrawal.

1. Disulfiram
• Blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase. This results in the accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea.
• Disulfiram has found some use in the patient seriously desiring to stop alcohol ingestion.
Neuroleptic Drugs

Typical neuroleptic (low potency): Chlorpromazine, Prochlorperazine, Promethazine, Thioridazine
Typical neuroleptic (high potency): Fluphenazine, Haloperidol, Pimozide, Thiothixene
Atypical neuroleptic: Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone, Sertindole

Used primarily to treat schizophrenia, but they are also effective in other psychotic states, such as manic states and delirium.

The traditional or typical neuroleptics have their antipsychotic action on blocking dopamine receptors. These drugs vary in potency: chlorpromazine is a low potency drug, and fluphenazine is high-potency agent. Efficacy is the same for all these drugs.

The newer agents are referred to as atypical, because they have fewer extrapyramidal adverse effects than the traditional agents. These drugs appear to owe their unique activity to blockade of serotonin receptors.

Psychosis producing drugs: Levodopa, CNS stimulants (cocaine, amphetamines, khat, cathinone, methcathinone), apomorphine and phencyclidine.

Schizophrenia

- Characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances.
- Positive symptoms (increased sensations): hallucinations, delusions, paranoia, ideas of reference
- Negative symptoms (decreased sensations): apathy, social withdrawal, anhedonia, emotional blunting, cognitive deficits, lack of motivation to interact with the environment
- 1% of the population affected, which is the same incidence as diabetes mellitus.
- Schizophrenia has a strong genetic component.
- It is thought that schizophrenia is caused by an excess of dopaminergic neurons.

Anatomy in schizophrenic patients: enlarged cerebral ventricles, atrophy of the cortical layers, and reduced volume of the basal ganglia.

Typical neuroleptics

- Limited efficacy against negative symptoms
  A. Phenothiazines
    - Aliphatic: Chlorpromazine, Trifluopromazine
    - Piperidine: Thioridazine, Piperacetazine, Mesoridazine
    - Piperazine: Fluphenazine, Perfenazine, Acetophenazine, Carphenazine, Prochlorperazine, Triperazine
  B. Thioxanthines
    - Thiothixene, Chlorprothixene
  - Closely related to the phenothiazines
  C. Butyrophenones
    - Haloperidol, Droperidol
  D. Adverse effects of typical neuroleptics
    - Extrapyramidal syndrome (EPS) – occurs at clinically effective dose
    - Tardive dyskinesia
    - Neuroleptic malignant syndrome: muscle rigidity, elevated CPK, elevated WBC. Treatment – neuroleptic withdrawal, cooling, dantrolene, bromocriptine (DA agonist)
    - Prolactin elevation
    - Thioridazine: retinal deposits causing visual impairments, high doses leads to fatal ventricular arrhythmias
    - Sertindole: prolonged QT segment leading to arrhythmias

Atypical neuroleptics

- Clinically display less EPS
- More effective against negative symptoms
- Some improvement in cognition
- Balanced D2/D1 antagonism and strong 5-HT2 antagonists
  A. Clozapine
    - EPS are minimal
    - May help treat TD
    - Still shows orthostatic hypotension effects, sedation, weight gain, and increased heart rate
    - Increased risk for seizures 2-3 %
Agranulocytosis in 1%

Neuroleptic drugs

A. Mechanism of action

- All the neuroleptic drugs block dopamine receptors in the brain and the periphery. The action is primarily due to blocking of D2 receptors in the mesolimbic system of the brain.
- On the other hand, the atypical drug clozapine has high affinity for the D4 receptor, which may explain its minimal ability to cause extrapyramidal side effects.
- The actions of the neuroleptic drugs are antagonized by agents that raise the dopamine concentration, for example, levodopa and amphetamines.
- The newer atypical agents appear to exert part of their unique action through inhibition of serotonin receptors.
- Know the difference between typical antipsychotics and atypicals!

B. Actions

- The antipsychotic actions of neuroleptic drugs appear to reflect a blockade at dopamine and/or serotonin receptors.
- However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors. The undesirable side effects of these agents are often a result of actions at these other receptors.
- All the neuroleptic drugs reduce the hallucinations and delusions associated with schizophrenia (the positive symptoms) by blocking dopamine receptors in the mesolimbic system.
- The negative symptoms, such as blunted affect, anhedonia (not getting pleasure from normally pleasurable stimuli), apathy, and impaired attention, as well as cognitive impairment are not as responsive to therapy, but some atypical drugs, such as clozapine, ameliorate the negative symptoms to some extent.
- All the drugs also have a calming effect and reduce spontaneous physical movement.
- In contrast to the CNS depressants, the neuroleptics do not depress the intellectual function of the patient, and motor incoordination is minimal.
- The antipsychotic effects usually take several weeks to occur.
- Dystonias, Parkinson-like symptoms, akathisia (motor restlessness) and tardive dyskinesia (inappropriate postures of the neck, trunk and limbs) occur with chronic treatment.
- With the exception of thioridazine, most of the neuroleptic drugs have anticholinergic effects that are mediated by blocking D2 receptors of the CTZ of the medulla. The atypical antipsychotic drugs are not effective antiemetics.
- Antimuscarinic effects: blurred vision, dry mouth, sedation, confusion, inhibition of GI and urinary tract smooth muscle, leading to constipation and urinary retention.
- Blockade of alpha adrenergic receptors causes orthostatic hypotension and light-headedness.
- In the pituitary, neuroleptics block D2 receptors leading to an increase in prolactin release.
- Sedation occurs in those drugs that are potent antagonists of the H1 histamine receptor, including chlorpromazine and clozapine.

C. Therapeutic uses

- Treatment of schizophrenia: the only effective treatment for schizophrenia. Not all patients respond, and complete normalization of behaviour is seldomly achieved. The newer agents are effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms. Clozapine is reserved for treatment of individuals who are unresponsive to other neuroleptics, because its use is associated with blood dyscrasias.
- Prevention of severe vomiting and nausea: most commonly prochlorperazine
- The neuroleptic drugs can be used as tranquillizers to manage agitated and disruptive behaviour. Neuroleptics are used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety.
- Chlorpromazine is used to treat intractable hiccups.
- Promethazine is not a good antipsychotic drug, however, this agent is used in treating pruritus because of its antihistaminic properties.
- Pimozide is primarily indicated for treatment of the motor and phonic tics of Tourette syndrome.

D. Absorption and metabolism

- PO
  - Fluphenazine and Haloperidol are available as slow-release depot form
  - Readily pass into the brain, have a large volume of distribution, bind well to plasma proteins, and are metabolized in the liver (P450).
  - Significant first pass metabolism
  - Most have active metabolites, although not important in therapeutic effect, with one exception. The metabolite of thioridazine, mesoridazine, is more potent than the parent compound and accounts for most of the therapeutic effect.
  - T ½ 10-24 hours
Some panic disorders also respond to TCAs.

Imipramine has been used to control bed-wetting in children by causing contraction of the internal sphincter of the bladder.

TCAs, particularly amitriptyline, have been used to treat chronic pain (neuropathic pain) in a number of conditions in which the cause of the pain is unclear.

D. Pharmacokinetics
- PO
- Lipophilic structure → penetrate the BBB, and long half life

E. Adverse effects
- Antimuscarinic effects: blurred vision, xerostomia, urinary retention, constipation, and aggravation of glaucoma and epilepsy.
- Increased catecholamine activity and Na channel blockade: cardiac overstimulation that can be life threatening if an overdose of one of the drugs is taken. Arrhythmias.
- Alpha adrenergic blockade: orthostatic hypotension and reflex tachycardia. In clinical practice, this is the most serious problem in the elderly.
- Antihistaminic effects: sedation, drowsiness and weight gain
- Sexual dysfunction, including loss of libido, impaired erection and ejaculation and anorgasmia decreases the compliance.
- TCAs should be used with caution in manic-depressive patients, because they may unmask manic behaviour.
- TCAs have narrow therapeutic index: five to six fold the maximal daily dose of imipramine can be lethal.

F. Drug interactions
- MAO inhibitors: mutual enhancement – hypertension, hyperpyrexia, convulsions, and coma
- Direct acting adrenergic drugs: potentiate effects of biogenic amine drugs by preventing their removal from the synaptic cleft
- Ethanol and other CNS depressants: toxic sedation
- Indirect acting adrenergic drugs: block effects of indirect acting sympathomimetic drugs by preventing the drugs from reaching their intracellular sites of action

Monoamine oxidase inhibitors
- MAO inactivate any excess neurotransmitter molecules (NE, 5HT) that may leak out of synaptic vesicles when the neuron is at rest. The MAO in MAOIs permit the neurotransmitters to escape degradation.
- Use of MAOIs is now limited due to the complicated dietary restrictions of patients taking MAOIs.

A. Mechanism of action
- Most MAOIs, such as phenelzine, form stable complexes with the enzyme, causing irreversible inactivation.
- These drugs inhibit not only MAO in the brain but also peripheral oxidases that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods.

B. Actions
- Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of SSRIs and TCAs, is delayed several weeks.
- Phenelzine and tranylcypromine have a mild, amphetamine-like stimulant effect.

C. Therapeutic uses
- MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs, or who experience strong anxiety.
- These drugs are also useful in the treatment of phobic states.
- A special subcategory of depression, called atypical depression, may respond to MAOIs. Atypical depression is characterized by labile mood, rejection sensitivity, and appetite disorders.

D. Pharmacokinetics
- PO
- Antidepressant effects require 2-4 weeks of treatment.
- Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of two weeks of delay must be allowed after termination of MAOI therapy.

E. Adverse effects
- Tyramine, contained in certain foods, such as aged cheeses, chicken liver, beer, and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAO inhibitor are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in headache, tachycardia, nausea, hypertension, cardiac arrhythmias, and stroke.
Treatment of Neurodegenerative Diseases

- Anti-Parkinson Drugs: Amantadine, Benztropine, Biperiden, Bromocriptine, Carbidopa, Entacapone, Levodopa, Pergolide, Pramipexole, Ropinirole, Selegline (Deprenyl), Tolcapone, Trihexyphenidyl
- Anti-Alzheimer Drugs: Donezepil, Galantamine, Memantine, Rivastigmine, Tacrine

Neurotransmission in the CNS
- Acetylcholine: involved in arousal, short term memory, and learning
- NE: involved in arousal, wakefulness, mood, and CV regulation
- DA: emotion and reward systems
- Serotonin: feeding behaviour, control of body temperature, modulation of sensory pathways including nociception, regulation of mood and emotion, and in sleep/wakefulness
- GABA: IPSP
- Glycine: IPSP
- Glutamate
- Substance P: mediates nociception within the spinal cord
- Met-enkephalin: mediates analgesia etc.

Neurodegenerative diseases
- Include Alzheimer disease, Parkinson disease, Huntington disease, and ALS.
- These devastating diseases are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition or both.
- The most prevalent of these is Alzheimer.

Overview of Parkinson disease
- Characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities.
- TRAP: tremor, rigidity, akinesia (bradykinesia), postural reflexes
- Tremor: increased at rest, rhythmic 3-5/sec, often asymmetrical, arms/legs/jaw
- Abnormal gait: simian posture, loss of arm swing, sensory tricks
- 1/100 individuals over 65 years of age.

A. Etiology
- The cause is unknown for most patients.
- The disease is correlated with a reduction in the activity of inhibitory dopaminergic neurons in the substantia nigra and corpus striatum, parts of the brain’s basal ganglia system that are involved in motor control.
- The dopaminergic nigrostriatal tract is a part of the extrapyramidal system, responsible for motor control.
- The symptoms of Parkinson disease appear when 80% of the dopaminergic neurons are damaged.
- The dopamine-acetylcholine balance is destroyed (the dopaminergic system usually inhibit the acetylcholinergic system). Loss of dopaminergic neurons in the substantia nigra leads to excessive cholinergic activity in these pathways.
- Visualized by PET scan.
- Genetic factors do not play a dominant role.
- Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions.
- Drugs such as haloperidol, chlorpromazine, metoclopramide, prochlorperazine, and valproate, whose major pharmacologic action is blockade of dopamine receptors in the brain, may also produce parkinsonian symptoms.
- Risk factors include age over 50, genetic factors, sex (male), exposure to pesticides and herbicides, reduced estrogen levels, reduced folate levels

B. Strategy of treatment
- Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

Drugs used in Parkinson disease
- Currently available drugs offer temporary relief from the symptoms of the disorder, but do not arrest or reverse the neuronal degeneration caused by the disease.
- Treatment of Parkinson: drugs that increase dopamine levels, dopamine receptor agonists, and acetylcholine receptor antagonists
- Drugs which restore the dopamine levels in nigro-striatal dopaminergic tract: levodopa and carbidopa, COMT inhibitors, dopamine agonists, amantadine, selegline

A. Levodopa and carbidopa
NSAIDs

- NSAIDs: Aspirin, Diflunisal, Diclofenac, Etodolac, Fenamates, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meloxicam, Methylsalicylate, Nabumetone, Naproxen, Nimesulide, Oxaprazin, Piroxicam, Sulfasalazine, Tolmetin
- COX 2 inhibitors: Celecoxib
- Other analgesics: Acetaminophen

Nonsteroidal anti-inflammatory drugs

- A group of chemically dissimilar agents.
- They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostaglandin biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.
- Inhibition of prostaglandins leads to inhibition of the inflammatory response.
- Normal inflammatory response: series of events that aid our survival in response to injury, mediated by: histamine, serotonin, complement, bradykinin, prostaglandins, and leukotriens
- Pathologic role of prostaglandins: fever, asthma, ulcers, diarrhea, dysmenorrhea, inflammation, bone erosion, pain
- Physiologic role of prostaglandins: temperature control, bronchial tone, cytoprotection, intestinal mobility, myometrial tone, and semen viability
- Indication: anti-inflammation, analgesic, anti-pyretic, treatment of gout, prophylaxis of heart disease (only aspirin!), prophylaxis of colorectal cancer, treatment of Alzheimer disease.

A. Aspirin and other salicylates
- About 15% of patients show an intolerance to aspirin.
  1. Mechanism of action
     - Aspirin is unique in that it irreversibly acetylates COX. The other NSAIDs, including salicylate,
       are all reversible inhibitors of COX.
     - Aspirin is rapidly deacetylated by esterases in the body, producing salicylate, which has anti-
       inflammatory, antipyretic and analgesic effects.
  2. Actions
     - Three major therapeutic actions – they reduce inflammation, pain and fever.
     - Anti-inflammatory actions: Aspirin inhibits inflammation in arthritis, but it neither arrests the
       progress of the disease nor induces remission. It may take up to 3 weeks before the anti-
       inflammatory effects become apparent.
     - Analgesic action: Prostaglandin E2 is thought to sensitize nerve endings to the action of
       bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.
     - By decreasing PGE2 synthesis, aspirin and other NSAIDs repress the sensation of pain.
     - However, combinations of opioids and NSAIDs are effective in treating pain caused by
       malignancy.
     - Antipyretic action: The salicylates lower body temperature in patients with fever by impeding
       PGE2 synthesis and release.
     - Respiratory actions: At therapeutic doses, aspirin increases alveolar ventilation. At toxic doses,
       central respiratory paralysis occurs, and respiratory acidosis ensues due to continued production of
       CO2.
     - GI effects: Normally, PGI2 inhibits gastric acid secretion, whereas PGE2 and PGF2alpha stimulate
       synthesis of protective mucus in both the stomach and small intestine. In the presence of aspirin,
       these prostanooids are not formed, resulting in increased gastric secretion and diminished mucus
       protection. This may cause epigastric distress, ulceration and/or hemorrhage.
     - Effect on platelets: TXA2 enhances platelet aggregation, whereas PGI2 decreases it. Because
       platelets lack nuclei, they cannot synthesize new enzyme, and the lack of TXA2 persists for the
       lifetime of the platelet (3-7 days). As a result of the decrease in TXA2, platelet aggregation is
       reduced, producing an anticoagulant effect with a prolonged bleeding time.
     - Single platelets only have COX-1, the COX-2 specific drugs are not anti-thrombolytic.
     - Actions on the kidney: decreased synthesis of PGs can result in retention of sodium and water and
       may cause edema and hyperkalemia in some patients (due to increased vasoconstriction when
       inhibiting the synthesis of PGE2 and PGI2). Interstitial nephritis can also occur with all NSAIDs
       except aspirin.
     - Prolongation of gestation by inhibition of uterine motility
  3. Therapeutic uses
     - Antipyretics and analgesics: sodium salicylate, choline salicylate, choline magnesium salicylate,
       and aspirin are used as antipyretics and analgesics in the treatment of gout, rheumatic fever, and
       RA. Commonly treated conditions requiring analgesia include headache, arthralgia, and myalgia.
• With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and a toxic intermediate (N-acetylbenzoiminoquinine) reacts with the hepatic cells causing cell death.
• Hepatic necrosis, a very serious and potentially life threatening condition, can result. Renal tubular necrosis may also occur.
• Liver damage occurs especially in alcoholics and in anorexia (decreased glutathione).
• Administration of N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, can be lifesaving if administered within ten hours of the overdose. N-acetylcysteine is also used as prevention of renal failure when iodine is given.
• Methionine can also be given.
• NSAIDs + Acetaminophen → greater analgesic effect than either alone.
• M2 and M3 receptors
• Ipratropium bromide in COPD – as effective or even superior to beta agonists
• Ipratropium is slow in onset and nearly free of side effects.

G. Theophylline
• Phosphodiesterase inhibition
• Narrow therapeutic window, and an overdose of the drug may cause seizures or potentially fatal arrhythmias.
• Furthermore, theophylline interacts adversely with many drugs.
• Increased clearance of theophylline: enzyme induction (rifampicin, phenobarbital, ethanol), tobacco, high protein, low carbohydrate diet, BBQ meal, childhood
• Decreased clearance: enzyme inhibition by cimetidine, erythromycin, allopurinol; congestive heart failure, liver disease, viral infection and vaccination, high carbohydrate diet, old age

H. Omalizumab
• A monoclonal antibody that selectively binds to human immunoglobulin E. this leads to decreased binding of IgE to the high affinity IgE receptor on the surface of mast cells and basophils. Reduction in surface bound IgE limits the degree of release of mediators of the allergic response.
• Very expensive.

Antitussive drugs
• Minor causes of cough: viral infections, postnasal drip, psychogenic, allergy
• Serious causes of cough: asthma, bronchitis, tuberculosis, long cancer, heart failure, pneumonia, foreign body
• When to treat cough? When it is unproductive (disturbance of sleep, cause of syncope).
• Complications: rib fractures, pneumothorax, rupture of subconjunctival veins, urinary incontinence, rupture of surgical wounds, syncope

A. Centrally acting drugs
• Morphine: strong antitussive
• Codeine: opioid derivative; weaker, more commonly used; the antitussive action is noted at lower doses than those required for analgesia.
• Hydrocodone
• Hydromorphone
• Dextromethorphan: a synthetic derivative of morphine. It is nonanalgesic or additive potential and is less constipating than codeine.
• Oxeladine
• Pentoxyverine
• Noscapine
• Pholcodine

B. Drugs acting on periphery
• Benzonatate: no central effects
• Plant products: marshmallow root, colts foot, mullein flowers, mallow flower and leaf

Expectorants
A. Drugs acting on mucociliary transport and surface tension
• Ipecacuanha
• N-acetylcysteine, Mercaptoethane, Mecysteine
• Trypsine, Chymotrypsine
• Deoxyribonuclease
• Carbocysteine
• Hydrating agents: Sodium chloride, sodium bicarbonate, water
• Tylooxapol
• Eprazinone, Guaiifenezeine, Ammonium bicarbonate, Ammonium chloride

Respiratory stimulants
• Doxapram: partial stimulation of the carotid chemoreceptors
• Almitrine dimesilate: selective stimulation of the carotid chemoreceptors
- Involved in the synthesis of body tissues, especially the epithelia (skin, mucosae)
- No clearly defined pharmacological uses

E. Vitamin B6 – Pyridoxine
- Cofactor for enzymes involved in amino acid metabolism
- Involved in heme and neurotransmitter synthesis, metabolism of glycogen, lipid, steroids
- Active form: pyridoxal phosphate (PLP)
- Dietary sources: present in all food groups
- Deficiency: dermatitis, peripheral neuropathy, depression, confusion, seizures, microcytic anemia
- May be caused by drugs that interact with PLP – isoniazid, penicillamine, cycloserine, hydralazine
- Vitamin B6 enhances the peripheral decarboxylation of levodopa and reduces its effectiveness in Parkinson disease
- Therapeutic uses: prevention and treatment of vit B6 deficiency

F. Vitamin B7 – Biotin
- Important for growth, reproduction and structure of epidermal tissues
- Deficiency do not normally occur in humans
- In infants and small children skin changes may occur (Leiner’s disease)

G. Folate
- Regulation of folate in the body: converted to tetrahydrofolate (THF), circulated to liver via blood, little is stored
- Function of folate: Single carbon transfers: homocysteine to methionine, purines and pyrimidines, normal growth and development
- Folate, neural tube defects, and spina bifida: folate supplementation decreases risk in some women
- Folate deficiency → macrocytic anemia: red blood cells remain immature
- Folate deficiency: alcoholics, intestinal disease, some drugs, elderly, genetic variations

H. Vitamin B12 – Cobalamin
- Coenzyme that catalyzes production of succinyl CoA, uses amino acids for fatty acids for ATP production, conversion of homocysteine to methionine, allows use of folate
- Deficiency → pernicious anemia

Vitamin A
- Beta carotene is converted to vitamin A in the intestinal mucosa
- 90 % is stored in the liver
- Carotenoids can be stored in adipose tissue
- Teratogenic

A. Functions
- Essential role in the function of retina
- Necessary for growth and differentiation of epidermal tissue
- Required for growth of bone, epidermis and embryonic development
- Enhances immune function

B. Vitamin A deficiency
- Eye – keratomalacia, night blindness
- Bronchorespiratory tract – increased incidence of respiratory infection due to changes in the epithelium
- Skin – keratinisation and drying
- Genitourinary tract – urinary calculi, impairment of spermatogenesis, degeneration of testes, abortion
- GI tract – alteration in intestinal epithelium and metaplasia
- Sweat glands – atrophy and keratinisation
- Retardation of growth
- VADD – vitamin A deficiency disorder

C. Therapeutic uses of vitamin A
- Increased requirements: infancy, pregnancy, lactation
- Night blindness and milder conjunctival changes
- Xerophthalmia
- Dermatological diseases such as acne, psoriasis
- Cancer and other uses

D. Vitamin A toxicity
- Acute toxicity: abdominal pain, nausea, vomiting, headache, dizziness, papilledema
- Chronic toxicity: bone and joint pain, hair loss, dryness and fissures of lips, anorexia, benign intracranial hypertension and pseudotumor cerebri, low grade fever, pruritis, weight loss, hepatosplenomegaly

Vitamin C
- Daily requirement: 60 mg (increased in smokers)

A. Functions
Prescription writing

- See also calculations on separate paper!!
- Prescription orders should always be written in the metric system.
- 1 g = 1,0
- Water: 1 ml = 1 g = 1,0

Household measures
- A teaspoon – 5 ml
- A table spoon – 15 ml
- A glass – 200 ml
- 1 ml of water contains – 20 drops
- 1 ml of sirupus simplex – 18 drops
- 1 ml ethanol 70 % - 55 drops
- 1 ml ethanol 90 % - 63 drops
- 1 ml of tinturae belladonnae or ipecacuanhae – 57 drops

Per os
- Solution
- Mixture
- Suspension
- Sirupus
- Guttae
- Infusum: herbal tea
- Maceratio: plant semen
- Tincture: dry plant + alcohol
- Intractum: fresh plant + alcohol
- Succus: plant juice
- Extractum fluidum, siccum
- Pulvis: powder
- Tabuleta: tablets
- Capsula
- Granulate: granules
- Species

Per rectum, per vaginam
- Suppositorium anale
- Enema: fluid
- Suppositorium vaginal

Per inhalationem
- Aerosolum
- Species
- Ampulla
- Guttae

Per injectionem
- Ampulla
- Solution ad infusionem

Ad usum externum
- Solution
- Guttae
- Tincture
- Unguentum
- Pasta
- Linimentum
- Pulvis
- Tabuletta (to dissolve in water)

Prescription
1. **Inscriptio** – date, place, stamp of institution
2. **Nomen aegroti** – name, surname, age and address of the patient
3. **Praeposito** – recipe (take), Rp.
4. **Praescriptio** – name, dose or concentration, stature, amount of the drug
5. **Subscription** – method of preparing the stature of the drug, ex. misce fiat solution
6. **Signatura** – let it be given and labelled, D.S., ex. Take 1 teaspoon 4 times daily.
7. **Nomen medici** – signature and seal of the physician with private address and phone number

**Powder**
- Pulverization to particles less than 0,5 mm.
- Weight 0,3-1,0 g
- Inert additives: saccharum album, saccharum lactis, calcium lacticum, amylum tritici
- Ad usum internum
- Ad usum externum: conspargens (dusting powder), basis (drug) + inert additives (ground), ground: amylum solani (potato starch), amylum tritici, calcium carbonicum, talcum, zincum oxydatum
- Not divided: carbonis medicinalis, magnesii sulfurici

**Suppositories**
- Suppositoria analia: weight 2,0 g
- Suppositoria vaginalia: weight 2,0-5,0 g
- Basis (drug) + ground: stable in room temperature (not fluid), eg, oleum cacao
- Local action (antinflammarory, local anesthetic) – establish concentration in %
- Systemic action (sedatives, analgesics) – establish the dose
- Amount of suppositories

**Solutiones**
- Basis (drug) + solvent (solvens, menstruum): aqua destillata, alcohol aethylicus 70, 90, 95 %, glycerolum, oleum rapae, oleum paraffinum, oleum lini

**Drops (guttae)**
- For internal use usually prescribe 10-30 drops for a dose (one part of one dose of the drug).
- Guttae ad usum externum: conjunctival sac, nose, ears, throat, mouth, establish concentration and general amount of the drug in prescription.

**Mixturae**
- Mixtures of solution with tinctures, extracts, o/w, and different correctives (drug which improves taste).
- Shake before use.
- Prescribe 60,0-250,0 g (teaspoon, tablespoon).

**Unguenta (ointments)**
- Ad usum externum (skin, mucosa, conjunctiva)
- Establish concentration!
- Grounds: vaselinum album, vaselinum falvum, eucerinum, paraffinum liquidum, lanolinum, unguentum glyceroli, silicon gel, oleum cacao, oleum rapae, oleum olivae

**Species (herbs)**
- One or more raw plant materials with weak activity
- Ad usum externum or internum or ad inhalationem (in asthma)
- Usually one part of raw material of the plant for ten parts of water (1:10)

**Tinctura**
- Fluid, non concentrated extracts in alcohol (1:10) – one part of raw material and ten parts of alcohol

**Extracta**
- Raw materials treated with ethyl alcohol or water and by evaporation
- Extractum fluidum – establish volume
- Extractum siccum – establish the dose
- Extractum belladonnae siccum: dose – 0,01-0,02, activity: spasmolytic
- Extractum ipecacuanhae siccum: dose – 0,05, activity: expectorans

**Oils**
- Very low concentrations 0,1-1 %