جامعة تكريت – كلية الطب البيطري

الدراسات العليا \ فرع الادوية والفسلجة والكيمياء الحياتية

ماجستير أدوية

أ د حسام الدين النجار

First Term \ 2024-2025

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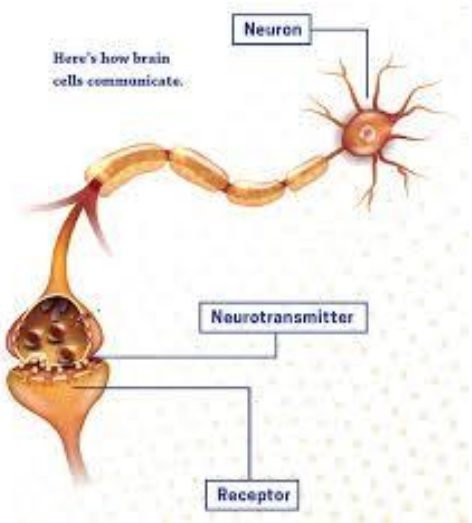
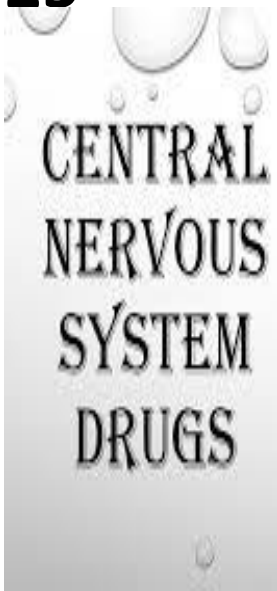
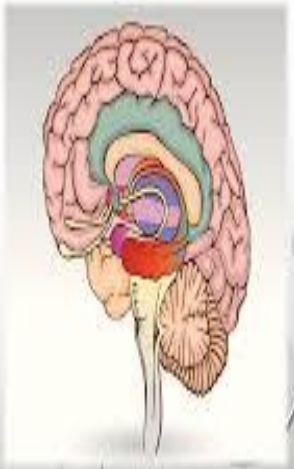


Advanced Pharmacology

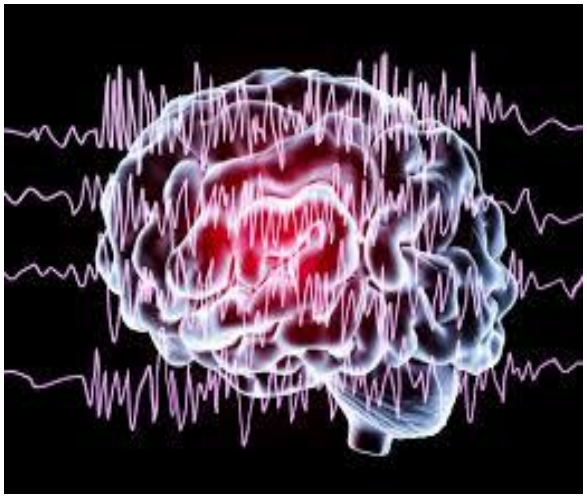
CNS DRUGS

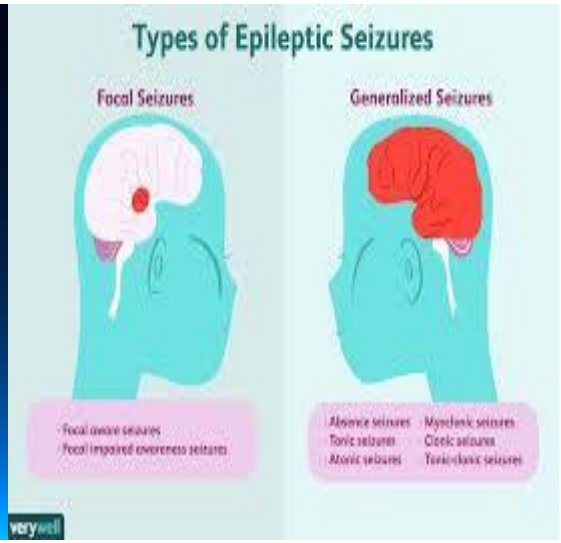




Epilepsy is a chronic disease in which seizures result from the abnormal discharge of cerebral neurones.

EPILEPSY





Antiepileptic drugs

The seizures are classified empirically. Partial (focal) seizures begin at a specific locus in the brain and may be limited to clonic jerking of an extremity.

However, the discharge may spread and become generalized (secondarily generalized seizure). Primarily generalized seizures are those in which there is no evidence of localized onset, both cerebral hemispheres being involved from the onset.

They include tonic–clonic attacks (grand mal – periods of tonic rigidity followed later by massive jerking of the body) and absences (petit mal – changes in conscious ness usually lasting less than 10 s).

Status epilepticus is defined as continuous seizures lasting at least 30 min or a state in which fits follow each other without consciousness being fully regained. Urgent treatment with intravenous agents is necessary to stop the fits, which, if unchecked, result in exhaustion and cerebral damage.

Lorazepam or diazepam is used initially followed by phenytoin if necessary. If the fits are not controlled, the patient is anaesthetized with propofol or thiopental.

Antiepileptic drugs control seizures by mechanisms that usually involve either the enhancement of γ-aminobutyric acid (GABA) mediated inhibition or a reduction of Na+ fluxes .

Ethosuximide and valproate inhibit a spike-generating Ca2+ current in thalamic neurones .

- **Causes of epilepsy**

The aetiology is unknown in 60–70% of cases, but heredity is an important factor. Damage to the brain (e.g. tumours, asphyxia, infec tions or head injury) may subsequently cause epilepsy. **Convulsions may be precipitated in epileptics by several groups of drugs, including phenothiazines, tricyclic antidepressants and many antihistamines.**

Calcium (Ca2+) channels mediate numerous important physiological processes, and are abundant in many types of cells [1,2]. In neurons, voltage-gated Ca2+ (CaV) channels are expressed in most plasma membrane compartments and they are involved in regulating cell excitability, gene transcription and synaptic transmission.

Calcium (Ca2+) is an universal second messenger that regulates the most important activities of all eukaryotic cells. It is of critical importance to neurons as it participates in the transmission of the depolarizing signal and contributes to synaptic activity.

Mechanisms of action of anticonvulsants

- **Inhibition of sodium channels**

Carbamazepine, lamotrigine, valproate, phenytoin and probably topiramate act by producing a use-dependent block of neuronal Na+ channels.

- **Their anticonvulsant action is a result of their ability to prevent high-frequency repetitive activity. The drugs bind preferentially to inactivated (closed) Na+ channels, stabilizing them in the inactivated state and the Na+ current is progressively reduced until it is eventually insufficient to evoke an action potential.**
- Neuronal transmission at normal frequencies is relatively unaffected because a much smaller proportion of the Na+ channels are in the inactivated state.

- **Enhancement of GABA action Vigabatrin is an irreversible inhibitor of GABA-transaminase, which increases brain GABA levels and central GABA release.**
- **Tiagabine inhibits the reuptake of GABA, and by increasing the amount of GABA in the synaptic cleft, increases central inhibition.**
- **The benzodiazepines (e.g. clobazam, clonazepam) and phenobarbital also increase central inhibition, by enhancing the action of synaptically released GABA at the GABAA receptor–Cl– channel complex .**
- **Phenobarbital may also reduce the effects of glutamate at excitatory synapses.**
- **Valproate also seems to increase GABAergic central inhibition by mechanisms that may involve stimulation of glutamic acid decarboxylase activity and/or inhibition of GABA-T. GABA-T is both a key synthetic enzyme and a degradative enzyme. GABA-T metabolizes GABA to succinic semialdehyde**

- **Inhibition of calcium channels**

Absence seizures involve oscillatory neuronal activity between the thalamus and cerebral cortex. This oscillation involves (T-type) Ca2+ channels in the thalamic neurones, which produce low threshold spikes and allow the cells to fire in bursts.

Drugs that control absences (ethosuximide, valproate and lamotrigine) reduce this Ca2+ current, dampening the thalamocortical oscillations that are critical in the generation of absence seizures.

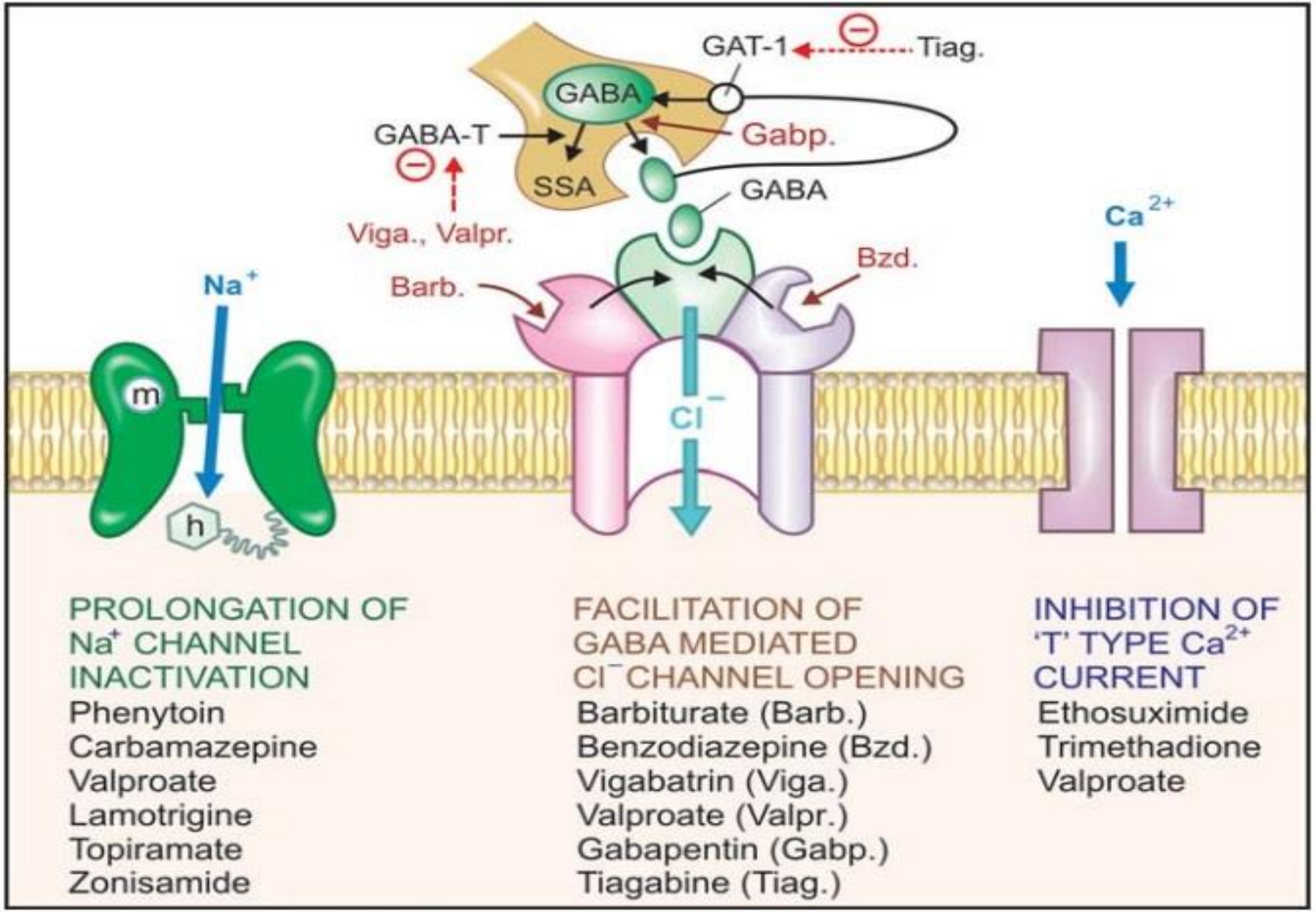


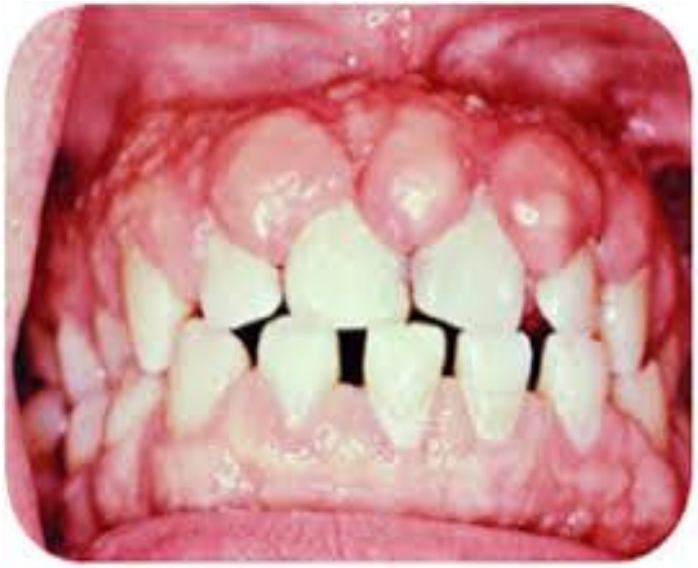
Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase;
SSA: Succinic semialdehyde; GAT-1: GABA transporter

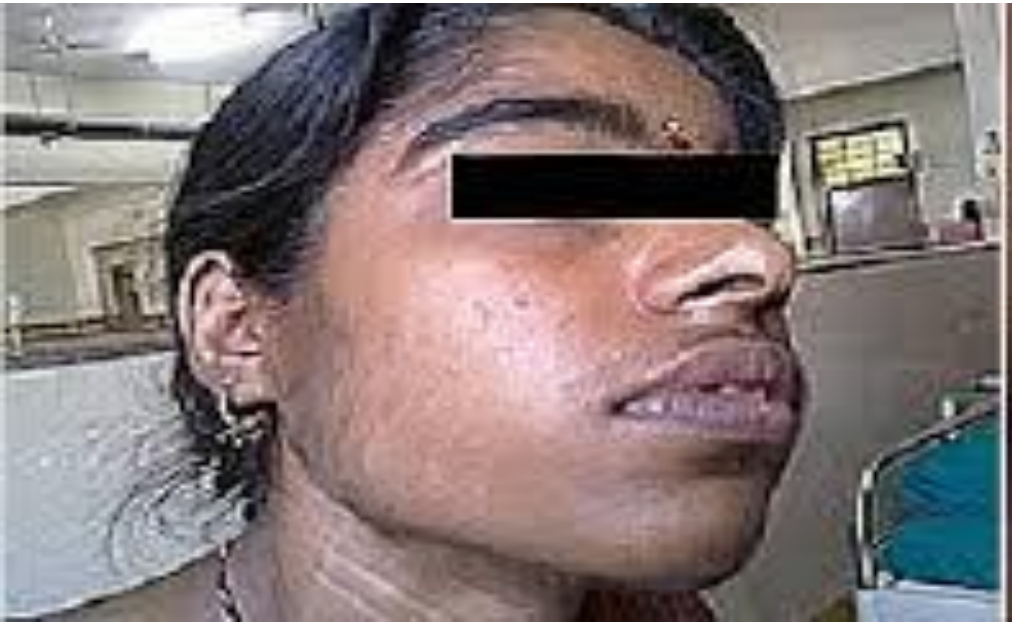
Drugs used in partial and generalized tonic–clonic (grand mal) seizures: Treatment with a single drug is preferred because this reduces adverse effects and drug interactions.

Carbamazepine and valproate are the first-line drugs in epilepsy because they cause relatively few adverse effects and seem to have least detrimental effects on cognitive function and behaviour.

Some anticonvulsants, especially phenytoin, phenobarbital and carbamazepine, are potent liver enzyme inducers and stimulate the metabolism of many drugs, e.g. oral contraceptives, warfarin, theophylline.

- **Carbamazepine is metabolized in the liver to carbamazepine 10,11-epoxide, an active metabolite that partly contributes to both its anticonvulsant action and neurotoxicity.**
- Mild neurotoxic effects are common (nausea, dizziness, drowsiness, blurred vision and ataxia) and often determine the limit of dosage.
- Agranulocytosis is a rarer idiosyncratic reaction to carbamazepine. **Phenytoin is hydroxylated in the liver by a saturable enzyme system. Measurement of serum drug levels is extremely valuable because, once the metabolizing enzymes are saturated, a small increase in dose may produce toxic blood levels of the drug. Adverse effects include ataxia, nystagmus gum hypertrophy, acne, greasy skin, coarsening of the facial features and hirsutism.**





- **Phenobarbital is probably as effective as carbamazepine and phenytoin in the treatment of tonic–clonic and partial seizures, but it is much more sedative.**
- **Tolerance occurs with prolonged use and sudden withdrawal may precipitate status epilepticus.**
- Drugs used to treat absences (petit mal) Ethosuximide is only effective in the treatment of absences and myoclonic seizures (brief jerky movements without loss of consciousness). It is widely used as an anti-absence drug because it has relatively mild adverse effects (e.g. nausea, vomiting).

Body weight

Bone health

Glucose metabolism

Antiepileptic drugs

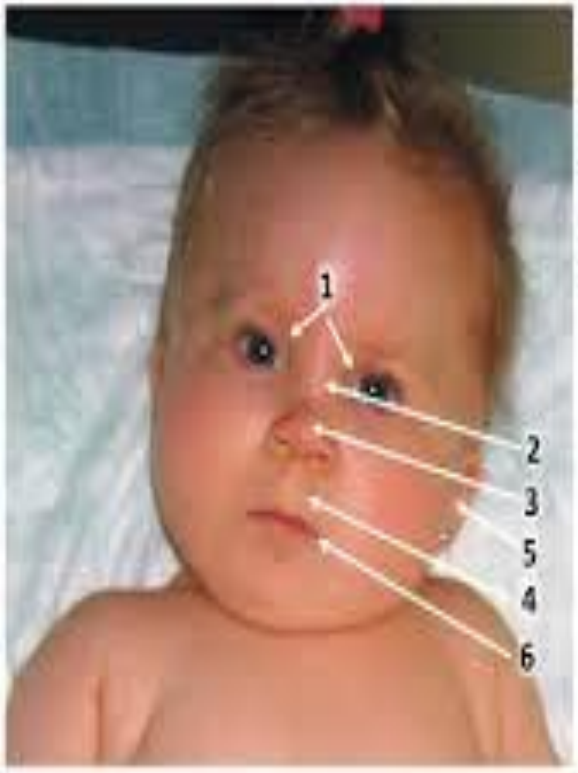
Antioxidant defence system

Vitamin homeostasis

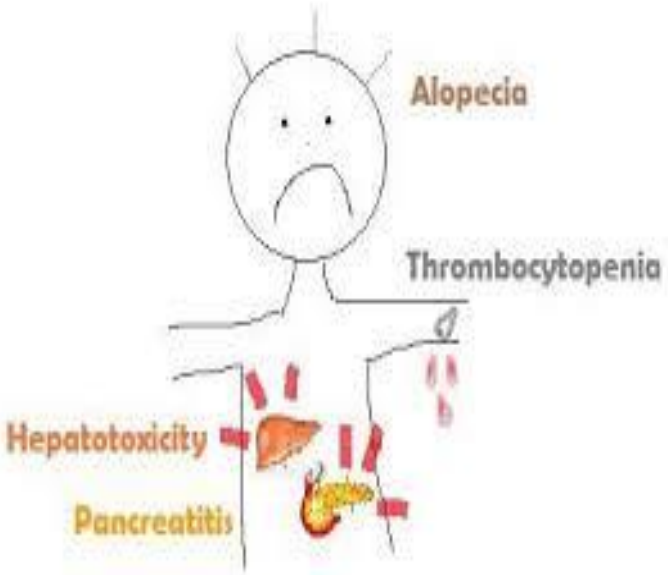
Lipid metabolism

Pregnancy

- **Drugs effective in tonic–clonic (grand mal) and absence (petit mal) seizures Valproate.**
- The advantages of valproate are its relative lack of sedative effects, its wide spectrum of activity and the mild nature of most of its adverse effects (nausea, weight gain, bleeding tendencies and transient hair loss).
- The main disadvantage is that occasional idiosyncratic responses cause severe or fatal hepatic toxicity.
- Lamotrigine is used alone or in combination with other agents.
- **Adverse effects include blurred vision, dizziness and drowsiness. Serious skin reactions may occur, especially in children. These include Stevens–Johnson syndrome and toxic epidermal necrolysis.**
- **Benzodiazepines. Clonazepam is a potent anticonvulsant but is very sedative and tolerance occurs with prolonged oral administration.**



1. Hypotelorism
2. Maxillary hypoplasia
3. Small upturned nose
4. Long upper lip with shallow philtrum
5. Low set ears
6. Small mouth



WHAT IS VALPROATE USED FOR?

Valproate is FDA approved to treat various conditions:

- Migraine/ headaches
- Bipolar disorder
- Epileptic seizures

It is found in Depakote, Depakene, and Depacon and is used in other off label medications that are recognized by the FDA.

WHAT WOMEN SHOULD KNOW ABOUT VALPROATE

- **Women who are of childbearing age** should be on an effective means of birth control to prevent exposure to an unborn child.
- **Women who plan to become pregnant** should discuss their options with their doctor.
- **Women who become pregnant** while on valproate should speak with a doctor immediately.

- **Drug withdrawal:**

Abrupt withdrawal of antiepileptic drugs can cause rebound seizures. It is difficult to know when to withdraw antiepileptics but, if a patient has been seizure-free for 3 or 4 years, gradual withdrawal may be tried.

Pregnancy Anticonvulsant therapy in pregnancy requires care because of the teratogenic potential of many of these drugs, especially valproate and phenytoin. Also there is concern that in utero exposure to valproate may damage neuropsychological development even in the absence of physical malformation.

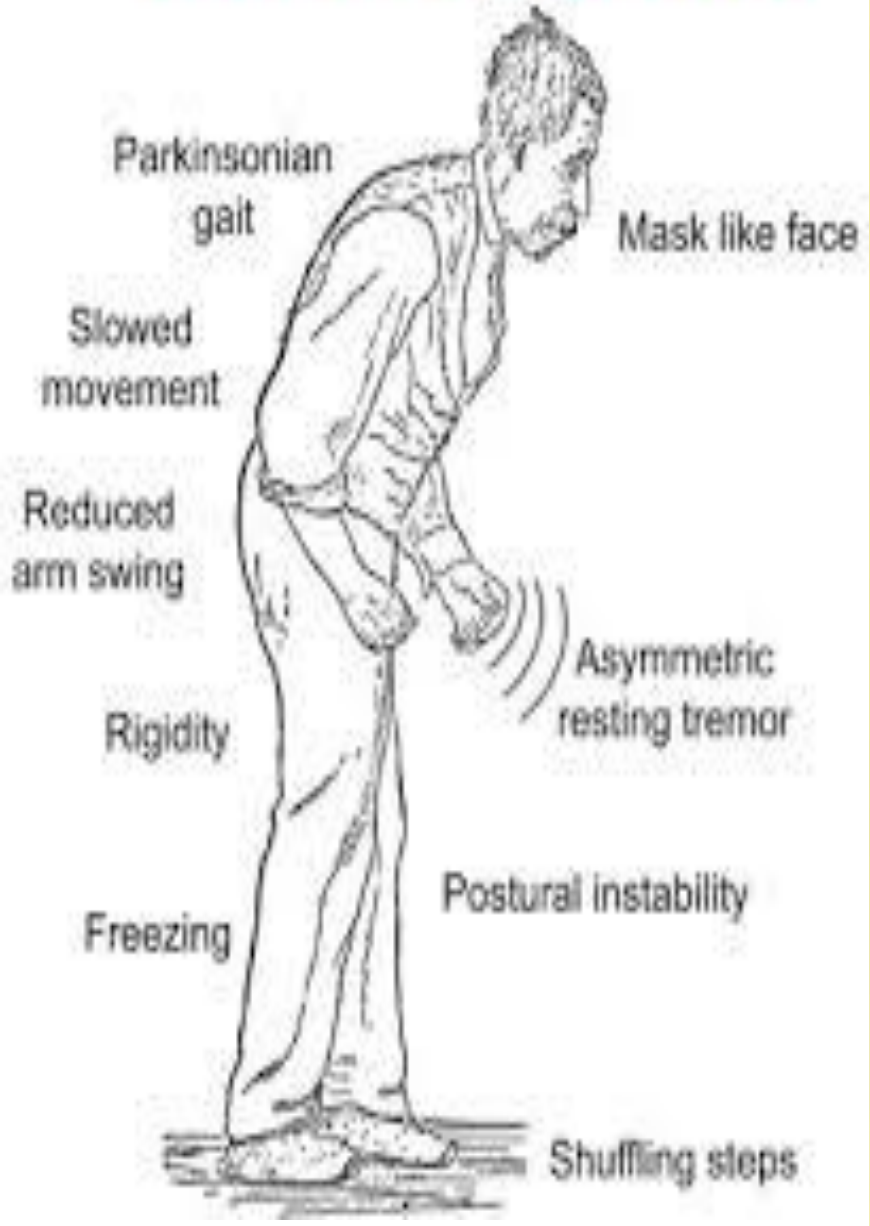
Parkinson's disease

is a disease of the basal ganglia and is characterized by a poverty of movement, rigidity and tremor.

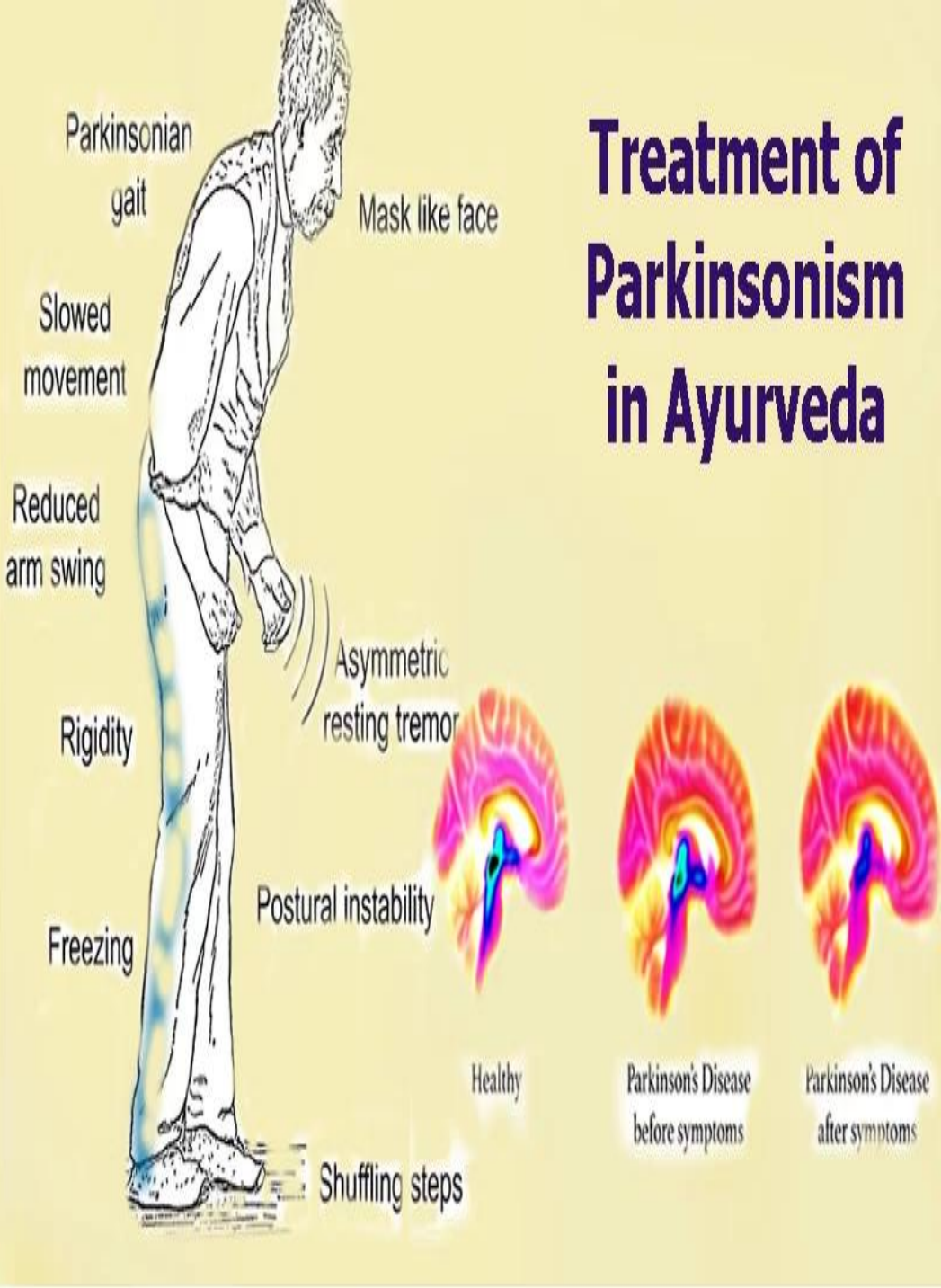
It is progressive and leads to increasing disability unless effective treatment is given. In the early 1960s, analysis of brains of patients dying with Parkinson's disease revealed greatly decreased levels of dopamine (DA) in the basal ganglia (caudate nucleus, putamen, globus pallidus).

Parkinson's disease thus became the first disease to be associated with a specific transmitter abnormality in the brain.

Parkinsonism



Treatment of Parkinsonism in Ayurveda



The main pathology in Parkinson's disease is extensive degeneration of the dopaminergic but the cause of the degeneration is usually unknown .

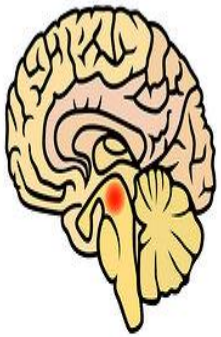
The cell bodies of this tract are localized in the substantia nigra in the midbrain, and it seems that frank symptoms of Parkinson's disease appear only when more than 80% of these neurones have degenerated.

About one third of patients with Parkinson's disease eventually develop dementia.

- **Replacement therapy with dopamine itself is not possible in Parkinson's disease because dopamine does not pass the blood–brain barrier**. **However, its precursor, levodopa (ldopa), does penetrate the brain, where it is decarboxylated to dopamine .**
- When orally administered, levodopa is largely metabolized outside the brain, and so it is given with a selective extracerebral decarboxylase inhibitor (carbidopa or benserazide).
- **This greatly decreases the effective dose by reducing peripheral metabolites and reduces peripheral adverse effects (nausea, postural hypotension).**
- **Levodopa, together with a peripheral decarboxylase inhibitor, is the mainstay of treatment.** Other dopaminergic drugs used in Parkinson's disease are directly acting dopamine agonists and amantadine, which causes dopamine release.

- **Inhibition of monoamine oxidase B (MAOB) with selegiline potentiates the actions of levodopa.**
- Entacapone inhibits catechol O methyltransferase (COMT) and prevents the peripheral conversion of levodopa to (inactive) 3 O methyldopa. It increases the plasma half life of levodopa and increases its action.

- **As the nigrostriatal neurones progressively degenerate in Parkinson's disease, the release of (inhibitory) dopamine declines and the excitatory cholinergic interneurones in the striatum become relatively 'over active' .**
- This simple idea provides the rationale for treatment with antimuscarinic agents.They are most useful in controlling the tremor that is usually the presenting feature in Parkinson's disease. **Withdrawal of antimuscarinic drugs may worsen symptoms.**

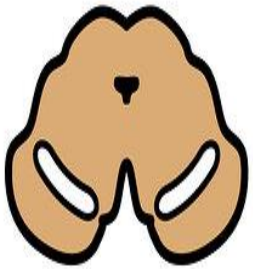


Parkinson's Disease

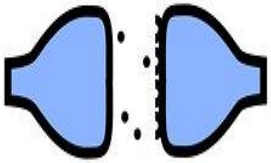
tremor

dopamine

Diminished substantia nigra



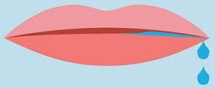
Neuron affected by Parkinson's



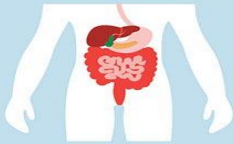
Parkinson's Disease Symptoms

Possible early non-motor symptoms:

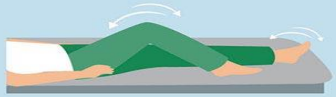
Loss of sense of smell.



Drooling.



Constipation and gastrointestinal problems.



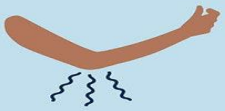
Sleep problems such as restless leg syndrome.

Mask-like facial expression.

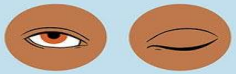
Common motor-related symptoms:

Slowed movements.

Tremor while muscles are at rest.



Rigidity or stiffness.

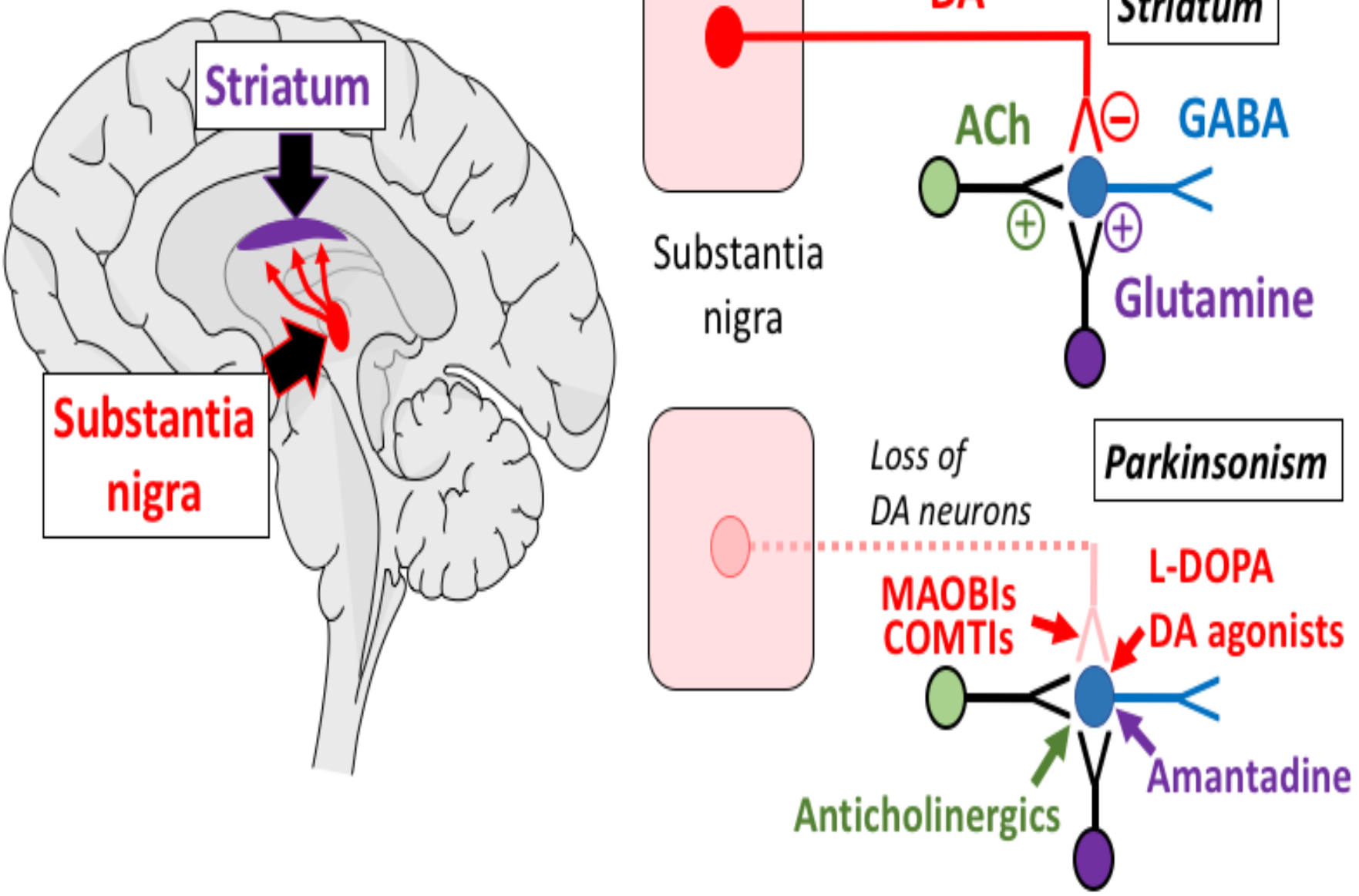


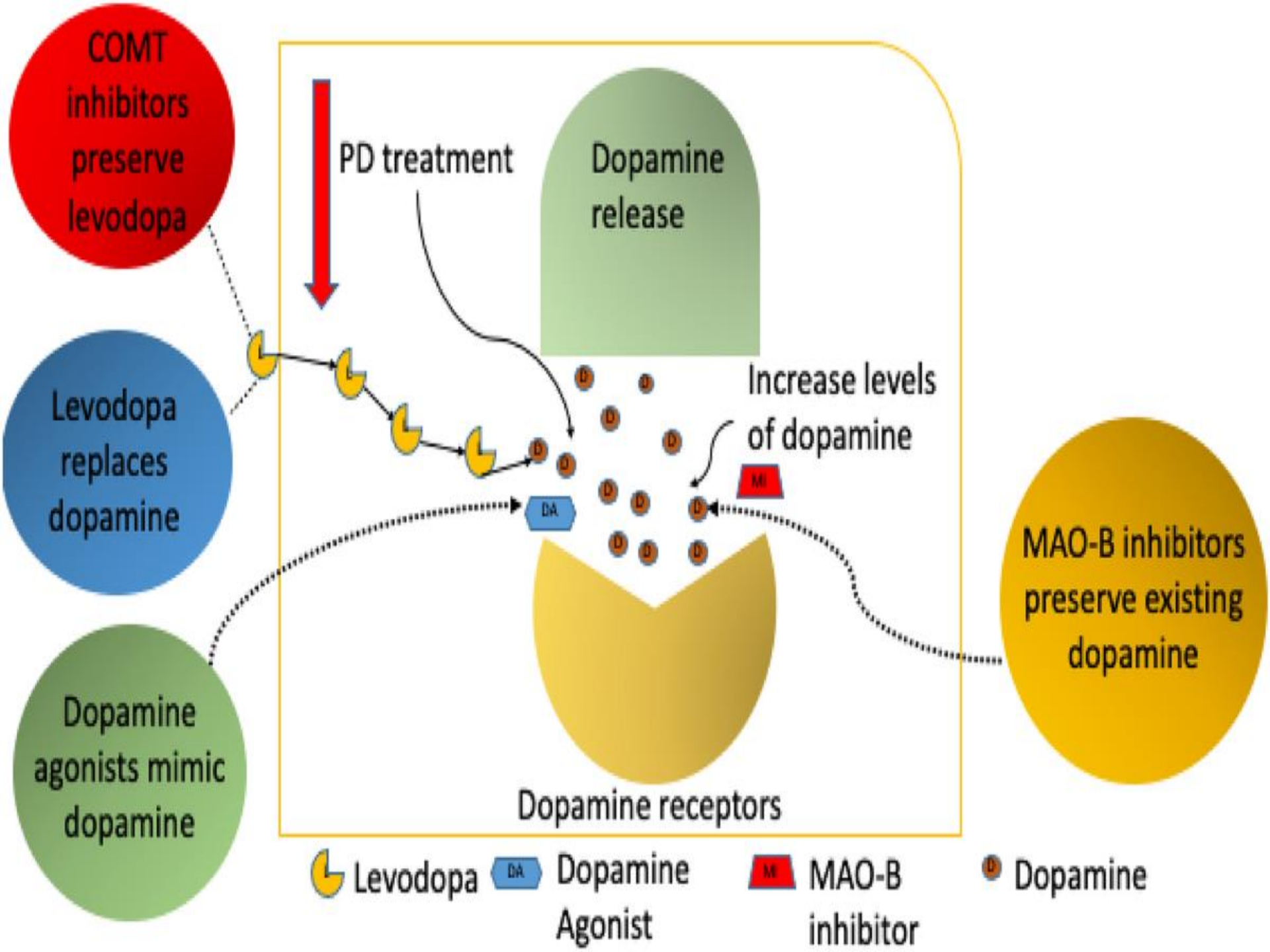
Blinking less often than usual.

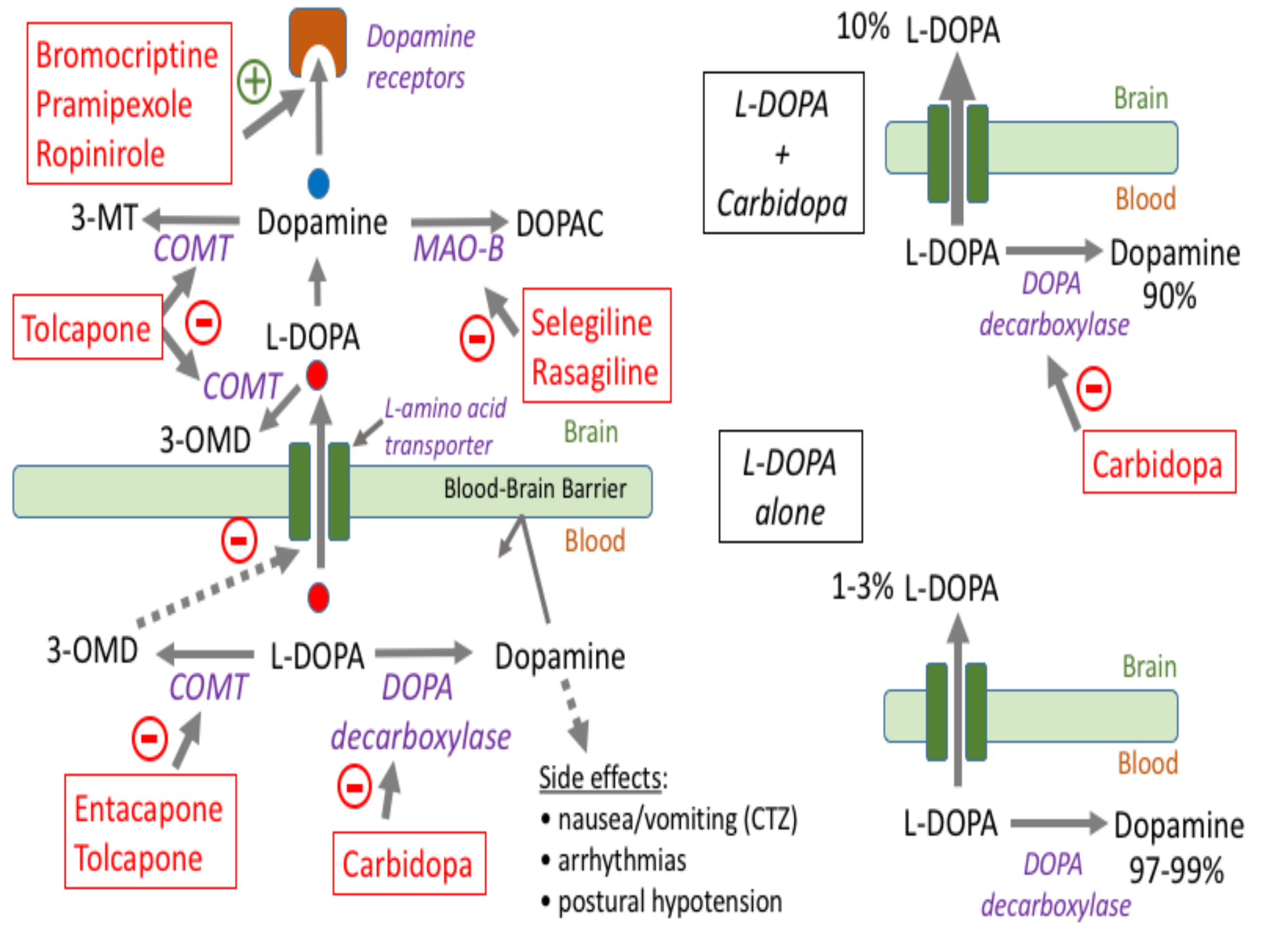
Trouble swallowing.

Unstable posture or walking gait.

Cleveland Clinic


Striatum
Substantia nigra
Normal Striatum
DA
ACh
GABA
Glutamine
Substantia nigra
Loss of DA neurons
Parkinsonism
L-DOPA
MAOBIs
COMTIs
DA agonists
Amantadine
Anticholinergics


COMT inhibitors preserve levodopa
PD treatment
Dopamine release
Levodopa replaces dopamine
Increase levels of dopamine
DA
MI
MAO-B inhibitors preserve existing dopamine
Dopamine agonists mimic dopamine
Dopamine receptors
Levodopa
DA
Dopamine Agonist
MI
MAO-B inhibitor
D
Dopamine


Bromocriptine
Pramipexole
Ropinirole
Dopamine receptors
3-MT
COMT
Dopamine
MAO-B
DOPAC
Tolcapone
COMT
L-DOPA
Selegiline
Rasagiline
3-OMD
L-amino acid transporter
Brain
Blood-Brain Barrier
Blood
3-OMD
COMT
L-DOPA
DOPA decarboxylase
Dopamine
Entacapone
Tolcapone
Carbidopa
Side effects:
• nausea/vomiting (CTZ)
• arrhythmias
• postural hypotension
L-DOPA + Carbidopa
10% L-DOPA
Brain
Blood
L-DOPA
DOPA decarboxylase
Dopamine
90%
Carbidopa
L-DOPA alone
1-3% L-DOPA
Brain
Blood
L-DOPA
DOPA decarboxylase
Dopamine
97-99%

- **Dopaminergic drugs Levodopa with a selective extracerebral decarboxylase inhibitor is the most effective treatment for most patients with Parkinson's disease.**
- **Mechanism of action Levodopa is the immediate precursor of dopamine and is able to penetrate the brain, where it is converted to dopamine.**
- **The site of this decarboxylation in the parkinsonian brain is uncertain, but as dopa decarboxylase is not rate limiting, there may be sufficient enzyme in the remaining dopaminergic nerve terminals.**
- In any event, the release of dopamine replaced in the brain by levodopa therapy must be very abnormal, and it is remarkable that most patients with Parkinson's disease benefit, often dramatically, from its administration.

- **Adverse Effects:**

Adverse effects are frequent, and mainly result from widespread stimulation of dopamine receptors.

Nausea and vomiting are caused by stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema, which lies outside the blood–brain barrier.

This can be reduced by the peripherally acting dopamine antagonist domperidone.

Psychiatric side effects are the most common limiting factor in levodopa treatment and include vivid dreams, hallucinations, psychotic states and confusion.

These effects are probably caused by stimulation of mesolimbic or mesocortical dopamine receptors (remember over activity in these systems is associated with schizophrenia).

Postural hypotension is common, but often asymptomatic. Dyskinesias are an important adverse effect that, in the early stages of Parkinson's disease, usually reflect overtreatment and respond to simple dose reduction (or fractionation).

Dopamine agonists

These include ergot derivatives, e.g. bromocriptine, and newer non ergot drugs, e.g. ropinirole.

The ergot derivatives may cause fibrotic changes leading to restrictive valvular heart disease. **Dopamine agonists have no advantage over levodopa and the adverse effects are similar (nausea, psychiatric symptoms, postural hypotension).**

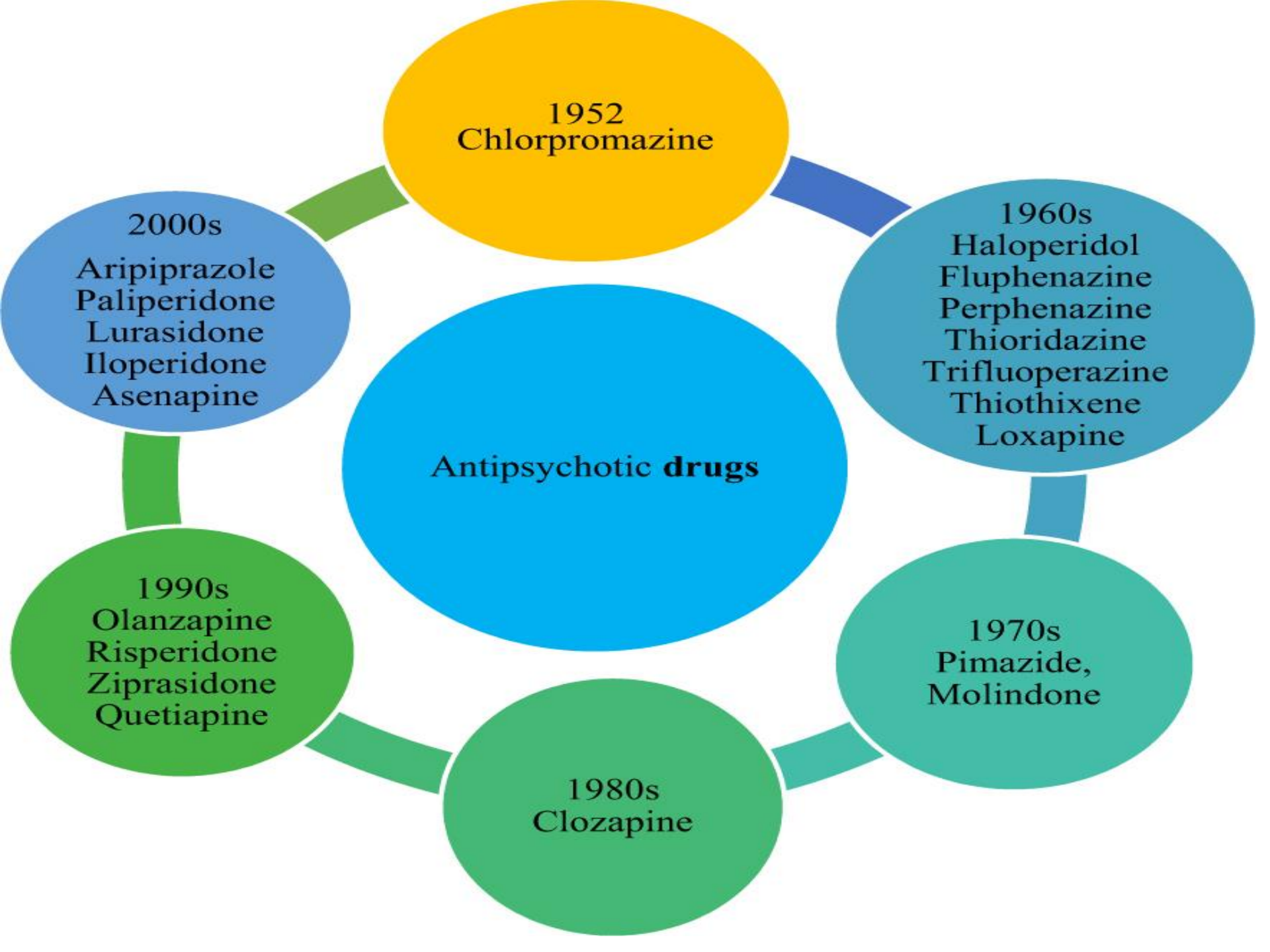
- Drugs causing dopamine release **Amantadine** has muscarinic blocking actions and probably increases dopamine release.
- It has modest antiparkinsonian effects in a few patients, but tolerance soon occurs.
- **MAOB and COMT inhibitors** Selegiline selectively inhibits MAOB present in the brain, for which dopamine, but neither norepinephrine nor serotonin, is a substrate. It reduces the metabolism of dopamine in the brain and potentiates the actions of levodopa, the dose of which can be reduced by up to one third.
- **Because selegiline protects animals from the effects of MPTP, (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a chemical that induces Parkinson-like symptoms in patients and animals). it was hoped that the drug might slow the progression of Parkinson's disease in patients.**

- **Entacapone inhibits COMT.** It slows the elimination of levodopa and prolongs the duration of a single dose. It has no antiparkinsonian action alone, but initial studies suggest that it augments the action of levodopa and reduces the 'off' time in late disease.
- **Antimuscarinics** Muscarinic antagonists produce a modest improvement in the early stages of Parkinson's disease, but the bradykinesia that is responsible for most of the functional disability responds least well. **Furthermore, adverse effects are common and include dry mouth, urinary retention and constipation. The main use of these drugs is in the treatment of drug induced parkinsonism .**

Antipsychotic drugs (neuroleptics)

Schizophrenia

- **Schizophrenia is a syndrome characterized by specific psychological manifestations.** These include **auditory hallucinations, delusions, thought disorders and behavioural disturbances.** Recent evidence suggests that **schizophrenia is caused by developmental abnormalities involving the medial temporal lobe (parahippocampal gyrus, hippoc ampus d frontal lobe cortex.**


1952
Chlorpromazine
1960s
Haloperidol
Fluphenazine
Perphenazine
Thioridazine
Trifluoperazine
Thiothixene
Loxapine
Antipsychotic **drugs**
1970s
Pimazide,
Molindone
1980s
Clozapine
1990s
Olanzapine
Risperidone
Ziprasidone
Quetiapine
2000s
Aripiprazole
Paliperidone
Lurasidone
Iloperidone
Asenapine

- **Schizophrenia can be a genetically determined illness, but there is also evidence implicating intrauterine events and obstetric complications.**
- **Neuroleptic drugs control many of the symptoms of schizophrenia. They have most effect on the positive symptoms, such as hallucinations and delusion.**
- **Negative symptoms, such as social withdrawal and emotional apathy, are less affected by neuroleptic drugs.**
- About 30% of patients show only limited improvement, and 7% show no improvement even with prolonged treatment.

- **The neuroleptics are all antagonists at dopamine receptors, suggesting that schizophrenia is associated with increased activity in the dopaminergic mesolimbic and/or mesocortical pathway.**
- **In agreement with this idea, amfetamine (which causes dopamine release) can produce a psychotic state in normal subjects.**
- Recent experiments using single photon emission computed tomography (SPECT) have shown that, in schizophrenics, there is a greater occupancy of D2 receptors, implying greater dopaminergic stimulation.

- **Neuroleptic drugs require several weeks to control the symptoms of schizophrenia and most patients will require maintenance treatment for many years.**
- **Relapses are common even in drug maintained patients and more than two thirds of patients relapse within 1 year if they stop drug treatment.**
- Unfortunately, neuroleptics also block dopamine receptors in the basal ganglia and this frequently results in distressing and disabling movement disorders (extrapyramidal effects). **These include parkinsonism, acute dystonic reactions (which may require treatment with antimuscarinic drugs), akathisia (motor restlessness) and tardive dyskinesia (orofacial and trunk move ments), which may be irreversible.**

- **In the pituitary gland, dopamine acting on D2dopamine receptors inhibits prolactin release.**
- **This effect is blocked by neuroleptics, and the resulting increase in prolactin release often causes endocrine side effects.**
- Many neuroleptics have muscarinic receptor and α adrenoceptor blocking actions and cause autonomic side-effects including **postural hypotension, dry mouth and constipation.**

- **Dopamine receptors:** **Dopamine receptors were originally subdivided into two types (D1 and D2). Currently, there are five cloned dopamine receptors that fall into these two classes. The D1 like receptors include D1 and D5, while the D2 like receptors include D2, D3 and D4.**
- **The dopamine receptors all display the seven trans membrane spanning domains characteristic of G protein linked receptors and are linked to adenylyl cyclase stimulation (D1) or inhibition (D2).**

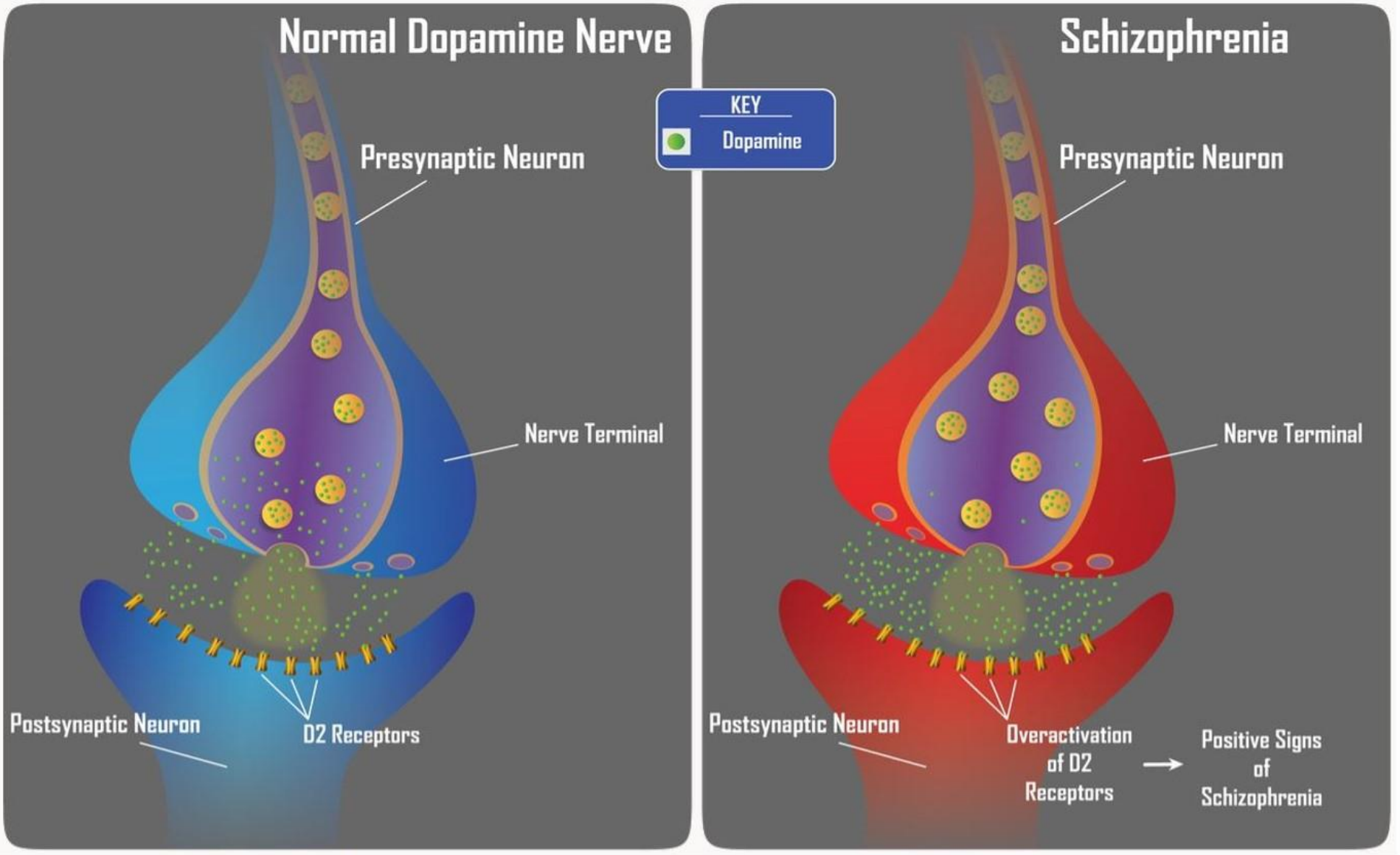


Figure 18.2. Excessive Dopamine Neurotransmission in Schizophrenia

Original drawing by Nathan Olivier

- D1-like dopamine receptors (subtypes D1, D5) are involved mainly in postsynaptic inhibition. Most neuroleptic drugs block D1 receptors, but this action does not correlate with their antipsychotic activity.
- **In particular, the butyrophenones are potent neuroleptics, but are weak D1 receptor antagonists.**
- **D2-like dopamine receptors (subtypes D2, D3, D4) are involved in presynaptic and postsynaptic inhibition.**
- **The D2 receptor is the pre dominant subtype in the brain and is involved in most of the known functions of dopamine.**
- **D2 receptors occur in the limbic system, which is concerned with mood and emotional stability, and in the basal ganglia, where they are involved in the control of movement.**

- **Mechanism of action of neuroleptics**

The affinity of neuroleptic drugs for the D2 receptor correlates closely with their antipsychotic potency, and the blockade of D2 receptors in the forebrain is believed to underlie their therapeutic actions.

Unfortunately, blockade of D2 receptors in the basal ganglia usually results in movement disorders.

Some neuroleptics, in addition to blocking D2 receptors, are also antagonists at 5HT2 receptors, and it is thought by some that this may somehow reduce the movement disorders caused by D2antagonism.

Chemical classification Drugs with a wide variety of structures have antipsychotic activity, but they all have in common the ability to block dopamine receptors.

- **Phenothiazines**:

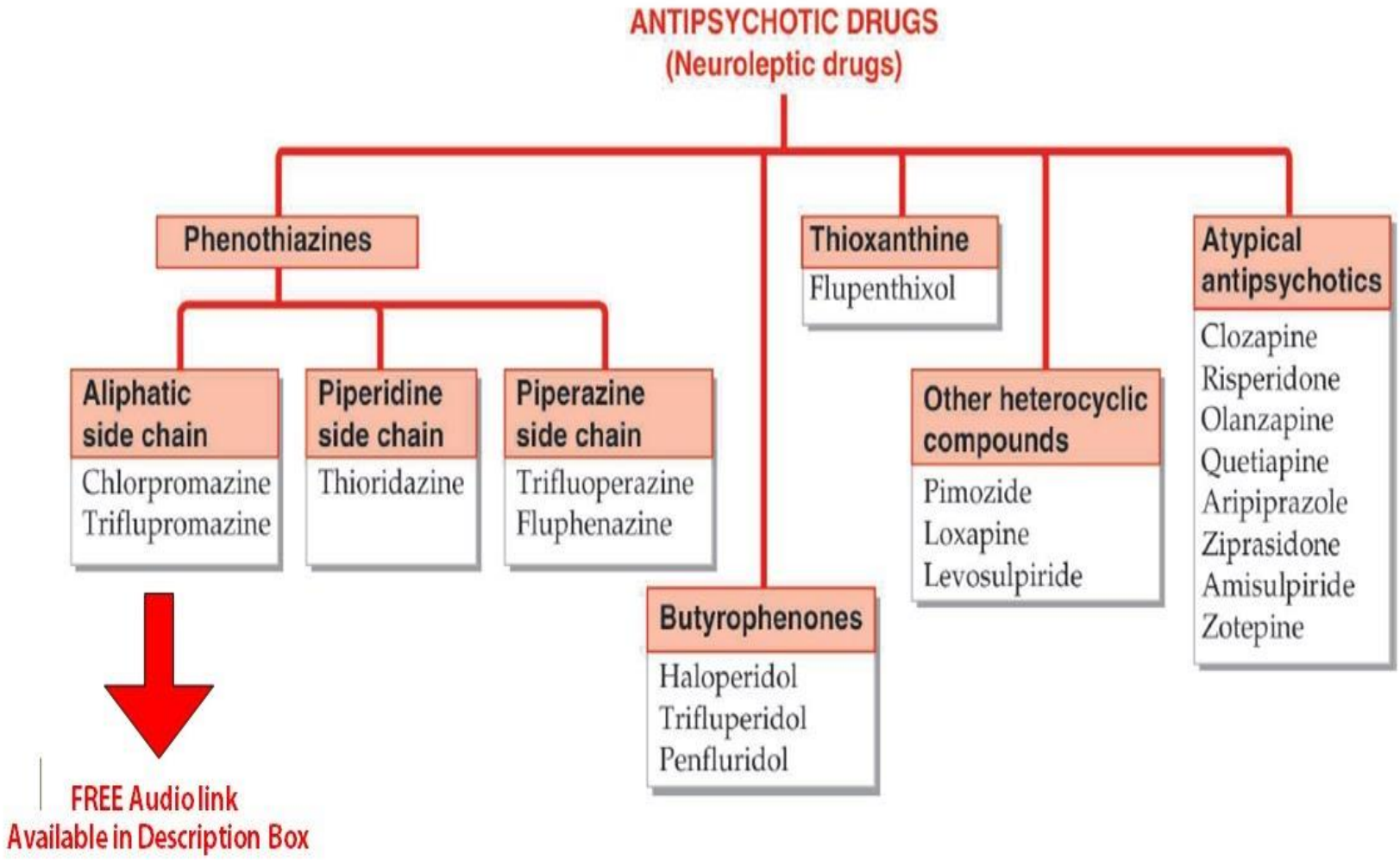
Phenothiazines are subdivided according to the type of side chain attached to the N atom of the phenothiazine ring.

Type 1: Propylamine side-chain Phenothiazines with an aliphatic side chain have relatively low potency and produce nearly all of the side effects.

Chlorpromazine was the first phenothiazine used in schizophrenia and is widely used, although it produces more adverse effects than newer drugs.

It is very sedative and is particularly useful in treating violent patients. **Adverse effects include sensitivity reactions, such as agranulocytosis, haemolytic anaemia, rashes, cholestatic jaundice and photosensitization.**

Antipsychotics Drugs Classification



Type 2: Piperidine side-chain The main drug in this group was thioridazine. It was the first drug to be relatively rarely associated with movement disorders, perhapsbecause of its potent antimuscarinic effects.

Unfortunately, thiori dazine was associated with ventricular arrthythmias, conduction block and sudden death, and has been withdrawn.

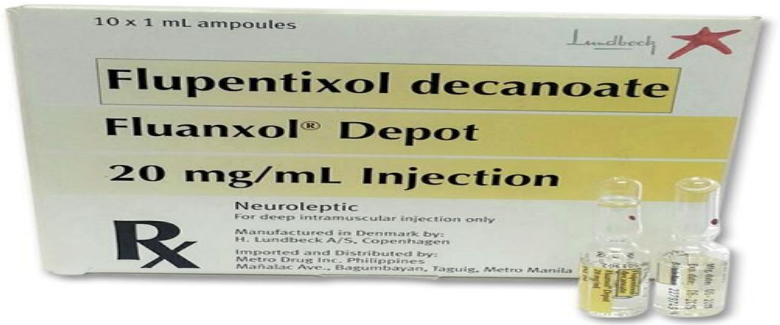
Type 3: Piperazine side-chain Drugs in this group include fluphenazine, perphenazine and trifluoperazine. They are less sedative and less anticholinergic than chlorpromazine, but are particularly likely to cause movement disorders, especially in the elderly.

- **Other chemical classes: Butyrophenones as Haloperidol has little anticholinergic action and is less sedative and hypotensive than chlorpromazine.**

However, there is a high incidence of movement disorders. Atypical drugs are so called because they are associated with a lower incidence of movement disorders and are better tolerated than other antipsychotics.

- **Risperidone** is a newer drug that is non-sedative and lacks anti cholinergic and α blocking actions. It blocks 5HT2 receptors, but is a more potent antagonist than clozapine at D2 receptors. At low doses, it does not cause extrapyramidal effects, but this advantage is lost with higher doses.
- **Sulpiride is a very specific D2 blocker** that is widely used because it has a low liability for extrapyramidal effects and, although quite sedating, can be well tolerated. It has been suggested that sulpiride has a higher affinity for mesolimbic D2 receptors than striatal D2 receptors.

- **Depot preparations Schizophrenic patients are now treated mainly in the community.**
- **This has led to an increased use of long acting depot injections for maintenance therapy.**
- Oily injections of the decanoate derivatives of flupenthixol, haloperidol, risperidone and fluphenazine may be given by deep intramuscular injection at intervals of 1–4 weeks, but these preparations increase the incidence of movement disorders.



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