# 26 Drugs used in Parkinsonism and Alzheimer's Disease

**Parkinsonism** is a chronic, progressive, motor disorder characterised by rigidity, tremors and bradykinesia. Other symptoms include excessive salivation, abnormalities of posture and gait, seborrhoea and mood changes. It was described by James Parkinson in 1817 and is therefore named after him.

The incidence is about 1 per cent of population above 65 years of age. It is usually idiopathic in origin but can also be drug induced. In idiopathic parkinsonism, there is degeneration of nigrostriatal neurons in the basal ganglia resulting in dopamine deficiency (Fig. 26.1). The balance between inhibitory dopaminergic neurons and excitatory cholinergic neurons is disturbed. Dopamine synthesized in the dopaminergic nerve terminals acts on dopamine receptors. Of the 5 subtypes ($D_1$– $D_5$) of the DA receptors, all types are present in different parts of the brain, but striatum is rich in $D_1$ and $D_2$ subtypes and are important in the pathophysiology of parkinsonism.

Antiparkinsonian drugs can only help to alleviate the symptoms and improve the quality of life. The two strategies in the treatment are:

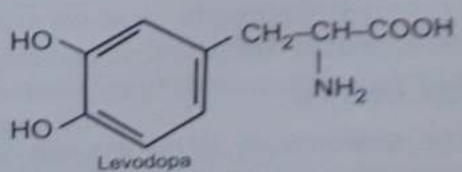
i. To enhance dopamine activity
ii. To depress cholinergic overactivity.

Often combination of drugs are used to influence both functions. Drugs used in Parkinson's disease (PD) can be classified as:

## Classification

1. **Drugs that increase dopamine influence**
   - i. **DA precursor**
     Levodopa
   - ii. **Dopaminergic agonists**
     Bromocriptine, Pergolide
     Lisuride, Ropinirole, Pramipexole
   - iii **Inhibit dopamine metabolism**
     - *$MAO_B$ inhibitors*
       Selegiline, Rasagiline
     - *COMT inhibitors*
       Tolcapone, Entacapone
   - iv. **DA releaser**
     Amantadine
2. **Drugs influencing cholinergic system**
   - i. **Central anticholinergics**
     Benzhexol (Trihexyphenidyl),
     Benztropine, Biperidine
   - ii. **Antihistamines**
     Diphenhydramine
     Orphenadrine, Promethazine

## DOPAMINE PRECURSOR



Levodopa

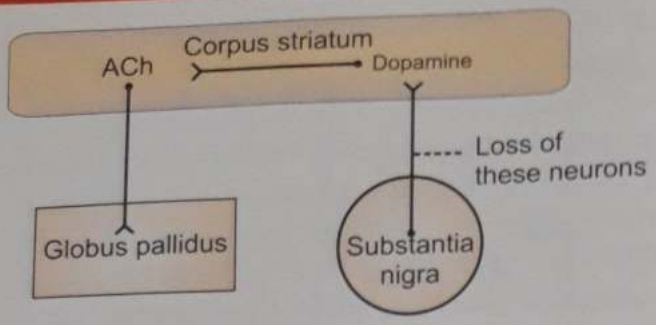



**Fig. 26.1:** Pathophysiology of parkinsonism

**Levodopa:** Though parkinsonism is due to dopamine deficiency, dopamine is of no therapeutic value because it does not cross the blood-brain barrier. Levodopa is a prodrug which is converted to dopamine in the body. Levodopa crosses the BBB and is taken up by the surviving nigrostriatal neurons. It is converted to DA in the dopaminergic neurons of the striatum.

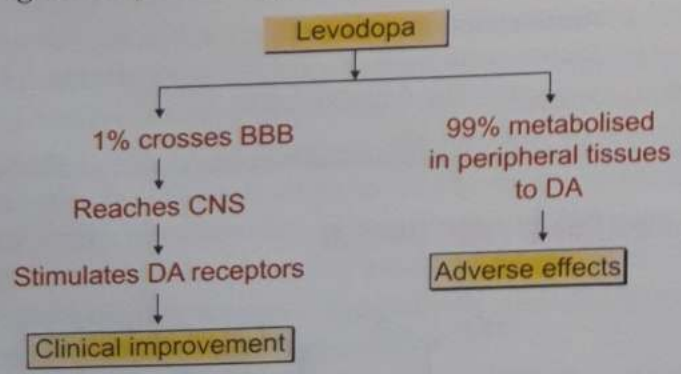
Levodopa —*Dopa decarboxylase*→ Dopamine

### *Antiparkinsonian Effect*

On administration of levodopa, there is an overall improvement in the patient as all the symptoms subside.

Bradykinesia, rigidity and tremors respond. There is an improvement in sialorrhea, seborrhoea, mood changes and general motor performance. The patient shows more interest in the surroundings.

However, some studies have shown that levodopa may generate oxidative stress damaging the dopaminergic neurons on long term use.




### Other Actions

Large amounts of levodopa are converted to dopamine in the periphery which brings about other actions.

- *CTZ:* Dopamine stimulates the CTZ to induce vomiting.
- *CVS:* It causes postural hypotension, tachycardia and arrhythmias. Dopamine is a catecholamine.
- *Endocrine:* Dopamine suppresses the prolactin secretion.

### *Pharmacokinetics*

Levodopa is rapidly absorbed from the small intestine. An active transport process that is meant for amino acids is responsible for absorption and transport of levodopa into the brain across the BBB. Therefore some amino acids in food compete with levodopa for both absorption and transport into the brain. Presence of food delays its absorption. If gastric emptying is delayed, bioavailabilty is reduced due to higher first pass metabolism. It undergoes first pass metabolism in the gut and the liver. Its t½ is 1–2 hours. 1–2% of an oral dose reaches the brain.

### *Adverse Reactions*

As nearly 99% of levodopa is converted to dopamine in the periphery, several adverse effects are expected. Nausea, vomiting, anorexia, postural hypotension, palpitation and occasionally arrhythmias can occur due to stimulation of $\beta_1$ adrenergic receptors. Tolerance develops to these effects after some time. Taste sensation may be altered. These peripheral effects can be prevented by concurrent administration of domperidone which is a peripheral dopamine antagonist.

Behavioural effects like anxiety, depression, hallucinations, mania, trauma, confusion and sometimes psychosis can occur. Dopaminergic drugs including levodopa should not be withdrawn abruptly—may precipitate neuroleptic malignant syndrome.

Excessive dopaminergic activity (due to levodopa) in the limbic system could be responsible for these effects.

**Abnormal involuntary movements** like facial tics, grimacing, choreoathetoid movements of the limbs may develop after a few months of use and require reduction in the dose of levodopa.

**Fluctuation in response** to levodopa can occur after 2–5 years of use - known as 'on-off' phenomenon - where the patient swings alternately from periods of good response to severe disabling disease.

### Uses

Levodopa is the most effective drug in idiopathic parkinsonism but is not useful in drug induced parkinsonism.

### Drug Interactions

1. Pyridoxine enhances peripheral decarboxylation of levodopa and thus reduces its availability to the CNS.
2. Phenothiazines and metoclopramide are DA antagonists. They reverse the effects of levodopa.
3. Non - selective MAO inhibitors prolong the action of levodopa and may result in hypertensive crisis.

### Precautions and Contraindications

- Levodopa should be avoided in patients with psychosis and narrow angle glaucoma.
- Levodopa should be used with caution in patients with IHD, hepatic and renal disorders.
- Peptic ulcer - risk of gastrointestinal bleeding.
- Malignant melanoma and its premalignant skin lesions - careful monitoring required because levodopa is the precursor of melanin and may stimulate the growth of melanoma.

## CARBIDOPA AND BENSERAZIDE

These are peripheral dopa decarboxylase inhibitors. When carbidopa or benserazide are given with levodopa, they prevent the formation of dopamine in the periphery. They do not cross the BBB and hence allow levodopa to be converted to DA in the CNS. The combination is synergistic and therefore levodopa is always given with carbidopa/benserazide.

Levodopa
↓ *Dopa decarboxylase*
Dopamine

### Advantages of the Combination

1. Dose of L-dopa can be reduced by 75%.
2. Response to L-dopa appears earlier.
3. Side effects like vomiting and tachycardia are largely reduced.
4. Pyridoxine does not interfere with the treatment.

### Preparations and Dose

Fixed dose combination of 1:10 or 1:4 i.e 10 mg carbidopa with 100 mg levodopa or 25 mg carbidopa with 100/250 mg levodopa is available. LEVOPA- C, TIDOMET forte levodopa 250 mg + carbidopa 25 mg tab. SYNDOPA carbidopa- 25, 50 mg, Levodopa - 100, 200 mg. BENSPAR levodopa 100 mg + Bensesaride 25 mg.

## Dopamine Receptor Agonists

Dopaminergic agonists have the advantages of directly stimulating the DA receptors and do not depend on the enzymes for convertion to active metabolites (unlike levodopa). They are less likely to generate free radicals which could damage the dopaminergic neurons. They are longer acting than levodopa and are the first line drugs in Parkinson's disease.

**Bromocriptine and pergolide** the older agents are ergot derivatives. Bromocriptine is an agonist at $D_2$ and a partial agonist at $D_1$ while pergolide is an agonist at both $D_1$ and $D_2$ receptors. The newer agents **ropinirole** and **pramipexole** are non-ergot derivatives, are selective $D_2$ and $D_3$ agonists, are better tolerated than older agents and quickly attain therapeutic levels (hence dose titration can be done faster). Their adverse effects are milder except that they may cause some sleep disorders. Being longer acting they are less likely to cause dyskinesia and 'on-off' phenomenon.

DA agonists are well absorbed given orally. Dopamine agonists are all longer acting because of which they are useful in the treatment of 'on-off' phenomenon.

**Adverse effects** include nausea, vomiting, anorexia, dyspepsia and skin eruptions. Ergot derivatives can cause postural hypotension or

hypertension initially and first dose phenomenon → sudden cardiovascular collapse. Cardiac arrhythmias can occur.

Psychiatric disturbances like hallucinations, confusion, impulsive behaviour (betting, gambling, sexual overactivity due to loss of impulse control) are reported but are reversible. Sleep disorders with uncontrolled sleep may require withdrawal of DA agonists. Pergolide is withdrawn due to cardiovascular toxicity.

### Uses

Newer agents are preferred over the older ones. Ropinirole and pramipexole are used for -

1. Initiation of therapy in PD as first line drugs.
2. In the treatment of on-off phenomena.

**Pramipexole** 0.125–1.5 mg TDS. PARPEX 0.5, 1, 1.5 mg.

**Ropinirole** 0.25–4–8 mg TDS. ROPIN, ROPITOR 0.25, 0.5, 1, 2 mg tab

**Rotigotine** another DA agonist was used as a transdermal patch but was withdrawn because of crystal formation on the patches. **Lisuride** is similar to bromocriptine but is also a serotonin receptor agonist and not commonly used.

**Apomorphine** is used subcutaneously for short periods as 'rescue' medication to tide over akinesia in patients receiving regular dopaminergic medication since apomorphine is an emetic.

## DRUGS THAT INHIBIT DA METABOLISM

### $MAO_B$ Inhibitor

Of the two types of monoamine oxidases (*see* page 284) MAO-B selectively metabolises dopamine. Selegiline is a selective $MAO_B$ inhibitor in therapeutic doses but in higher doses it also inhibits $MAO_A$ $MAO_B$ is present in DA containing regions of the CNS. Selegiline prolongs the action of levodopa by preventing its degradation. Some studies suggest that selegiline may delay the progression of parkinsonism.

### Adverse Effects

Include nausea, postural hypotension, confusion and hallucinations.

### Uses

Mild cases of parkinsonism are started on selegiline. It is also used as an adjunct to levodopa as it prolongs the action of levodopa and the dose of levodopa can be reduced.

Dose: 5 mg each at breakfast and lunch; should be avoided at night as it causes insomnia. SELERIN, JVMAX 5 mg tab.

**Rasagiline** is more potent than selegiline. It may also slow the course and progression of disease by a neuroprotective effect like selegiline.

The risk of drug interactions - serotonin syndrome (*see* page 285) if taken with TCA or SSRIs should be borne in mild.

### COMT Inhibitors

**Tolcapone and entacapone** inhibit the peripheral metabolism of levodopa by inhibiting the enzyme COMT — thereby they increase the bioavailability of levodopa. Tolcapone crosses the BBB and enhances the availability of levodopa in the brain. The duration of action of levodopa is prolonged and the response is smoother with reduced on-off periods.

Both are rapidly absorbed; entacapone has peripheral effects whereas tolcapone has both central and peripheral effects.

### Adverse Effects

Adverse effects are nausea, orthostatic hypotension, dyskinesias, confusion and hallucinations mostly due to increased effects of l-dopa. Dose of levodopa should be reduced by 30%. Tolcapone can also cause hepatotoxicity and this makes entacapone more preferred.

COMT inhibitors are used as add-on drugs in parkinsonism.

Entacapone Dose: 200 mg 1 tab with every dose of levodopa. COMTAN, ENTACOM 200, 400 mg tab.

## DRUGS THAT RELEASE DOPAMINE

**Amantadine** is an antiviral drug but was found to be effective in parkisonism. It enhances the release of DA in the brain and also diminishes the reuptake of DA. Amantadine is also an adenosine receptor antagonist and adenosine receptors are found to inhibit the D2 receptors. Thus this action may also help patients with parkinsonism. The response starts early and its adverse effects are

minor. Large doses produce insomnia, dizziness, vomiting, postural hypotension, hallucinations, ankle oedema and livido reticularis.

Amantadine is used in mild cases of parkinsonism. It can also be used along with levodopa as an adjunct. Amantadine is used for short periods as the response may be blunted after a few weeks. Dyskinesias may also subside.

Dose: 100 mg BD- TDS. AMANTREL, COMANTREL 100 mg tab.

## ANTICHOLINERGICS

The cholinergic overactivity is overcome by anticholinergics. They block the muscarinic receptors in the striatum.Tremors, seborrhoea and sialorrhoea are reduced more than rigidity. Atropine derivatives like benzhexol (trihexyphenidyl), biperidin, procyclidine and benztropine are used. Antihistamines like orphenadrine owe their beneficial effects in parkinsonism to their anticholinergic properties. Atropine-like side effects such as dry mouth, constipation, urinary retention and blurred vision may be encountered.

### *Uses*

Anticholinergics are used as: (i) Adjuncts to levodopa, (ii) drugs of choice in drug-induced parkinsonism.

**Benzhexol** Dose: 2–10 mg/day PARKIN, PACITANE 2 mg tab.

**Orphenadine:** Dose:100 - 300 mg/ day. ORPHIDAL 50 mg tab.

**Peribedil:** Dose: 50–100 mg/day. TRIVASTAL - LA 50 mg tab.

## DRUG INDUCED EXTRAPYRAMIDAL REACTIONS

Drugs like reserpine, metoclopramide and phenothiazines can induce extrapyramidal reactions. Reserpine depletes dopamine (catecholamines) stores, while metoclopramide and phenothiazines are dopamine antagonists. Several types of extrapyrimidal reactions may be induced-symptoms of **drug induced parkinsonism** is almost similar to idiopathic parkinsonism.

**Treatment:** Whenever possible the drug responsible for it should be withdrawn - this usually reverses the symptoms. Low doses of benzhexol (or other anticholinergics) are given along with antipsychotics to prevent and treat EPS.

**Dystonias** which are painless, spasmodic contractions of muscles (e.g. torticollis, trismus) may be seen following metoclopramide or phenothiazines. Promethazine inj 25 mg may be followed by 1–2 oral doses.

Levodopa or other dopamine agonists are not effective in drug - induced parkinsonism because DA receptors are blocked by drugs like metoclopramide and phenothiazines.

## DRUGS USED IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by progressive

### CLINICAL PHARMACOLOGY

- Parkinsonism should be treated only when symptoms are bad enough to intiate therapy.
- Treatment is mostly symptomatic
- 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 main–stay of treatment in PD.
- All drugs are started with a low dose and gradually titrated.
- After about 2–3 yr of use, disease progression, decreased response and on-off phenomena may complicate treatment.
- To smoothen the on-off phenomena ropinirole/pramipexole and entacapone may be used as adjuvants.
- Drug holidays: When adverse effects become seriously troublesome or when the response to drugs is inadequate, a drug holiday for a short period (3–21 days) may be tried. Some of the adverse effects may subside and the response after restarting may be better. However, there are certain disadvantages like increased risk of venous thrombosis, pulmonary embolism and depression - due to untreated illness making the patient bedridden-hence it is no more recommended.

impairment of memory and cognitive functions. Other symptoms like depression, anxiety and disturbed sleep may also be seen. Pathological features include atrophy of the cerebral cortex and loss of neurons - mainly cholinergic neurons with multiple senile (amyloid) plaques and neurofibrillary tangles in the brain. Since there is loss of cholinergic neurons, drugs that enhance cholinergic function have been tried. Many other drugs have also been used to improve cognitive functions with variable results.

**Drugs used in Alzheimer's disease**

**Cholinesterase inhibitors**
*Tacrine, rivastigmine, donepezil, galantamine*

**Nootropic agents** (cognition enhancers)
*Piracetam, aniracetam*

**NMDA receptor antagonist**
*Memantine*

**Others**
*Piribedil, ginko biloba*

**Tacrine** is a centrally acting cholinesterase inhibitor. It enhances cholinergic transmission in the brain. But it is short acting and also causes various side effects including nausea, vomiting abdominal cramps, diarrhoea and hepatotoxicity. The newer agents ***rivastigmine, donepezil*** and ***galantamine*** are better tolerated with fewer side effects. They are selective central anticholinesterases - hence do not cause the GI side effects which are due to peripheral cholinergic activity. They increase acetylcholine levels in the surviving neurons and have produced good response–cognitive function improves and the symptom score shows benefit. They are not hepatotoxic and are longer acting. All are started at low doses which are gradually increased. Donepezil has the advantage of longer action and once a day administration.

*Preparations*

**Rivastigmine** 1.5–6 mg BD. RIVAMER 1.5, 3, 4.5 and 6 mg cap.

**Donepezil:** 5 mg HS. DONECEPT 5, 10 mg cap.

**Galantamine:** 4 mg BD. GALAMER 4, 8, 12 mg tab

**Nootropic agents** have not shown consistent results in Alzheimer's disease (*see* page 286).

**Memantine** is a NMDA receptor antagonist found to be useful in patients with moderate to severe AD. The benefit is thought to be due to blockade of glutamate - induced excitotoxicity. Memantine is well tolerated as the adverse effects are mild and reversible–may cause dizziness and headache. It is used in moderate to severe AD. Started with 5 mg OD and increased to 10 mg BD.

**NSAIDs:** Small doses of aspirin (and other NSAIDs) have been shown to delay the onset of AD. However, further studies are needed to prove their benefit.

## AMYOTROPIC LATERAL SCLEROSIS

**Amyotropic lateral sclerosis** is a rapidly progressive motor neuron disorder that is characterised by damage to motor neurons of the ventral horn of the spinal cord that control the voluntary muscles. Manifestations include progressive muscle weakness, atrophy, fasciculations and spasticity. Both upper and lower motor neurons are affected. Till now it was treated symptomatically–for example muscle relaxants like baclofen are used for spasticity. The only drug that was recently made available for the treatment of ALS is riluzole.

**Riluzole** blocks the sodium channels and calcium channels. It is a NMDA/glutamate receptor antagonist. It increases survival. It is orally effective, highly protein bound and given 50 mg BD. It is well tolerated. Nausea, diarrhoea and rarely hepatotoxicity are noted.

**Ginkobiloba:** An extract of the chinese plant contains ginkcoflavon glycosides. It is thought to act as a PAF antagonist has been used as a cognition enhancer–but the benefits have yet to be proved.

GINKOCER, GINKOBA 40 mg tab.