Chapter 31 Antiparkinsonian Drugs

These are drugs that have a therapeutic effect in parkinsonism.

Parkinsonism It is an extrapyramidal motor disorder characterized by *rigidity, tremor* and *hypokinesia* with secondary manifestations like defective posture and gait, mask-like face and sialorrhoea; dementia may accompany. If untreated the symptoms progress over several years to end-stage disease in which the patient is rigid, unable to move, unable to breathe properly; succumbs mostly to chest infections/embolism.

Parkinson's disease (PD) is a progressive degenerative disorder, mostly affecting older people, first described by James Parkinson in 1817. Majority of the cases are idiopathic, some are arteriosclerotic while postencephalitic are now rare. Wilson's disease (hepatolenticular degeneration) due to chronic copper poisoning, is a rare cause.

The most consistent lesion in PD is degeneration of neurones in the substantia nigra pars compacta (SN-PC) and the nigrostriatal (dopaminergic) tract. This results in deficiency of dopamine (DA) in the striatum which controls muscle tone and coordinates movements. An imbalance between dopaminergic (inhibitory) and cholinergic (excitatory) system in the striatum occurs giving rise to the motor defect. Though the cholinergic system is not primarily affected, its suppression (by anticholinergics) tends to restore balance.

The cause of selective degeneration of nigrostriatal neurones is not precisely known, but appears to be multifactorial. Oxidation of DA by MAO-B and aldehyde dehydrogenase generates hydroxyl free radicals ('OH) in the presence of ferrous iron (basal ganglia are rich in iron). Normally these free radicals are quenched by glutathione and other protective mechanisms. Age-related and/or otherwise acquired defect in protective mechanism allows the free radicals to damage lipid membranes and DNA resulting in neuronal degeneration. Genetic predisposition may contribute to the high vulnerability of substantia nigra neurones.

Ageing induces defects in mitochondrial electron transport chain. Environmental toxins and/or genetic factors may accentuate these defects in specific areas. A synthetic toxin N-methyl-4-phenyl tetrahydropyridine (MPTP), which occurred as a contaminant of some illicit drugs, produces nigrostriatal degeneration and manifestations similar to PD by impairing energy metabolism in dopaminergic neurones. It has been proposed that MPTP-like chemicals may be present in the environment, small quantities of which accelerate age related or otherwise predisposed neuronal degeneration of parkinsonism, but there is no proof.

Excess of the excitatory transmitter glutamate can cause 'excitotoxic' neuronal death by inducing Ca^{2+} overload through NMDA receptors.

Drug-induced temporary parkinsonism due to neuroleptics, metoclopramide (dopaminergic blockers) is now fairly common, while that due to reserpine (DA depleter) is historical.

Belladonna alkaloids had been empirically used in PD. A breakthrough was made in 1967 when *levodopa* was found to produce dramatic improvement. Its use was based on sound scientific investigations made in the preceding 10 years that:

- DA is present in the brain;
- it (along with other monoamines) is depleted by reserpine;
- reserpine induced motor defect is reversed by DOPA (the precursor of DA);
- striatum of patients dying of PD was deficient in DA.

Thus, parkinsonism was characterized as a DA deficiency state and levodopa was used to make good this deficiency, because DA itself does not cross the blood-brain barrier. In the subsequent years, a number of levodopa potentiators and DA agonists have been developed as adjuvants/alternatives.

CLASSIFICATION

I. *Drugs affecting brain dopaminergic system*

(a) *Dopamine precursor* : Levodopa (l-dopa)
(b) *Peripheral decarboxylase inhibitors* : Carbidopa, Benserazide.
(c) *Dopaminergic agonists*: Bromocriptine, Ropinirole, Pramipexole
(d) *MAO-B inhibitor:* Selegiline, Rasagiline
(e) *COMT inhibitors:* Entacapone, Tolcapone

(f) *Glutamate (NMDA receptor) antagonist (Dopamine facilitator):* Amantadine.

II. *Drugs affecting brain cholinergic system*

(a) *Central anticholinergics:* Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

(b) *Antihistaminics :* Orphenadrine, Promethazine.

LEVODOPA

Levodopa has a specific salutary effect in PD: efficacy exceeding that of any other drug used alone. It is inactive by itself, but is the immediate precursor of the transmitter DA. More than 95% of an oral dose is decarboxylated in the peripheral tissues (mainly gut and liver). DA thus formed is further metabolized, and the remaining acts on heart, blood vessels, other peripheral organs and on CTZ (though located in the brain, i.e. floor of IV ventricle, it is not bound by blood-brain barrier). About 1–2% of administered levodopa crosses to the brain, is taken up by the surviving dopaminergic neurones, converted to DA which is stored and released as a transmitter. Brains of parkinsonian patients treated with levodopa till death had higher DA levels than those not so treated. Further, those patients who had responded well had higher DA levels than those who had responded poorly.

ACTIONS

1. CNS Levodopa hardly produces any effect in normal individuals or in patients with other neurological diseases. Marked symptomatic improvement occurs in parkinsonian patients. Hypokinesia and rigidity resolve first, later tremor as well. Secondary symptoms of posture, gait, handwriting, speech, facial expression, mood, self care and interest in life are gradually normalized. Therapeutic benefit is nearly complete in early disease, but declines as the disease advances.

The effect of levodopa on behaviour has been described as a 'general alerting response'. In some patients this progresses to excitement—frank psychosis may occur. Embarrassingly disproportionate increase in sexual activity has also been noted. Dementia, if present, does not improve; rather it predisposes to emergence of psychiatric symptoms.

Levodopa has been used to produce a non-specific 'awakening' effect in hepatic coma.

Two subtypes of DA receptors (D1, D2) were originally described. Three more (D3, D4, D5) have now been identified and cloned. All are G protein coupled receptors and are grouped into two families:

D1 like (D1, D5) Are excitatory: act by increasing cAMP formation and PIP_2 hydrolysis thereby mobilizing intracellular Ca^{2+} and activating protein kinase C through IP_3 and DAG.

D2 like (D2, D3, D4) Are inhibitory: act by inhibiting adenylyl cyclase/opening K^+ channels/depressing voltage sensitive Ca^{2+} channels.

The various subtypes of DA receptors are differentially expressed in different areas of the brain, and appear to play distinct roles. Both D1 and D2 receptors are present in the striatum and are involved in the therapeutic response to levodopa. They respectively regulate the activity of two pathways having opposite effects on the thalamic input to the motor cortex (Fig. 31.1). Thus, stimulation of excitatory D1 as well as inhibitory D2 receptors in the striatum achieves the same net effect of smoothening movements and reducing muscle tone.

Dopamine receptor in SN-PC and in pituitary is also of D2 type. The D3 receptors predominate in nucleus accumbans and hypothalamus, but are sparse in caudate and putamen, while D4 and D5 are mostly distributed in neocortex, midbrain, medulla and hippocampus.

2. CVS The peripherally formed DA can cause tachycardia by acting on β adrenergic receptors. Though DA can stimulate vascular adrenergic receptors as well, rise in BP is not seen. Instead, postural hypotension is quite common. This may be a central action. Excess DA and NA formed in the brain decrease sympathetic outflow; also DA formed in autonomic ganglia can impede ganglionic transmission.

Gradual tolerance develops to both cardiac stimulant and hypotensive actions.

3. CTZ Dopaminergic receptors are present in this area and DA acts as an excitatory transmitter. The DA formed peripherally gains access to the CTZ without hindrance—elicits nausea and vomiting. Tolerance develops gradually to this action.

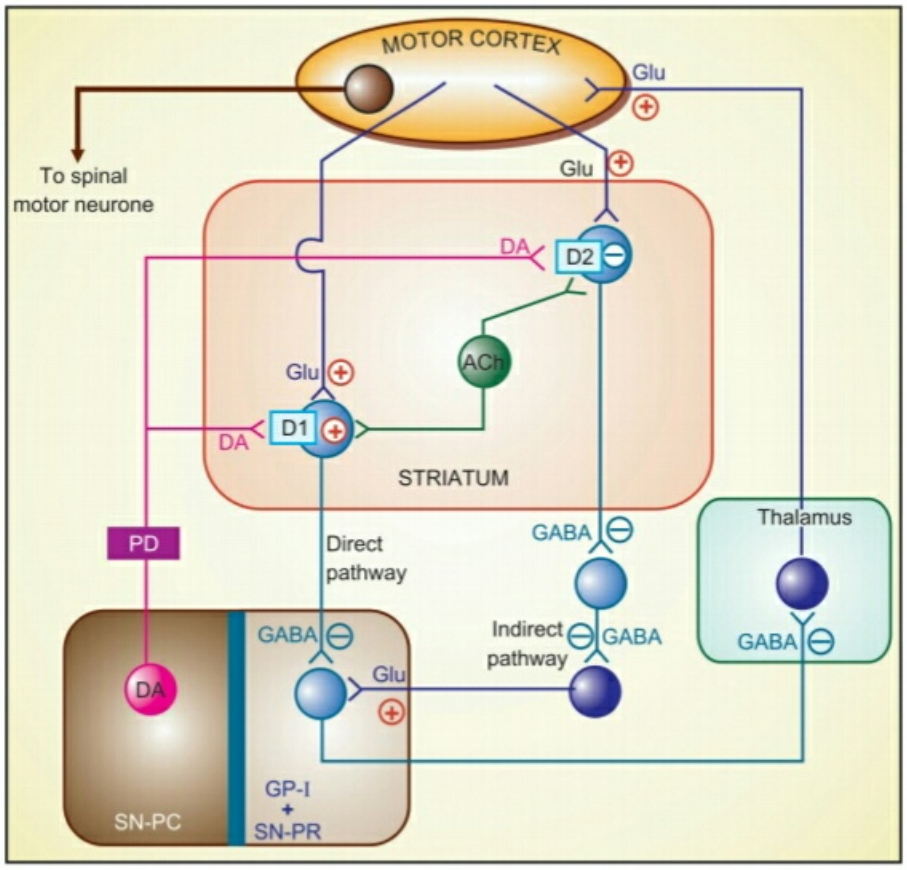

Fig. 31.1: Simplified scheme of side loop circuits in the basal ganglia that provide modulatory input to the motor cortex. The striatal GABAergic neurones receive side-loop excitatory glutamatergic (Glu) input from the motor cortex and modulatory dopaminergic (DA) projections from the substantia nigra pars compacta (SN-PC). There are also balancing cholinergic (ACh) interneurones. The striatal neurones express both excitatory D1 and inhibitory D2 receptors. The output from the striatum to substantia nigra pars reticulata (SN-PR) and internal globus pallidus (GP-I) follows a direct and an indirect pathway. The direct pathway modulated by DI receptors releases inhibitory transmitter GABA, while the dominant indirect pathway modulated by D2 receptors has two inhibitory (GABAergic) relays and an excitatory (glutamatergic) terminal. Due to this arrangement, dopaminergic action in the striatum exerts inhibitory influence on SN-PR and GP-I *via* both the pathways. The output neurones from SN-PR and GP-I feedback on the motor cortex through the thalamus using an inhibitory GABAergic link and an excitatory glutamatergic terminal. The basal ganglia modulatory loop serves to smoothen output to the spinal motor neurone and reduce basal tone.

The degenerative lesion (in SN-PC) of Parkinson's disease (PD) decreases dopaminergic input to the striatum, producing an imbalance between DA and ACh, resulting in hypokinesia, rigidity and tremor.

4. Endocrine DA acts on pituitary mammotropes to inhibit prolactin release and on somatotropes to increase GH release. Though prolactin levels in blood fall during levodopa therapy, increased GH levels are not noted in parkinsonian patients. Probably the mechanisms regulating GH secretion are altered in these patients.

PHARMACOKINETICS

Levodopa is rapidly absorbed from the small intestines by utilizing the active transport process meant for aromatic amino acids. Bioavailability of levodopa is affected by:

(i) Gastric emptying: if slow, levodopa is exposed to degrading enzymes present in gut wall

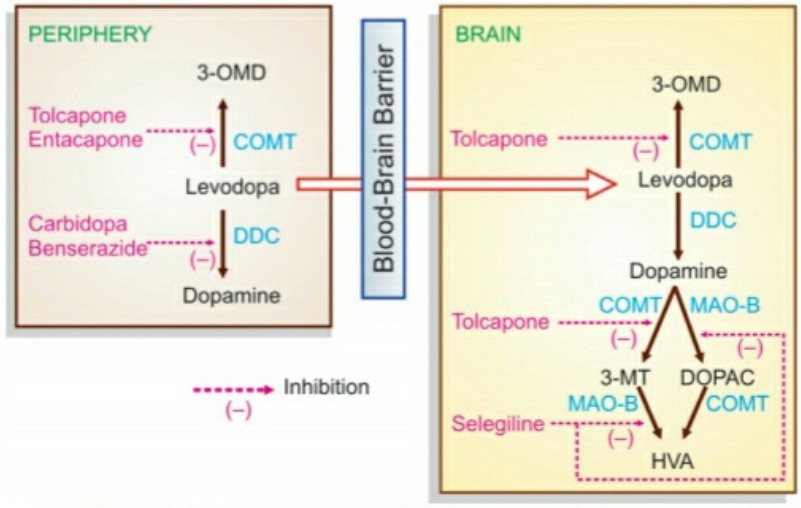

Fig. 31.2: Metabolic pathways of levodopa in the periphery and the brain.
3-OMD—3-O-methyldopa; COMT—Catechol-O-methyl transferase; MAO—monoamine oxidase; 3-MT—3-methoxytyramine; DOPAC—3,4 dihydroxy phenylacetic acid; HVA—Homovanillic acid (3-methoxy-4-hydroxy phenylacetic acid), DDC—Dopa decarboxylase

and liver for a longer time—less is available to penetrate blood-brain barrier.

(ii) Amino acids present in food compete for the same carrier for absorption: blood levels are lower when taken with meals.

Levodopa undergoes high first pass metabolism in g.i. mucosa and liver. The peripheral and central pathway of metabolism of levodopa is depicted in Fig. 31.2.

About 1% of administered levodopa that enters brain, aided by amino acid carrier mediated active transport across brain capillaries, also undergoes the same transformation. The plasma t½ of levodopa is 1–2 hours. Pyridoxal is a cofactor for the enzyme dopa-decarboxylase. The metabolites are excreted in urine mostly after conjugation.

ADVERSE EFFECTS

Side effects of levodopa therapy are frequent and often troublesome. Most are dose-related and limit the dose that can be administered, but are usually reversible. Some are prominent in the beginning of therapy while others appear late.

At the initiation of therapy These side effects can be minimized by starting with a low dose.

1. *Nausea and vomiting* It occurs in almost every patient. Tolerance gradually develops and then the dose can be progressively increased.

2. *Postural hypotension* It occurs in about 1/3 of patients, but is mostly asymptomatic; some patients experience dizziness, few have fainting attacks. It is more common in patients receiving antihypertensives. Tolerance develops with continued treatment and BP normalizes.

3. *Cardiac arrhythmias*
4. *Exacerbation of angina*

Due to β adrenergic action of peripherally formed DA; more in patients with pre-existing heart disease.

5. *Alteration in taste sensation*

After prolonged therapy

1. *Abnormal movements (dyskinesias)* Facial tics, grimacing, tongue thrusting, choreoathetoid movements of limbs start appearing after a few months of use of levodopa at optimum

therapeutic dose. These dyskinesias worsen with time and practically all patients get involved after few years. Their intensity corresponds with levodopa levels. No tolerance develops to this adverse effect, but dose reduction decreases severity. Abnormal movements may become as disabling as the original disease itself, and are the most important dose-limiting side effects.

2. *Behavioural effects* Range from mild anxiety, nightmares, etc. to severe depression, mania, hallucinations, mental confusion or frank psychosis. Excessive DA action in the limbic system is probably responsible (antidopaminergic drugs are antipsychotic). Levodopa is contraindicated in patients with psychotic illness.

3. *Fluctuation in motor performance* After 2–5 years of therapy, the level of control of parkinsonian symptomatology starts showing fluctuation. 'End of dose' deterioration (wearing off) which is initially gradual, develops into rapid 'switches' or 'on-off' effect. With time 'all or none' response develops, i.e. the patient is alternately well and disabled. Abnormal movements may jeopardise even the 'on' phase. This is probably a reflection of progression of the disorder. With progressive degeneration of DA neurones the ability to regulate storage and release of DA may be largely lost: DA is then synthesized in the striatum on a moment-to-moment basis resulting in rapid and unpredictable fluctuations in motor control. Dose fractionation and more frequent administration tends to diminish these fluctuations for a time.

Cautious use of levodopa is needed in the elderly; patients with ischaemic heart disease; cerebrovascular, psychiatric, hepatic and renal disease; peptic ulcer; glaucoma and gout.

Dose: Start with 0.25 g BD after meals, gradually increase till adequate response is obtained. Usual dose is 2–3 g/day.

LEVOPA, BIDOPAL 0.5 g tab.

Interactions

1. Pyridoxine: Abolishes the therapeutic effect of levodopa (not combined with carbidopa) by enhancing its peripheral decarboxylation so that less of it remains available to cross to the brain.
2. Phenothiazines, butyrophenones, metoclopramide reverse the therapeutic effect of levodopa by blocking DA receptors. The antidopaminergic domperidone blocks levodopa induced nausea and vomiting without abolishing its antiparkinsonian effect, because domperidone does not cross blood-brain barrier, but reaches CTZ. Reserpine abolishes levodopa action by preventing entry of DA into synaptic vesicles.
3. Nonselective MAO inhibitors: prevent degradation of DA and NA that is synthesized in excess from the administered levodopa at peripheral sites. This may cause hypertensive crisis.
4. Antihypertensive drugs: postural hypotension caused by levodopa is accentuated in patients receiving antihypertensive drugs; reduce their dose if levodopa is started.
5. Atropine, and antiparkinsonian anticholinergic drugs have additive therapeutic action with low doses of levodopa, but retard its absorption—more time is available for peripheral degradation—efficacy of levodopa may be reduced.

PERIPHERAL DECARBOXYLASE INHIBITORS

Carbidopa and *benserazide* are extracerebral dopa decarboxylase inhibitors; they do not penetrate blood-brain barrier and do not inhibit conversion of levodopa to DA in the brain. Administered along with levodopa, they increase its t½ in the periphery and make more of it available to cross blood-brain barrier and reach its site of action.

Benefits of the combination are—

1. The plasma t½ of levodopa is prolonged and its dose is reduced to approximately 1/4th.
2. Systemic concentration of DA is reduced, nausea and vomiting are not prominent—therapeutic doses of levodopa can be attained quickly.
3. Cardiac complications are minimized.
4. Pyridoxine reversal of levodopa effect does not occur.

5. 'On-off' effect is minimized since cerebral DA levels are more sustained.
6. Degree of improvement may be higher; some patients, not responding adequately to levodopa alone, also improve.

Problems not resolved or accentuated are—

1. Involuntary movements
2. Behavioural abnormalities

} may even be more pronounced and appear earlier.

3. Excessive day time sleepiness in some patients.
4. Postural hypotension.

Currently, levodopa is practically always used along with a decarboxylase inhibitor, except in patients who develop marked involuntary movements with the combination.

Combination of levodopa with carbidopa has been given the name 'Co-careldopa'.

Preparations and dose

	Carbidopa (per tab/cap)		*Levodopa*
TIDOMET-LS, SYNDOPA-110, SINEMET, DUODOPA-110	10 mg	+	100 mg
TIDOMET PLUS, SYNDOPA PLUS	25 mg	+	100 mg
TIDOMET FORTE, SYNDOPA-275	25 mg	+	250 mg

BENSPAR, MADOPAR: Benserazide 25 mg + levodopa 100 mg cap.

Usual daily maintenance dose of levodopa is 0.4–0.8 g along with 75–100 mg carbidopa or 100–200 mg benserazide, given in 3–4 divided doses. Therapy is started at a low dose and suitable preparations are chosen according to the needs of individual patients, increasing the dose as required.

DOPAMINERGIC AGONISTS

The DA agonists can act on striatal DA receptors even in advanced patients who have largely lost the capacity to synthesize, store and release DA from levodopa. Moreover, they are longer acting, can exert subtype selective activation of DA receptors involved in parkinsonism and not share the concern expressed about levodopa of contributing to dopaminergic neuronal damage by oxidative metabolism.

Bromocriptine (*see* Ch. 17) It is an ergot derivative which acts as potent agonist on D2, but as partial agonist or antagonist on D1 receptors. Improvement in parkinsonian symptoms occurs within ½–1 hr of an oral dose of bromocriptine and lasts for 6–10 hours. If used alone, doses needed in parkinsonism are high, expensive and often produce intolerable side effects, especially vomiting, hallucinations, hypotension, nasal stuffiness, conjunctival injection. Marked fall in BP with the 'first dose' has occurred in some patients, especially those on antihypertensive medication.

Bromocriptine has been largely replaced by the newer DA agonists ropinirole and pramipexole. However, it can be used in late cases as a supplement to levodopa to improve control and smoothen 'on off' fluctuations.

Dose: Initially 1.25 mg once at night, increase as needed upto 5 mg TDS.

PROCTINAL, SICRIPTIN, PARLODEL, 1.25, 2.5 mg tabs, ENCRIPT 2.5, 5 mg tabs.

Ropinirole and Pramipexole These are two nonergoline, selective D2/D3 receptor agonists with negligible affinity for D1 and nondopaminergic receptors. Pramipexole has relatively greater affinity for D3 receptors. The therapeutic effect as supplementary drugs to levodopa in advanced cases of PD as well as side effect profile is similar to bromocriptine, but they are better tolerated with fewer g.i. symptoms. Consequently dose titration for maximum improvement can be achieved in 1–2 weeks, while the same may take several months with bromocriptine.

Ropinirole and pramipexole are now frequently used as monotherapy for early PD as well. Trials have found them to afford symptom relief comparable to levodopa. Fewer cases treated with ropinirole needed supplemental levodopa than those treated with bromocriptine. The Parkinson Study Group and other multicentric trials have noted lower incidence of dyskinesias and motor fluctuations among patients treated with these drugs than those treated with levodopa. There is some indirect evidence that use of ropinirole/pramipexole in place of levodopa-carbidopa may be associated with slower rate of neuronal degeneration. Such

encouraging findings indicate that the newer DA agonists are effective alternatives to levodopa and may afford longer symptom-free life to PD patients.

Ropinirole is rapidly absorbed orally, 40% plasma protein bound, extensively metabolized, mainly by hepatic CYP1A2, to inactive metabolites, and eliminated with a terminal t½ of 6 hrs. It is thus longer acting than levodopa, useful in the management of motor fluctuations and reducing frequency of on-off effect.

Side-effects are nausea, dizziness, hallucinations, and postural hypotension. Episodes of day time sleep have been noted with ropinirole as well as pramipexole. The higher incidence of hallucinations and sleepiness may disfavour their use in the elderly. Patients should be advised not to drive if they suffer this side effect.

Ropinirole is FDA approved for use in 'restless leg syndrome'.

Ropinirole: Starting dose is 0.25 mg TDS, titrated to a maximum of 4–8 mg TDS. Early cases generally require 1–2 mg TDS.
ROPITOR, ROPARK, ROPEWAY 0.25, 0.5, 1.0, 2.0 mg tabs. Also 1,2,4 and 8 mg ER tabs are approved.

Pramipexole: It is twice as potent as ropinirole, but comparable in efficacy and tolerability. Starting dose 0.125 mg TDS, titrate to 0.5–1.5 mg TDS.
PRAMIPEX 0.5 mg tab; PARPEX 0.5, 1.0, 1.5 mg tabs, PRAMIROL 0.125, 0.25, 0.5, 1.0, 1.5 mg tabs.

Restless legs syndrome (RLS): It is a peculiar sensory-motor disorder affecting the legs during periods of relaxation, especially sleep. The affected subject feels an irresistable urge to constantly move the legs, usually associated with tingling, itching, discomfort, aching or cramps. The symptoms abate by walking and do not appear during activity. The disorder may be mild and go unnoticed. In some cases, symptoms are severe and disrupt sleep, resulting in day-time sleepiness. The disorder may be primary (idiopathic) or secondary to iron deficiency anaemia, folate or other vitamin deficiencies, varicose veins, peripheral neuropathy (diabetic/uraemic, etc.), or be associated with pregnancy. A genetic basis and mild dopaminergic hypofunction in the brain have been implicated.

The nonergot dopaminergic agonists are the most effective drugs. Relatively low doses: ropinirole (0.25–1.0 mg) or pramipexole (0.125–0.5 mg) taken 2–3 hours before bed-time each day afford dramatic relief in many cases. Other drugs used are benzodiazepines, gabapentin or pregabalin, but these are mostly reserved for nonresponsive cases.

MAO-B INHIBITOR

Selegiline (Deprenyl) It is a selective and irreversible MAO-B inhibitor. Two isoenzyme forms of MAO, termed MAO-A and MAO-B are recognized; both are present in peripheral adrenergic structures and intestinal mucosa, while the latter predominates in the brain and blood platelets. Unlike nonselective MAO inhibitors, selegiline in low doses (10 mg/day) does not interfere with peripheral metabolism of dietary amines; Accumulation of CAs and hypertensive reaction does not develop, while intracerebral degradation of DA is retarded (Fig. 31.2). This is responsible for the therapeutic effect in parkinsonism. Higher doses can produce hypertensive interactions with levodopa and indirectly acting sympathomimetic amines.

Selegiline alone has mild antiparkinsonian action in early cases. Administered with levodopa, it prolongs levodopa action, attenuates motor fluctuations and decreases 'wearing off' effect. As an adjuvant to levodopa, it is beneficial in 50–70% patients and permits 20–30% reduction in levodopa dose. However, advanced cases with 'on-off' effect are not improved and the peak dose levodopa side effects such as dyskinesias, mental confusion or hallucinations may be worsened. Moreover, clinical benefits derived from selegiline are short lived (6–26 months).

Based on the hypothesis that oxidation of DA and/or environmental toxins (MPTP-like) in the striatum by MAO to free radicals was causative in parkinsonism, it was proposed that early therapy with selegiline might delay progression of the disorder. However, no difference in the course of the disease has been detected on follow up of selegiline treated patients in large multicentric studies. Nevertheless, there is some recent data supporting a neuroprotective effect of rasagiline, another MAO-B inhibitor, in parkinsonism.

Adverse effects Postural hypotension, nausea, confusion, accentuation of levodopa induced involuntary movements and psychosis. Selegiline

is partly metabolized by liver into amphetamine which sometimes causes insomnia and agitation. Selegiline is contraindicated in patients with convulsive disorders.

Selegiline interacts with pethidine possibly by favouring its metabolism to norpethidine which causes excitement, rigidity, hyperthermia, respiratory depression. It may also interact with tricyclic antidepressants and selective serotonin reuptake inhibitors.

ELDEPRYL 5, 10 mg tab; SELERIN, SELGIN 5 mg tab;
Dose: 5 mg with breakfast and with lunch, either alone (in early cases) or with levodopa/carbidopa. Reduce by 1/4th levodopa dose after 2–3 days of adding selegiline.

Rasagiline Another newer selective MAO-B inhibitor with selegiline-like therapeutic effect in parkinsonism. However, it is 5 times more potent, longer acting and not metabolized to amphetamine. It is therefore given once a day in the morning, and does not produce excitatory side effects.

Dose: 1 mg OD in the morning.
RELGIN, RASALECT 0.5, 1.0 mg tabs, RASIPAR 1 mg tab.

COMT INHIBITORS

Two selective, potent and reversible COMT inhibitors *Entacapone* and *Tolcapone* have been introduced as adjuvants to levodopa-carbidopa for advanced PD. When peripheral decarboxylation of levodopa is blocked by carbidopa/benserazide, it is mainly metabolized by COMT to 3-O-methyldopa (*see* Fig. 31.2). Blockade of this pathway by entacapone/tolcapone prolongs the t½ of levodopa and allows a larger fraction of administered dose to cross to brain. Since COMT plays a role in the degradation of DA in brain as well, COMT inhibitors could preserve DA formed in the striatum and supplement the peripheral effect (Fig. 31.2). However, entacapone acts only in the periphery (probably because of short duration of action ~2 hr). For tolcapone also, the central action is less important.

Both entacapone and tolcapone enhance and prolong the therapeutic effect of levodopa-carbidopa in advanced and fluctuating PD. They may be used to smoothen 'wearing off', increase 'on' time, decrease 'off' time, improve activities of daily living and allow levodopa dose to be reduced. They are not indicated in early PD cases.

Entacapone: 200 mg with each dose of levodopa-carbidopa, max. 1600 mg/day.
ADCAPON 100 mg tab, COMTAN 200 mg tab.
Tolcapone: 100–200 mg BD or TDS.

Worsening of levodopa adverse effects such as nausea, vomiting, dyskinesia, postural hypotension, hallucinations, etc. occurs often when a COMT inhibitor is added. However, this can be minimised by adjustment of levodopa dose. Other prominent side effect is diarrhoea in 10–18% patients (less with entacapone) and yellow-orange discolouration of urine.

Because of reports of acute fatal hepatitis and rhabdomyolysis, tolcapone has been suspended in Europe and Canada, while in USA its use is allowed only in those not responding to entacapone. Entacapone is not hepatotoxic.

GLUTAMATE (NMDA receptor) ANTAGONIST (Dopamine facilitator)

Amantadine Developed as an antiviral drug for prophylaxis of influenza A_2, it was found serendipitiously to benefit parkinsonism. It acts rapidly but has lower efficacy than levodopa, which is equivalent to or higher than anticholinergics. About 2/3rd patients derive some benefit. However, tolerance develops over months and the efficacy is gradually lost. Amantadine promotes presynaptic synthesis and release of DA in the brain and has anticholinergic property. These were believed to explain all its beneficial effect in parkinsonism. However, an antagonistic action on NMDA type of glutamate receptors, through which the striatal dopaminergic system exerts its influence is now considered to be more important.

Amantadine can be used in milder cases, or in short courses to supplement levodopa for advanced cases. In the latter situation, it serves to suppress motor fluctuations and abnormal movements. Fixed dose of 100 mg BD is used (not titrated according to response). The effect of a single dose lasts 8–12 hours;
AMANTREL, COMANTREL 100 mg tab.

Side effects These are generally not serious: insomnia, restlessness, confusion, nightmares, anticholinergic effects and rarely hallucinations. A characteristic side effect due to local release of CAs resulting in postcapillary vasoconstriction is *livedo reticularis* (bluish discolouration) and edema of ankles.

Side effects are accentuated when it is combined with anticholinergics.

CENTRAL ANTICHOLINERGICS

These are drugs having a higher central : peripheral anticholinergic action ratio than atropine, but the pharmacological profile is similar to it. In addition, certain H_1 antihistaminics have significant central anticholinergic property. There is little to choose clinically among these drugs, though individual preferences vary.

They act by reducing the unbalanced cholinergic activity in the striatum of parkinsonian patients. All anticholinergics produce 10–25% improvement in parkinsonian symptoms lasting 4–8 hours after a single dose. Generally, tremor is benefited more than rigidity; hypokinesia is affected the least. Sialorrhoea is controlled by their peripheral action. The overall efficacy is much lower than levodopa. However, they are cheap and produce less side effects than levodopa. They may be used alone in mild cases or when levodopa is contraindicated. In others, they can be combined with levodopa in an attempt to lower levodopa dose.

Anticholinergics are the only drugs effective in drug (phenothiazine) induced parkinsonism.

The side effect profile is similar to atropine. Impairment of memory, organic confusional states and blurred vision are more common in the elderly. Urinary retention is possible in elderly males. The antihistaminics are less efficacious than anticholinergics, but are better tolerated by older patients. Their sedative action also helps. Orphenadrine has mild euphoriant action.

Trihexyphenidyl It is the most commonly used drug. Start with the lowest dose in 2–3 divided portions per day and gradually increase till side effects are tolerated.

1. Trihexyphenidyl (benzhexol): 2–10 mg/day; PACITANE, PARBENZ 2 mg tab.
2. Procyclidine: 5–20 mg/day; KEMADRIN 2.5, 5 mg tab.
3. Biperiden: 2–10 mg/day oral, i.m. or i.v.: DYSKINON 2 mg tab., 5 mg/ml inj.
4. Orphenadrine: 100–300 mg/day; DISIPAL, ORPHIPAL 50 mg tab.
5. Promethazine: 25–75 mg/day; PHENERGAN 10, 25 mg tab.

Some general points

1. None of the above drugs alter the basic pathology of PD—the disease continues to progress. Drugs only provide symptomatic relief and give most patients an additional 3–6 years of happier and productive life.

Considering that oxidative metabolism of DA generates free radicals which may rather hasten degeneration of nigrostriatal neurones, it has been argued that levodopa therapy might accelerate progression of PD. There is no proof yet for such a happening, and controlled prospective studies have not detected any difference in the progression of disease due to levodopa therapy. However, appearance of dyskinesias is related to dose and duration of levodopa therapy. Thus, it may be prudent to delay use of levodopa and begin with anticholinergics/amantadine/selegiline or newer direct DA agonists in early/mild/younger patients.

2. Initially, when disease is mild, only anticholinergics or selegiline may be sufficient. However, anticholinergics are often not tolerated by elderly patients, especially males. Monotherapy with newer DA agonists ropinirole or pramipexole is being increasingly employed for early cases, especially in younger patients, because of fewer motor complications. However, psychotic symptoms and sudden onset sleep has to be watched for. Selegiline may also be combined with levodopa during the deterioration phase of therapy to overcome 'wearing off' effect.

3. Combination of levodopa with a decarboxylase inhibitor is the standard therapy, and has replaced levodopa alone. Slow and careful initiation over 2–3 months, increasing the dose

as tolerance to early side effects develops and then maintenance at this level with frequent evaluation gives the best results. Full benefit lasts for about 2–3 years, then starts declining.

4. Subsequently the duration of benefit from a levodopa dose progressively shortens—end of dose 'wearing off' effect is seen. Dyskinesias appear, mostly coinciding with the peak of levodopa action after each dose. Relief of parkinsonian symptoms gets linked to the production of dyskinesias. Still later (4–8 years) the 'on-off' phenomena and marked dyskinesias may become so prominent that the patient is as incapacitated with the drug as without it. However, withdrawal of levodopa or dopamine agonists, particularly when higher doses have been employed, may precipitate marked rigidity hampering even respiratory excursions, hyperthermia, mental deterioration and a state resembling the 'neuroleptic malignant syndrome'.

5. Combination of levodopa with decarboxylase inhibitor increases efficacy and reduces early but not late complications.

6. Levodopa alone is now used only in those patients who develop intolerable dyskinesias with a levodopa-decarboxylase inhibitor combination.

7. Amantadine may be used with levodopa for brief periods during exacerbations.

8. The direct DA agonists, especially ropinirole/pramipexole, are commonly used to supplement levodopa in late cases to smoothen 'on off' phenomenon, to reduce levodopa dose and possibly limit dyskinesias.

9. In advanced cases, the COMT inhibitor entacapone may be added to levodopa-carbidopa to prolong its action and subdue 'on off' fluctuation. It can be given to patients receiving selegiline or DA agonists as well.

10. 'Drug holiday' (withdrawal of levodopa for 4–21 days) to reestablish striatal sensitivity to DA by increasing dopaminergic receptor population is no longer practiced.

☞ PROBLEM DIRECTED STUDY

31.1 A 70-year-old man has been under treatment for Parkinson's disease for the last 5 years. He is currently receiving Tab. levodopa 100 mg + carbidopa 25 mg two tablets in the morning, afternoon and night. He now suffers stiffness, shaking and difficulty in getting up from bed in the morning. These symptoms decrease about ½ hour after taking the medicine, but again start worsening by noon. He notices one-sided twitching of facial muscles which is more frequent 1–2 hour after each dose of levodopa-carbidopa.

(a) Should his levodopa-carbidopa medication be stopped/replaced by another drug or the dose be increased further? Alternatively, can another drug be added to his ongoing medication? If so, should levodopa-carbidopa dose be changed or left unaltered?

(see Appendix-1 for solution)