Antipsychotic Drugs

The psychopharmacological agents or psychotropic drugs are those having primary effects on *psyche* (mental processes) and are used for treatment of psychiatric disorders.

During the past 60 years psychiatric treatment has witnessed major changes due to advent of drugs which can have specific salutary effect in mental illnesses. All that could be done before 1952 was to dope and quieten agitated and violent patients.

The introduction of *chlorpromazine* (CPZ) in that year has transformed the lives of schizophrenics; most can now be rehabilitated to productive life.

Reserpine was discovered soon after. Though it is a powerful pharmacological tool to study monoaminergic systems in brain and periphery, its clinical use in psychiatry lasted only few years.

Next came the *tricyclic* and *MAO inhibitor antidepressants* in 1957–58 and covered another group of psychiatric patients.

Many novel and atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs) and other antidepressants have been introduced since the 1980s.

Psychoses These are severe psychiatric illness with serious distortion of thought, behaviour, capacity to recognise reality and of perception (delusions and hallucinations). There is inexplicable misperception and misevaluation; the patient is unable to meet the ordinary demands of life.

(a) *Acute and chronic organic brain syndromes (cognitive disorders)* Such as delirium and dementia with psychotic features; some toxic or pathological basis can often be defined. Prominent features are confusion, disorientation, defective memory, disorganized thought and behaviour.

(b) *Functional disorders* No underlying cause can be defined; memory and orientation are mostly retained but emotion, thought, reasoning and behaviour are seriously altered.

(i) *Schizophrenia* (split mind), i.e. splitting of perception and interpretation from reality—hallucinations, inability to think coherently.

(ii) *Paranoid states* with marked persecutory or other kinds of fixed delusions (false beliefs) and loss of insight into the abnormality.

(iii) *Mood (affective) disorders:* The primary symptom is change in mood state; may manifest as:
Mania—elation or irritable mood, reduced sleep, hyperactivity, uncontrollable thought and speech, may be associated with reckless or violent behaviour, or
Depression—sadness, loss of interest and pleasure, worthlessness, guilt, physical and mental slowing, melancholia, self-destructive ideation.

Neuroses These are less serious; ability to comprehend reality is not lost, though the patient may undergo extreme suffering. Depending on the predominant feature, it may be labelled as:

(a) *Anxiety* An unpleasant emotional state associated with uneasiness, worry, tension and concern for the future.

(b) *Phobic states* Fear of the unknown or of some specific objects, person or situations.

(c) *Obsessive-compulsive disorder* Limited abnormality of thought or behaviour; recurrent intrusive thoughts or rituallike behaviours which the patient realizes are abnormal or stupid, but is not able to overcome even on voluntary effort. The obsessions generate considerable anxiety and distress.

(d) *Reactive depression* due to physical illness, loss, blow to self-esteem or bereavement, but is excessive or disproportionate.

(e) *Post-traumatic stress disorder* Varied symptoms following distressing experiences like war, riots, earthquakes, etc.

ANTIPSYCHOTIC DRUGS
These are drugs having a salutary therapeutic effect in psychoses.

CLASSIFICATION
1. *Phenothiazines*

Aliphatic side chain: Chlorpromazine, Triflupromazine

Piperidine side chain: Thioridazine

Piperazine side chain: Trifluoperazine, Fluphenazine

2. *Butyrophenones* Haloperidol, Trifluperidol, Penfluridol

3. *Thioxanthenes* Flupenthixol

4. *Other heterocyclics* Pimozide, Loxapine

5. *Atypical antipsychotics:* Clozapine Aripiprazole Risperidone Ziprasidone Olanzapine Amisulpiride

Chlorpromazine:
Pharmacology of chlorpromazine (CPZ) is described as prototype; others only as they differ from it.

In normal individuals CPZ produces indifference to surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep from which the subject is easily arousable. Accordingly the typical antipsychotics which

exert CPZ-like action, have potent dopamine D2 receptor blocking property and produce extrapyramidal motor side effects. They are also called *'Neuroleptic drugs'.*
In a psychotic CPZ reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology. Disturbed thought and behaviour are gradually normalized, anxiety is relieved. Hyperactivity, hallucinations and delusions are suppressed. All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective doses. The aliphatic and piperidine side chain phenothiazines (CPZ, triflupromazine, thioridazine) have low potency, produce more sedation and cause greater potentiation of hypnotics, opioids, etc. The sedative effect is produced promptly, while antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect. Thus, the two appear to be independent actions.

Mechanism of action All antipsychotics (except clozapine-like atypical ones) have potent dopamine D2 receptor blocking action. Antipsychotic potency has shown good correlation with their capacity to bind to D2 receptor. Phenothiazines and thioxanthenes also block D1, D3 and D4 receptors, but there is no correlation of such blockade with their antipsychotic potency. Blockade of dopaminergic projections to the temporal and prefrontal areas constituting the 'limbic system' and in mesocortical areas is probably responsible for the antipsychotic action. A *'dopamine theory of schizophrenia'* has been propounded envisaging DA overactivity in limbic area to be responsible for the disorder. Accordingly, blockade of DA overactivity in limbic area produces the antipsychotic effect, while that in basal ganglia produces the parkinsonian adverse effects. However, DA overactivity in the limbic area is not the only abnormality in schizophrenia. Other monoaminergic (5-HT) as well as aminoacid (glutamate) neurotransmitter systems may also be affected. Moreover, DA activity in prefrontal cortex is actually diminished in schizophrenia.

The DA hypothesis fails to explain the antipsychotic activity of clozapine and other atypical antipsychotics which have weak D2 blocking action. However, they have significant 5-HT2 and α1 adrenergic blocking action, and some are relatively selective for D4 receptors. Thus, antipsychotic property may depend on a specific profile of action of the drugs on several neurotransmitter receptors.

ANS Neuroleptics have varying degrees of α adrenergic blocking activity. Anticholinergic property of neuroleptics is weak. The phenothiazines have weak H1-antihistaminic and anti-5-HT actions as well.

Local anaesthetic Chlorpromazine is as potent a local anaesthetic as procaine. However, it is not used for this purpose because of its irritant action. Other antipsychotic drugs have weaker/no membrane stabilizing action.

CVS Neuroleptics produce hypotension (primarily postural) by a central as well as peripheral action on sympathetic tone. The hypotensive action is more marked after parenteral administration and roughly parallels the α□adrenergic blocking potency. Hypotension is not prominent in psychotic patients, but is accentuated by hypovolemia. Partial tolerance to hypotensive action develops after chronic use. Reflex tachycardia accompanies hypotension. High doses of CPZ directly depress the heart and produce ECG changes.

Skeletal muscle Neuroleptics have no direct effect on muscle fibres or neuromuscular transmission. However, they reduce certain types of spasticity: the site of action being in the basal ganglia or medulla oblongata.

Endocrine Neuroleptics consistently increase prolactin release by blocking the inhibitory action of DA on pituitary lactotropes. This may result in galactorrhoea and gynaecomastia. They reduce gonadotropin secretion.
ACTH release in response to stress is diminished. As a result corticosteroid levels fail to increase under such circumstances. Release of GH is also reduced but this is not sufficient to cause growth retardation. Decreased release of ADH may result in an increase in urine volume. A direct action on kidney tubules may add to it, but Na+ excretion is not affected. Though in general, antipsychotic drugs do not affect blood sugar level, CPZ and few others have the potential to impair glucose tolerance or aggravate diabetes

Tolerance and dependence
Tolerance to the sedative and hypotensive actions develops within days or weeks, but maintenance doses for therapeutic effect in most psychotics remain fairly unchanged over years, despite increased DA turnover in the brain. The antipsychotic, extrapyramidal and other actions based on DA antagonism do not display tolerance.
PHARMACOKINETICS

Oral absorption of CPZ is somewhat unpredictable and bioavailability is low. More consistent effects are produced after i.m. or i.v. administration. It is highly bound to plasma as well as tissue proteins; brain concentration is higher than plasma concentration. It is metabolized in liver.

Thioridazine A low potency phenothiazine having marked central anticholinergic action. Incidence of extrapyramidal side effects is very low. Cardiac arrhythmias and interference with male sexual function are more common. Risk of eye damage limits long-term use.

Trifluoperazine These are high potency piperazine side chain phenothiazines. They have minimum autonomic actions. Hypotension, sedation and lowering of seizure threshold are not significant. They are less likely to impair glucose tolerance, cause jaundice and hypersensitivity reactions. However, extrapyramidal side effects are marked.

Haloperidol It is a potent antipsychotic with pharmacological profile resembling that of piperazine substituted phenothiazines. It produces few autonomic effects, is less epileptogenic, does not cause weight gain, jaundice is rare. It is the preferred drug for acute schizophrenia, Huntington's disease.

Flupenthixol
This thioxanthine is less sedating than CPZ; indicated in schizophrenia and other psychoses, particularly in withdrawn and apathetic patients, but not in those with psychomotor agitation or mania. Infrequently used now.

Pimozide It is a selective DA antagonist with little α□adrenergic or cholinergic blocking activity. Because of long duration of action (several days; elimination t½ 48–60 hours) after a single oral dose, it is considered good for maintenance therapy but not when psychomotor

agitation is prominent. Incidence of dystonic reactions is low, but it tends to prolong myocardial APD and carries risk of arrhythmias.

ATYPICAL ANTIPSYCHOTICS
These are newer (second generation) antipsychotics that have weak D2 blocking but potent 5-HT2 antagonistic activity. Extrapyramidal side effects are minimal, and they tend to improve the impaired cognitive function in psychotics.

Clozapine It is the first atypical antipsychotic; pharmacologically distinct from CPZ and related drugs in that it has only weak D2 blocking action, produces few/no extrapyramidal symptoms; tardive dyskinesia is rare and prolactin level does not rise. Both positive and negative symptoms of schizophrenia are improved. The differing pharmacological profile may be due to its relative selectivity for D4 receptors (which are sparse in basal ganglia) and additional 5-HT2 as well as α□adrenergic blockade. It is quite sedating, moderately potent anticholinergic, but paradoxically induces hyper-salivation. Significant H1 blocking property is present.

Risperidone Another compound whose antipsychotic activity has been ascribed to a combination of D_2 + 5-HT_2 receptor blockade. In addition it has high affinity for α1, α2 and H1 receptors: blockade of these may contribute to efficacy as well as side effects like postural hypotension.

USES

1. Psychoses

Schizophrenia The antipsychotics are used primarily in functional psychoses. They have an indefinable but definite therapeutic effect in all forms of schizophrenia: produce a wide range of symptom relief.

Mania Antipsychotics are required in high doses for rapid control of acute mania, and mania patients tolerate them very well. CPZ or haloperidol may be given i.m.—act in 1–3 days. Lithium or valproate may be started simultaneously or after the acute phase. Such combination therapy is more effective.

Organic brain syndromes Antipsychotic drugs have limited efficacy in dementia and delirium associated with psychotic features. They may be used in low doses on a short-term basis.

Anxiety Antipsychotics have antianxiety action but should not be used for simple anxiety because of psychomotor slowing, emotional blunting, autonomic and extrapyramidal side effects.

As antiemetic The typical neuroleptics are potent antiemetics. They control a wide range of drug and disease induced vomiting at doses much lower than those needed in psychosis. However, they should not be given unless the cause of vomiting has been identified.

Anti-Depressant Drugs

Depression is characterized by symptoms like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation or agitation, change in appetite and/or sleep, melancholia, suicidal thoughts.

ANTIDEPRESSANTS
These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other, and many of them have other associated properties.

CLASSIFICATION

I. *Reversible inhibitors of MAO-A (RIMAs)*
Moclobemide, Clorgyline

II. *Tricyclic antidepressants (TCAs)*

A. *NA + 5-HT reuptake inhibitors* Imipramine, Amitriptyline, Trimipramine, Doxepin, Dothiepin,

B. *Predominantly NA reuptake inhibitors* Desipramine, Nortriptyline, Amoxapine, Reboxetine

III. *Selective serotonin reuptake inhibitors (SSRIs)*
Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram, Dapoxetine

IV. *Serotonin and noradrenaline reuptake inhibitors (SNRIs)*
Venlafaxine, Duloxetine

V. *Atypical antidepressants*
Trazodone, Mianserin, Mirtazapine, Bupropion, Tianeptine, Amineptine,

MAO INHIBITORS
MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT). Two isoenzyme forms of MAO have been identified. MAO-A: Preferentially deaminates 5-HT and NA, and is inhibited by clorgyline, moclobemide. MAO-B: Preferentially deaminates phenylethylamine and is inhibited by selegiline.

The selective MAO-A inhibitors possess antidepressant property. Selegiline selectively inhibits MAO-B at lower doses (5–10 mg/day), but these are not effective in depression. It is metabolized to amphetamine and at higher doses it becomes nonselective MAO inhibitor—exhibits antidepressant and excitant properties.

Nonselective MAO Inhibitors
The nonselective MAO inhibitors elevate the mood of depressed patients; in some cases it may progress to hypomania and mania. Excitement and hypomania may be produced even in nondepressed individuals.
The active metabolites of nonselective MAO inhibitors inactivate the enzyme irreversibly.

Moclobemide
It is a reversible and selective MAO-A inhibitor with short duration of action; full MAO activity is restored within 1–2 days of stopping the drug. Because of competitive enzyme inhibition, tyramine is able to displace it from the enzyme, so that potentiation of pressor response to ingested amines is minor, and dietary restrictions are not required. Adverse effects are nausea, dizziness, headache, insomnia, rarely excitement and liver damage. Chances of interaction with other drugs and alcohol are remote, but caution is advised while coprescribing pethidine, SSRIs and TCAs.

TRICYCLIC ANTIDEPRESSANTS
Imipramine, an analogue of CPZ was found during clinical trials (1958) to selectively benefit depressed but not agitated psychotics. In contrast to CPZ, it inhibited NA and 5-HT reuptake into neurones. A large number of congeners were soon added and are called *tricyclic antidepressants (TCAs)*.

PHARMACOLOGICAL ACTIONS

CNS Effects differ in normal individuals and in the depressed.
In normal individuals It induces a peculiar clumsy feeling, tiredness, light-headedness, sleepiness, difficulty in concentrating and thinking, unsteady gait. These effects tend to provoke anxiety. There is no mood elevation or euphoria; effects are rather unpleasant and may become more so on repeated administration.
In depressed patients Little acute effects are produced, except sedation (in the case of drugs which have sedative property). After 2–3 weeks of continuous treatment, the mood is gradually elevated, patients become more communicative and start taking interest in self and surroundings. Thus, TCAs are not euphorients but only antidepressants. In depressed patients who have preponderance of REM sleep, this phase is suppressed and awakenings during night are reduced.

Mechanism of action The TCAs and related drugs inhibit NET and SERT which mediate active reuptake of biogenic amines NA and 5-HT into their respective neurones and thus potentiate them. They, however, differ markedly in their selectivity and potency for different amines.

Reuptake inhibition results in increased concentration of the amines in the synaptic cleft in both CNS and periphery. Tentative conclusions drawn are:
• Inhibition of DA uptake correlates with stimulant action; but is not primarily involved in antidepressant action.
• Inhibition of NA and 5-HT uptake is associated with antidepressant action.

ANS Most TCAs are potent anticholinergics— cause dry mouth, blurring of vision, constipation and urinary hesitancy as side effect.

CVS Effects on cardiovascular function are prominent, occur at therapeutic concentrations and may be dangerous in overdose.
Tachycardia: due to anticholinergic and NA potentiating actions.
Postural hypotension: due to inhibition of cardiovascular reflexes and □1 blockade.
ECG changes and cardiac arrhythmias: T wave suppression or inversion is the most consistent change. Arrhythmias occur in overdose mainly due to interference with intraventricular conduction.

Pharmacokinetics
The oral absorption of TCAs is good, though often slow. They are highly bound to plasma and tissue proteins, therefore have large volumes of distribution. They are extensively metabolized in liver;

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

To overcome limitations of TCAs, a large number of newer (second generation) antidepressants have been developed since 1980s. The most significant of these are the SSRIs. They selectively inhibit membrane associated SERT or both SERT and NET.

Fluoxetine A bicyclic compound, is the first SSRI to be introduced, and the longest acting. Its plasma t½ is 2 days and that of its active demethylated metabolite is 7–10 days.

Other uses of SSRIs The SSRIs are now 1st choice drugs for OCD, panic disorder, social phobia, eating disorders, premenstrual dysphoric disorder and PTSD.

SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS

Venlafaxine A novel antidepressant referred to as SNRI, because it inhibits uptake of both NA and 5-HT but, in contrast to older TCAs, does not interact with cholinergic, adrenergic or histaminergic receptors or have sedative property. Mood changes and hot flushes in menopausal syndrome, some anxiety and eating disorders are also benefited by venlafaxine. It does not produce the usual side effects of TCAs; tends to raise rather than depress BP and is safer in overdose. Prominent side effects are nausea, sweating, anxiety, dizziness, impotence and withdrawal reactions on discontinuation.

ATYPICAL ANTIDEPRESSANTS

Trazodone It is the first atypical antidepressant; less efficiently blocks 5-HT uptake and has prominent α adrenergic and weak 5-HT2 antagonistic actions. It is sedative but not anticholinergic, causes bradycardia rather than tachycardia, does not interfere with intra-cardiac conduction—less prone to cause arrhythmia and better suited for the elderly. Nausea is felt, especially in the beginning. Mild anxiolytic effect has been noted.

Mirtazapine This antidepressant acts by a novel mechanism, *viz*. blocks 2 auto- (on NA neurones) and hetero- (on 5-HT neurones) receptors enhancing both NA and 5-HT release.

ANTIANXIETY DRUGS

Anxiety It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat.

Antianxiety drugs These are an ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of anxiety, produce a restful state of mind without interfering with normal mental or physical functions.

CLASSIFICATION

1. *Benzodiazepines* Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Alprazolam.

2. *Azapirones* Buspirone, Gepirone, Ispapirone

3. *Sedative anti-histaminic* Hydroxyzine

4. β*blocker* Propranolol

BENZODIAZEPINES
Some members have a slow and prolonged action, relieve anxiety at low doses without producing significant CNS depression. BZDs act primarily by facilitating inhibitory GABAergic transmission, but other additional mechanisms of action have been suggested. Higher doses induce sleep and impair performance. *Side effects* that occur in their use to relieve anxiety are—sedation, light-headedness, psychomotor and cognitive impairment, confusional state (especially in the elderly), increased appetite and weight gain, alterations in sexual function.

Chlordiazepoxide It was the first BZD to be used clinically. Oral absorption is slow. A smooth long lasting effect is produced. It is preferred in chronic anxiety states. Chlordiazepoxide is often combined with other drugs in psychosomatic disorders,

AZAPIRONES:

Buspirone It is the first azapirone, a new class of antianxiety drugs, distinctly different from BZDs. The mechanism of anxiolytic action is not clearly known, but may be dependent on its selective partial agonistic action on 5-HT1A receptors. By stimulating presynaptic 5-HT1A autoreceptors, it reduces the activity of dorsal raphe serotonergic neurones. Buspirone has weak dopamine D2 blocking action but no antipsychotic or extrapyramidal effects. A mild mood elevating action has been noted occasionally, which may be due to facilitation of central noradrenergic system. Buspirone is rapidly absorbed; undergoes extensive first pass metabolism; one metabolite is active and excretion occurs both in urine and faeces. Side effects are minor: dizziness, nausea, headache, light-headedness, rarely excitement. It may cause rise in BP in patients on MAO inhibitors, but does not potentiate CNS depressants.

βBlockers

Many symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying, etc.) are due to sympathetic overactivity, and these symptoms reinforce anxiety. They do not affect the psychological symptoms such as worry, tension and fear, but are valuable in acutely stressful situations.

ANTIMANIC AND MOOD STABILIZING DRUGS

LITHIUM CARBONATE

Lithium is a small monovalent cation. In 1949, it was found to be sedative in animals and to exert beneficial effects in manic patients.

Actions and mechanism

1. *CNS* Lithium has practically no acute effects in normal individuals as well as in bipolar patients. It is neither sedative nor euphorient; but on prolonged administration, it acts as a mood stabiliser in bipolar disorder. Given to patients in acute mania, it gradually suppresses the episode taking 1–2 weeks; continued treatment prevents cyclic mood changes. The markedly reduced sleep time of manic patients is normalized.

The mechanism of antimanic and mood stabilizing action of lithium is not known. However, the following mechanisms have been proposed:

(a) Li^+ partly replaces body Na^+ and is nearly equally distributed inside and outside the cells (contrast Na^+ and K^+ which are unequally distributed); this may affect ionic fluxes across brain cells or modify the property of cellular membranes.

(b) Lithium decreases the presynaptic release of NA and DA in the brain of treated animals without affecting 5-HT release. This may correct any imbalance in the turnover of brain monoamines.

(c) The above hypothesis cannot explain why Li^+ has no effect on people not suffering from mania. An attractive hypothesis has been put forward based on the finding that lithium in therapeutic concentration range inhibits hydrolysis of inositol-1-phosphate by inositol monophosphatase. As a result, the supply of free inositol for regeneration of membrane phosphatidylinositides, which are the source of IP3 and DAG, is reduced. The hyperactive neurones involved in the manic state may be preferentially affected, because supply of inositol from extracellular sources is meagre. Thus, lithium may ignore normally operating receptors, but ‘search out’ and selectively, though indirectly, dampen signal transduction in the overactive receptors functioning through phosphatidyl inositol hydrolysis.

Other effects:

- Lithium inhibits the action of ADH on distal tubules in the kidney and causes a diabetes insipidus like state.
- An insulin-like action on glucose metabolism is exerted.
- Leukocyte count is increased by lithium therapy.
- Lithium inhibits release of thyroid hormones resulting in feedback stimulation of thyroid through pituitary.

Pharmacokinetics

Lithium is slowly but well absorbed orally and is neither protein bound nor metabolized. It first distributes in extracellular water, then gradually enters cells and penetrates into brain, ultimately attaining a rather uniform distribution in total body water. The CSF concentration of Li+ is about half of plasma concentration.

Adverse effects Side effects are common, but are mostly tolerable. Toxicity occurs at levels only marginally higher than therapeutic levels.
1. Nausea, vomiting and mild diarrhoea occur initially, can be minimized by starting at lower doses.
2. Thirst and polyuria are experienced by most, some fluid retention may occur initially, but clears later.
3. Fine tremors are noted even at therapeutic concentrations.
4. CNS toxicity manifests as plasma concentration rises producing coarse tremors, giddiness, ataxia, motor incoordination, nystagmus, mental confusion, slurred speech, hyper-reflexia.

ALTERNATIVES TO LITHIUM

Sodium valproate A reduction in manic relapses is noted when valproate is used in bipolar disorder. It is now a first line treatment of acute mania in which high dose valproate acts faster than lithium and is an alternative to antipsychotic ± benzodiazepine. It can be useful in those not responding to lithium or not tolerating it.

Carbamazepine Soon after its introduction as antiepileptic, carbamazepine (CBZ) was found to prolong remission in bipolar disorder. Its efficacy in mania and bipolar disorder has now been confirmed. However, it is less popular than valproate as an alternative to lithium.

Lamotrigine There is now strong evidence of efficacy of this newer anticonvulsant for prophylaxis of depression in bipolar disorder. Lamotrigine is not effective for treatment as well as prevention of mania. It is now extensively used in the maintenance therapy of type II bipolar disorder, because in this condition risk of inducing mania is minimal. Lamotrigine can be combined with lithium to improve its efficacy.

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.

Parkinson's disease (PD) is a progressive degenerative disorder, mostly affecting older people, first described by
James Parkinson in 1817.

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.

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).

Ageing induces defects in mitochondrial electron transport chain. Environmental toxins and/or genetic factors may accentuate these defects in specific areas.

Excess of the excitatory transmitter glutamate can cause 'excitotoxic' neuronal death by inducing Ca2+ overload through NMDA receptors.

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. 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.

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.

   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 PIP2 hydrolysis thereby mobilizing intracellular Ca2+ and activating protein kinase C through IP3 and DAG.

   D2 like (D2, D3, D4) Are inhibitory: act by inhibiting adenylyl cyclase/opening K+ channels/depressing voltage sensitive Ca2+ channels.

   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. 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.

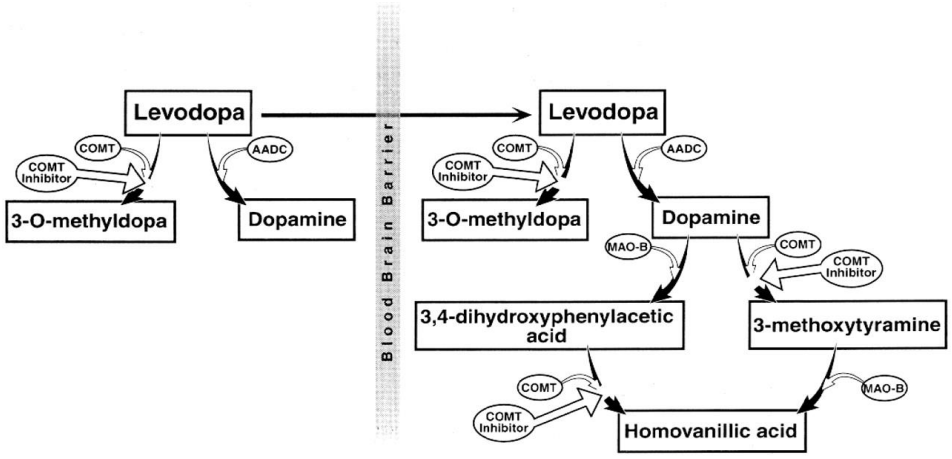
2. **CVS** The peripherally formed DA can cause tachycardia by acting on β□adrenergic receptors. Though DA can stimulate vascular adrenergic receptors as well, rise in BP is not seen. Instead, postural hypotension is quite common. This may be a central action. Excess DA and NA formed in the brain decrease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

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.

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 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.



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.

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 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.

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. This is responsible for the therapeutic effect in parkinsonism. Higher doses can produce hypertensive interactions with levodopa and indirectly acting sympathomimetic amines.

COMT INHIBITORS
Two selective, potent and reversible COMT nhibitors *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.

GLUTAMATE (NMDA receptor) ANTAGONIST (Dopamine facilitator)

Amantadine Developed as an antiviral drug for prophylaxis of influenza A2, 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. 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.

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 H1 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.

CNS Stimulants

CNS STIMULANTS
These are drugs whose primary action is tostimulate the CNS globally or to improve specific brain functions.

CLASSIFICATION
1. *Convulsants* Strychnine, Picrotoxin, Bicuculline, Pentylenetetrazol (PTZ).

2. *Analeptics* Doxapram

3. *Psychostimulants* Amphetamines, Methylphenidate, Atomoxetine, Modafinil, Armodafinil, Pemoline, Cocaine, Caffeine.

CONVULSANTS

1. Strychnine It is an alkaloid from the seeds of *Strychnos nux-vomica,* and a potent convulsant. The convulsions are reflex, tonic-clonic and symmetrical. Strychnine acts by blocking *post-synaptic* inhibition produced by the inhibitory transmitter glycine. Due to loss of synaptic inhibition, any nerve impulse becomes generalized, resulting in apparent excitation and convulsions.

Picrotoxin Obtained from 'fish berries' of East
Indies *Anamirta cocculus*. It is a potent convulsant—
convulsions are clonic, spontaneous and asymmetrical. Picrotoxin acts by blocking *presynaptic* inhibition mediated
through GABA.

ANALEPTICS
These are drugs which stimulate respiration and can have resuscitative value in coma or fainting.

Doxapram It acts by promoting excitation of central neurones. At low doses it is more selective for the respiratory centre than other analeptics.

PSYCHOSTIMULANTS
Amphetamines These are central sympathomimetics. Compared to amphetamine, higher central: peripheral activity ratio is exhibited by dextroamphetamine and methamphetamine. They stimulate mental rather than motor activity; convulsive doses are much higher.

Methylphenidate It is chemically and pharmacologically similar to amphetamine. Both act primarily by releasing NA and DA in the brain. Both produce increase in mental activity at doses which have little action on other central and peripheral functions. However, it is a CNS stimulant, and high doses can produce convulsions. Methylphenidate is well absorbed orally, metabolized and excreted in urine, plasma t½ is 4–6 hours, but central effect lasts much longer.

Twice daily dosing (morning and afternoon) is enough. Side effects are anorexia, insomnia, growth retardation, abdominal discomfort and bowel upset.

Opioid Analgesics

Opium A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule. It contains two types of alkaloids.

Phenanthrene derivatives (Nonanalgesic)
Morphine
Codeine
Thebaine

Benzoisoquinoline derivatives Nonanalgesic
Papaverine
Noscapine

MORPHINE
Morphine is the principal alkaloid in opium and is widely used till today. Therefore, it is described as prototype.

PHARMACOLOGICAL ACTIONS

1. **CNS** Morphine has site specific depressant and stimulant actions in the CNS by interacting primarily with the μ opioid receptor (for which it has the highest affinity), as a full agonist. The depressant actions are:

(a) *Analgesia:* Morphine is a strong analgesic. Though dull, poorly localized visceral pain is relieved better than sharply defined somatic pain; higher doses can mitigate even severe pain; degree of analgesia increasing with dose. It acts in the substantia gelatinosa of dorsal horn to inhibit release of excitatory transmitters (e.g. substance P) from primary afferents carrying pain impulses. Release of glutamate from primary pain afferents in the spinal cord and its postsynaptic action on dorsal horn neurones is inhibited by morphine. It also sends inhibitory impulses through descending pathways to the spinal cord. Several aminergic (5-HT, NA), GABAergic and other neuronal systems appear to be involved in the action of morphine.

(b) *Sedation* which is different from that produced by hypnotics is seen. Drowsiness and indifference to surroundings as well as to own body occurs without motor incoordination, ataxia or apparent excitement (contrast alcohol). Higher doses progressively induce sleep and then coma. Morphine has no anticonvulsant action, rather, fits may be precipitated.

(c) *Mood and subjective effects* These are prominent. Morphine has a calming effect; there is loss of apprehension, feeling of detachment, lack of initiative, limbs feel heavy and body warm, mental clouding and inability to concentrate occurs.

(d) *Respiratory centre* Morphine depresses respiratory centre in a dose dependent manner; rate and tidal volume are both decreased.

(e) *Cough centre* It is depressed by morphine, and is more sensitive than respiratory centre.

(f) *Temperature regulating centre* It is depressed; hypothermia occurs in cold surroundings.

(g) *Vasomotor centre* It is depressed at higher doses and contributes to the fall in BP.

(h) *CTZ:* Nausea and vomiting occur as side effects, especially if stomach is full and the patient stands or moves about. Thus, morphine appears to sensitize the CTZ to

vestibular and other impulses. Larger doses depress vomiting centre directly: emetics should not be tried in morphine poisoning.

(i) *Vagal centre* It is stimulated→ bradycardia is the usual response to morphine

2. **Neuro-endocrine** Hypothalamic activation by afferent collaterals is dampened. Hypothalamic influence on pituitary is reduced. As a result FSH, LH, ACTH levels are lowered, while prolactin and GH levels are raised. The sex hormone and cortisol levels are lowered.

3. **CVS** Morphine causes vasodilatation due to:
(a) histamine release.
(b) depression of vasomotor centre.
(c) direct action decreasing tone of blood vessels

4. **GIT** The enteric plexus neurones and g.i. mucosa are rich in opioid receptors. Action directly on intestines and in the CNS increases tone and segmentation but decreases propulsive movements. Spasm of pyloric, ileocaecal and anal sphincters. Decrease in all gastrointestinal secretions due to reduction in movement of water and electrolytes from mucosa to the lumen. This is mainly a peripheral action through opioid receptors on enteric plexus neurones, but also a central action.

5. **Smooth Muscles:**
Urinary bladder Tone of both detrusor and sphincter muscle is increased → urinary urgency and difficulty in micturition. Contractions of ureter are also increased.
Uterus The action is clinically insignificant, may slightly prolong labour.
Bronchi Morphine releases histamine, which can cause bronchoconstriction.

PHARMACOKINETICS

- The oral absorption of morphine is unreliable because of high and variable first pass metabolism; oral bioavailability is 1/6th to 1/4th of parenterally administered drug.
- About 30% is bound to plasma proteins.
- Distribution is wide; concentration in liver, spleen and kidney is higher than that in plasma. Only a small fraction enters brain rather slowly. Morphine freely crosses placenta and can affect the foetus more than the mother.
- It is primarily metabolized in liver by glucuronide conjugation. Morphine-6-glucuronide is an active metabolite which accumulates during chronic dosing and contributes to analgesia, despite its restricted passage across blood-brain barrier. Another metabolite morphine-3-glucuronide has neuroexcitatory property.
- Plasma t½ of morphine averages 2–3 hours. Effect of a parenteral dose lasts 4–6 hours. Elimination is almost complete in 24 hours and morphine is noncumulative.

Adverse effects:

- Sedation, mental clouding, lethargy and other subjective effects which may even be dysphoric in some subjects.
- Vomiting is occasional in recumbent patient; constipation is common and distressing.
- Respiratory depression, blurring of vision, urinary retention are other side effects.

- Allergic reactions manifesting as urticaria, swelling of lips occur infrequently. Anaphylactoid reaction is rare.

Acute morphine poisoning It may be accidental, suicidal or seen in drug abusers. In the nontolerant adult, 50 mg of morphine i.m. produces serious toxicity. The human lethal dose is estimated to be about 250 mg.. Stupor or coma, flaccidity, shallow and occasional breathing, cyanosis, pinpoint pupil, fall in BP and shock; convulsions may be seen in few, pulmonary edema occurs at terminal stages, death is due to respiratory failure.
Treatment: consists of respiratory support (positive pressure respiration also opposes pulmonary edema formation) and maintenance of BP (i.v. fluids, vasoconstrictors). Gastric lavage should be done with pot. permanganate to remove unabsorbed drug. Lavage is indicated even when morphine has been injected. Being a basic drug it is partitioned to the acid gastric juice, ionizes there and does not diffuse back into blood.
Specific antidote**:** Naloxone 0.4–0.8 mg i.v. repeated every 2–3 min till respiration picks up, is the specific antagonist of choice because it acts rapidly, does not have any agonistic action and does not *per se* depress respiration. Due to short duration of action, naloxone should be repeated every 1–4 hours, according to the response.

CLASSIFICATION OF OPIOIDS

1. *Natural opium alkaloids:* Morphine, Codeine

2. *Semisynthetic opiates*: Diacetylmorphine (Heroin), Pholcodeine, Ethylmorphine.

3. *Synthetic opioids:* Pethidine (Meperidine), Fentanyl, Methadone, Dextropropoxyphene, Tramadol.

Codeine It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine. It is less potent than morphine (1/10th as analgesic), also less efficacious; is a partial agonist at opioid receptor with a low ceiling effect. The degree of analgesia is comparable to aspirin (60 mg codeine ~ 600 mg aspirin); can relieve mild to moderate pain only.
However, codeine is more selective cough suppressant (1/3rd as potent as morphine); subanalgesic doses (10–30 mg) suppress cough.
Codeine has very low affinity for opioid receptors. The analgesic action has been ascribed to morphine generated by its demethylation by CYP2D6. Codeine fails to produce analgesia in subjects with polymorphic CYP2D6 who cannot demethylate codeine. However, receptors involved in the antitussive action appear to be distinct, because they bind codeine as well as morphine.
Codeine has good activity by the oral route (oral: parenteral ratio 1:2). A single oral dose acts for 4–6 hours. Constipation is a prominent side effect when it is used as analgesic. Codeine has been used to control diarrhoea.
Other side effects are milder. The abuse liability is low. Though codeine phosphate is water soluble and can be injected, parenteral preparation is not available.

Heroin (Diamorphine, Diacetylmorphine)
It is about 3 times more potent than morphine; more lipid soluble, therefore enters the brain more rapidly, but duration of action is similar. It is considered to be more euphorient (especially

on i.v. injection) and highly addicting. Because of its high potency, it has been favoured in illicit drug trafficking. The sedative, emetic and hypotensive actions are said to be less prominent. However, it has no outstanding therapeutic advantage over morphine and has been banned in most countries except U.K.

Pethidine (Meperidine)
Pethidine was synthesized as an atropine substitute in 1939, and has some actions like it. Though chemically unrelated to morphine, it interacts with □□opioid receptors and its actions are blocked by naloxone. Important differences in comparison to morphine are:
1. Dose to dose 1/10th in analgesic potency; however, analgesic efficacy approaches near to morphine and is greater than codeine.
2. It does not effectively suppress cough.
3. Spasmodic action on smooth muscles is less marked—miosis, constipation and urinary retention are less prominent.
4. It is equally sedative and euphoriant, has similar abuse potential. The degree of respiratory depression seen at equianalgesic doses is equivalent to that with morphine.
5. Tachycardia (due to antimuscarinic action) occurs instead of bradycardia.
6. It causes less histamine release and is safer in asthmatics.
7. It has local anaesthetic action: corneal anaesthesia is seen after systemic doses.

It is well absorbed, oral: parenteral activity ratio is higher (1/3 to 1/2). Pethidine is nearly completely metabolized in liver. The plasma t½ of pethidine is 2–3 hours. Acidification of urine increases excretion of unchanged pethidine.

USES:

As analgesic Opioid analgesics are indicated in severe pain of any type. However, they only provide symptomatic relief without affecting the cause. Morphine (or one of its parenteral congeners) is indicated especially in traumatic, visceral, ischaemic (myocardial infarction), postoperative, burn, cancer pain, renal colic and the like. Opioids, especially pethidine, have been extensively used for obstetric analgesia, but one must be prepared to deal with the foetal and maternal complications. Transdermal fentanyl is a suitable option for chronic cancer and other terminal illness pain.

Acute left ventricular failure: Morphine injected i.v. affords dramatic relief by—
(a) Reducing preload on heart due to vasodilatation and peripheral pooling of blood.
(b) Tending to shift blood from pulmonary to systemic circuit; relieves pulmonary congestion and edema.
(c) Allays air hunger and dyspnoea by depressing respiratory centre.
(d) Cuts down sympathetic stimulation by calming the patient, thereby reduces cardiac work.

Preanaesthetic medication Morphine and pethidine are used in few selected patients

Balanced anaesthesia and surgical analgesia Fentanyl, morphine, pethidine, alfentanil or sufentanil are an important component of anaesthetic techniques

Relief of anxiety and apprehension
Especially in myocardial infarction, internal bleeding (haematemesis, threatened abortion, etc.) morphine or pethidine have been employed. They may prevent worsening of the condition by suppressing reflex over-activity.

Cough Codeine or its substitutes are widely used for suppressing dry, irritating cough.

Diarrhoea The constipating action of codeine has been used to check diarrhoea and to increase the consistency of stools in colostomy. Loperamide and diphenoxylate are synthetic opioids used exclusively as anti-diarrhoeal.