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 ($\cdot$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 accumbens 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.
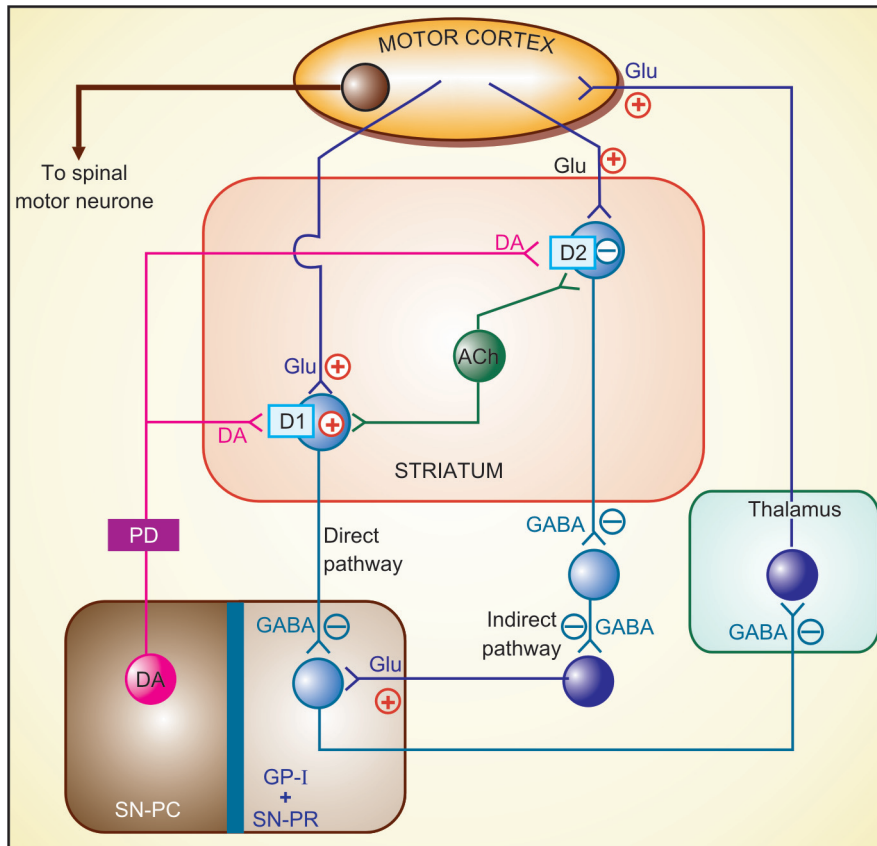
Fig. 31.1: Simplified scheme of side loop circuits in the basal ganglia that provide modulatory input to the motor cortex. The striatal GABAergic neurones receive side-loop excitatory glutamatergic (Glu) input from the motor cortex and modulatory dopaminergic (DA) projections from the substantia nigra 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
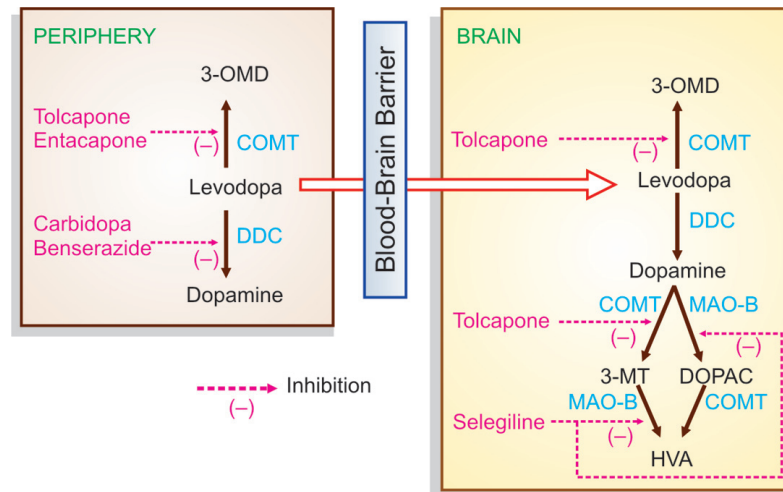
Fig. 31.2: Metabolic pathways of levodopa in the periphery and the brain.
3-OMD—3-O-methyldopa; COMT—Catechol-O-methyl transferase; MAO—monoamine oxidase; 3-MT—
3-methoxytyramine; DOPAC—3,4 dihydroxy phenylacetic acid; HVA—Homovanillic acid (3-methoxy-
4-hydroxy phenylacetic acid), DDC—Dopa decarboxylase

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 contra-indicated 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 unpredic-table 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, metoclo-pramide 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 degra-dation 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 anticho-linergic 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.

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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 ⎫ may even be more
2. Behavioural abnormalities ⎬ 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	Levodopa
		(per tab/cap)
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

CHAPTER 31

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)

Chapter 32 Drugs Used in Mental Illness: Antipsychotic and Antimanic 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. The trend has turned from custodial care towards restoring the individual patient to his place in the community. 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. Meprobamate (1954) aroused the hope that anxiety could be tackled without producing marked sedation. This goal has been realised more completely by the development of *Chlordiazepoxide* (1957) and other *benzodiazepines* in the 1960s. *Buspirone* is a significant later addition.

Little attention was paid to Cade's report in 1949 that *Lithium* could be used for excitement and mania: its effective use started in the 1960s and now it has a unique place in psychiatry. Interestingly some antiepileptics like carbamazepine, valproate and lamotrigine as well as some atypical antipsychotics, etc. have shown promise in mania and bipolar disorders.

Psychiatric diagnostic categories are often imprecise. The criteria adopted overlap in individual patients. Nevertheless, broad divisions have to be made, primarily on the basis of predominant manifestations, to guide the use of drugs. It is important to make an attempt to characterise the primary abnormality, because specific drugs are now available for most categories. Principal types are:

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.
A common form of mood disorder is *bipolar disorder* with cyclically alternating manic and depressive phases. The relapsing mood disorder may also be *unipolar* (mania or depression) with waxing and waning course.

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 ritual-like 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 dispro-portionate.

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

(f) *Hysterical*   Dramatic symptoms resembling serious physical illness, but situational, and always in the presence of others; the patient does not feign but actually undergoes the symptoms, though the basis is only psychic and not physical.

Pathophysiology of mental illness is not clear, though some ideas have been formed, e.g. dopaminergic overactivity in the limbic system may be involved in schizophrenia and mania, while monoaminergic (NA, 5-HT) deficit may underlie depression. Treatment is empirical, symptom oriented and not disease specific. However, it is highly effective in many situations. Depending on the primary use, the psychotropic drugs may be grouped into:

1. *Antipsychotic* (neuroleptic, ataractic, major tranquillizer) useful in all types of functional psychosis, especially schizophrenia.

(The term 'Neuroleptic' is applied to chlorpromazine/haloperidol-like conventional antipsychotic drugs which have potent D2 receptor blocking activity and produce psychic indifference, emotional quietening with extrapyramidal symptoms, but without causing ataxia or cognitive impairment.)

2. *Antimanic* (mood stabiliser) used to control mania and to break into cyclic affective disorders.

3. *Antidepressants*   used for minor as well as major depressive illness, phobic states, obsessive-compulsive behaviour, and certain anxiety disorders.

4. *Antianxiety* (anxiolytic-sedative, minor tran-quillizer) used for anxiety and phobic states.

5. *Psychotomimetic* (psychedelic, psycho-dysleptic, hallucinogen). They are seldom used therapeutically, but produce psychosis-like states. Majority of them are drugs of abuse, e.g. cannabis, LSD.

Tranquillizer   It is an old term meaning "a drug which reduces mental tension and produces calmness without inducing sleep or depressing mental faculties." This term was used to describe the effects of reserpine or chlorpromazine. However, it has been interpreted differently by different people; some extend it to cover both chlorpromazine-like and antianxiety drugs, others feel that it should be restricted to the antianxiety drugs only. Their division into *major* and *minor* tranquillizers is not justified, because the 'minor tranquillizers' (diazepam-like drugs) are not less important drugs: they are more frequently prescribed and carry higher abuse liability than the 'major tranquillizers' (chlorpromazine-like drugs). The term tranquillizer is, therefore, best avoided.

ANTIPSYCHOTIC DRUGS (Neuroleptics)

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*

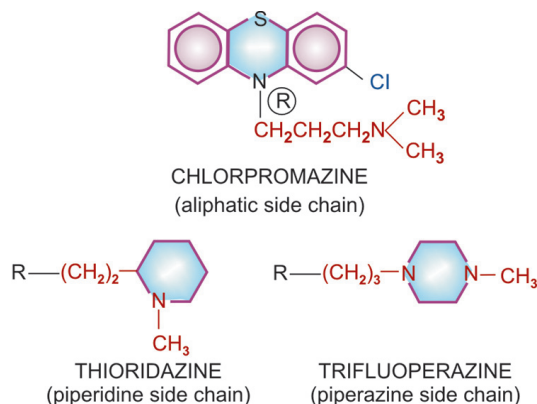| Clozapine	Aripiprazole
Risperidone	Ziprasidone
Olanzapine	Amisulpiride
Quetiapine	Zotepine

CHLORPROMAZINE
(aliphatic side chain)

THIORIDAZINE
(piperidine side chain)

TRIFLUOPERAZINE
(piperazine side chain)

Many more drugs have been marketed in other countries but do not deserve special mention. Pharmacology of chlorpromazine (CPZ) is described as prototype; others only as they differ from it. Their comparative features are presented in Table 32.1.

PHARMACOLOGICAL ACTIONS

1. CNS Effects differ in normal and psychotic individuals.

In normal individuals CPZ produces indifference to surroundings, paucity of thought, psycho-motor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep from which the subject is easily arousable. Spontaneous movements are minimized but slurring of speech, ataxia or motor incoordination does not occur. This has been referred to as the 'neuroleptic syndrome' and is quite different from the sedative action of barbiturates and other similar drugs. 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'*. The effects are perceived as 'neutral' or 'unpleasant' by most normal individuals.

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.

Performance and intelligence are relatively unaffected, but vigilance is impaired. Extrapyramidal motor disturbances (*see* adverse effects) are intimately linked to the antipsychotic effect, but are more prominent in the high potency compounds and least in thioridazine, clozapine and other atypical antipsychotics. A predominance of lower frequency waves occurs in the EEG and arousal response is dampened. However, no consistent effect on sleep architecture has been noted. The disturbed sleep pattern in a psychotic is normalized.

Chlorpromazine lowers seizure threshold and can precipitate fits in untreated epileptics. The piperazine side chain compounds have a lower propensity for this action. Temperature control is knocked off at relatively higher doses rendering the individual poikilothermic. Body temperature falls if surroundings are cold. The medullary respiratory and other vital centres are not affected, except at very high doses. It is very difficult to produce coma with overdose of these drugs. Neuroleptics, except thioridazine, have potent antiemetic action exerted through the CTZ. However, they are ineffective in motion sickness.

In animals, neuroleptics selectively inhibit *'conditioned avoidance response'* (CAR) without blocking the unconditioned response to a noxious stimulus. This action has shown good correlation with the antipsychotic potency of different compounds. However, these two effects (CAR in animals and antipsychotic effect in humans) may be based on different facets of action. In animals, a state of rigidity and immobility (catalepsy) is produced which resembles the bradykinesia seen clinically.

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. This contention is

strengthened by the observation that drugs which increase DA activity (amphetamines, levodopa, bromocriptine) induce or exacerbate schizophrenia. 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. The delayed onset of these effects may be explained by initial adaptive increase in the firing of DA neurones and DA turnover, which gradually subsides and a state of persistent inactivation supervenes as the drug is continued, corresponding to the emergence of the therapeutic effect as well as the extrapyramidal side effects.

However, DA overactivity in the limbic area is not the only abnormality in schizophrenia. Other monoaminergic (5-HT) as well as amino-acid (glutamate) neurotransmitter systems may also be affected. Moreover, DA activity in prefrontal cortex is actually diminished in schizophrenia. Only the positive symptoms (hallucinations, aggression, etc.) appear to be closely linked to DA overactivity in mesolimbic areas, but not the negative symptoms (apathy, cognitive deficit, withdrawal, etc). Not withstanding the above, reduction of dopaminergic neurotransmission is the major mechanism of antipsychotic action.

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-HT_2 and α_1 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. Positron emission tomography (PET) studies of D2 and other receptor occupancy in brains of antipsychotic drug treated patients have strengthened this concept.

Dopaminergic blockade in pituitary lactotropes causes hyperprolactinemia, while that in CTZ is responsible for the antiemetic action.

2. ANS Neuroleptics have varying degrees of α adrenergic blocking activity which may be graded as:

CPZ = triflupromazine = thioridazine > clozapine > fluphenazine > haloperidol > trifluoperazine > pimozide, i.e. more potent compounds have lesser α blocking activity.

Anticholinergic property of neuroleptics is weak and may be graded as:

thioridazine > CPZ > triflupromazine > trifluoperazine = haloperidol.

The phenothiazines have weak H_1-antihistaminic and anti-5-HT actions as well.

3. 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.

4. 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 (Q-T prolongation and suppression of T wave). CPZ exerts some antiarrhythmic action, probably due to membrane stabilization. Arrhythmia may occur in overdose, especially with thioridazine.

5. 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. Spinal reflexes are not affected.

6. 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, but amenorrhoea and infertility occur only occasionally. 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 in children or to be beneficial in acromegaly. 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, as well as elevate serum triglycerides. This is often associated with weight gain, which may be a causative factor along with accentuation of insulin resistance.

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.

Neuroleptics are hedonically (pertaining to pleasure) bland drugs, lack reinforcing effect so that chronic recipients do not exhibit drug seeking behaviour. Physical dependence is probably absent, though some manifestations on discontinuation have been considered withdrawal phenomena.

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. Volume of distribution, therefore, is large (20 L/kg). It is metabolized in liver, mainly by CYP 2D6 into a number of metabolites.

The acute effects of a single dose of CPZ generally last for 6–8 hours. The elimination t½ is variable, but mostly is in the range of 18–30 hours. The drug cumulates on repeated administration, and it is possible to give the total maintenance dose once a day. Some metabolites are probably active. The intensity of antipsychotic action is poorly correlated with plasma concentration. Nevertheless, therapeutic effect may be seen at 30–200 ng/ml. The metabolites are excreted in urine and bile for months after discontinuing the drug.

The broad features of pharmacokinetics of other neuroleptics are similar.

DISTINCTIVE FEATURES OF NEUROLEPTICS

Antipsychotic drugs differ in potency and in their propensity to produce different effects. This is summarized in a comparative manner in Table 32.1.

1. *Triflupromazine* An aliphatic side chain phenothiazine, somewhat more potent than CPZ. Used mainly as antiemetic; it frequently produces acute muscle dystonias in children; especially when injected.

2. *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.

3. *Trifluoperazine, fluphenazine* 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.

Fluphenazine decanoate can be given as a depot i.m. injection every 2–4 weeks in uncooperative psychotics.

ANATENSOL DECANOATE, PROLINATE 25 mg/ml inj.

TABLE 32.1   **Comparative properties and preparations of antipsychotic drugs**

Drug	Antipsychotic dose (mg/day)	Relative activity				Preparations
		Extrapyramidal	Sedative	Hypotensive	Antiemetic	
1. Chlorpromazine	100–800	++	+++	++	++	CHLORPROMAZINE, LARGACTIL 10, 25, 50, 100 mg tab. 5 mg/5 ml (pediatric) & 25 mg/5 ml (adult) Syr., 50 mg/2 ml inj.
2. Triflupromazine	50–200	+++±	+++	++	+++	SIQUIL 10 mg tab; 10 mg/ml inj.
3. Thioridazine	100–400	+	+++	+++	±	MELLERIL 25, 100 mg tab, THIORIL 10, 25, 50, 100 mg tab.
4. Trifluoperazine	2–20	+++	+	+	+++	TRINICALM 1, 5 mg tab, NEOCALM 5, 10 mg tab
5. Fluphenazine	1–10	+++	+	+	+++	ANATENSOL 1 mg tab, 0.5 mg/ml elixir.
6. Haloperidol	2–20	+++	+	+	+++	SERENACE 1.5, 5, 10, 20 mg tab; 2 mg/ml liq, 5 mg/ml inj., SENORM 1.5, 5, 10 mg tab, 5 mg/ml inj., HALOPIDOL 2, 5, 10, 20 mg tab, 2 mg/ml liq, 10 mg/ml drops
7. Trifluperidol	1–8	+++	+	+	+++	TRIPERIDOL 0.5 mg tab, 2.5 mg/ml inj.
8. Flupenthixol	3–15	+++	+	+	+	FLUANXOL 0.5, 1, 3 mg tab; FLUANXOL DEPOT 20 mg/ml in 1 and 2 ml amp.
9. Pimozide	2–6	+++	+	+	+	ORAP, NEURAP, PIMODAC 2, 4 mg tab.
10. Loxapine	20–50	++	+	++	+	LOXAPAC 10, 25, 50 mg caps, 25 mg/ 5 ml liquid
11. Clozapine	100–300	–	+++	+++	–	LOZAPIN, SIZOPIN, SKIZORIL 25, 100 mg tabs
12. Risperidone	2–8	++	++	++	–	RESPIDON, SIZODON, RISPERDAL 1, 2, 3, 4 mg tabs.
13. Olanzapine	2.5–20	+	+	++	–	OLACE, OLANDUS 2.5, 5, 7.5, 10 mg tabs, OLZAP 5, 10 mg tab
14. Quetiapine	50–400	±	+++	++	–	QUEL, SOCALM, SEROQUIN 25, 100, 200 mg tabs
15. Aripiprazole	5–30	±	±	±	–	ARIPRA, ARILAN, BILIEF 10, 15 mg tabs; ARIVE 10, 15, 20, 30 mg tabs.
16. Ziprasidone	40–160	+	+	+	–	AZONA, ZIPSYDON 20, 40, 80 mg tabs.

4. *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 and Gilles de la Tourette's syndrome. It is metabolised by CYP3A4 and 2D6 both. Elimination t½ averages 24 hours.

5. *Trifluperidol* It is similar to but slightly more potent than haloperidol.

6. *Penfluridol* An exceptionally long acting neuroleptic, recommended for chronic schizophrenia, affective withdrawal and social maladjustment.

Dose: 20–60 mg oral (max 120 mg) once weekly; SEMAP, FLUMAP, PENFLUR 20 mg tab.

7. *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.

8. *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. It has been particularly used in Gilles de la Tourett's syndrome and in ticks.

9. *Loxapine* A dibenzoxazepine having CPZ like DA blocking and antipsychotic activity. The actions are quick and short lasting (t½ 8 hr). No clear cut advantage over other antipsychotics has emerged.

ATYPICAL (Second generation) ANTIPSYCHOTICS

These are newer (second generation) antipsychotics that have weak D2 blocking but potent 5-HT$_2$ antagonistic activity. Extrapyramidal side effects are minimal, and they tend to improve the impaired cognitive function in psychotics.

1. *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 and clozapine is the most effective drug in refractory schizophrenia, i.e. patients not responding to typical neuroleptics may respond to it. The differing pharmacological profile may be due to its relative selectivity for D4 receptors (which are sparse in basal ganglia) and additional 5-HT$_2$ as well as α adrenergic blockade. It is quite sedating, moderately potent anticholinergic, but paradoxically induces hypersalivation. Significant H$_1$ blocking property is present.

Clozapine is metabolized by CYP1A2, CYP2C19 and CYP3A4 into active and inactive metabolites with an average t½ of 12 hours. Its major limitation is higher incidence of agranulocytosis (0.8%) and other blood dyscrasias: weekly monitoring of leucocyte count is required. Metabolic complication like weight gain, hyperlipidemia and precipitation of diabetes is another major limilation. High dose can induce seizures even in nonepileptics. Other side effects are sedation, unstable BP, tachycardia and urinary incontinence. Few cases of myocarditis have been reported which start like flu but may progress to death.

Clozapine is used as a reserve drug in refractory schizophrenia.

2. *Risperidone* Another compound whose antipsychotic activity has been ascribed to a combination of D2 + 5-HT$_2$ receptor blockade. In addition it has high affinity for α$_1$, α$_2$ and H$_1$ receptors: blockade of these may contribute to efficacy as well as side effects like postural hypotension. However, BP can rise if it is used with a SSRI. Risperidone is more potent D2 blocker than clozapine; extrapyramidal side effects are less only at low doses (<6 mg/day). Prolactin levels rise disproportionately during risperidone therapy, but it is less epileptogenic than clozapine, though frequently causes agitation. Weight gain and incidence of new-onset

diabetes is less than with clozapine. Caution has been issued about increased risk of stroke in the elderly.

3. *Olanzapine*   This atypical antipsychotic; resembles clozapine in blocking multiple monoaminergic (D2, 5-HT$_2$, α_1, α_2) as well as muscarinic and H$_1$ receptors. Both positive and negative symptoms of schizophrenia tend to benefit. A broader spectrum of efficacy covering schizo-affective disorders has been demonstrated, and it is approved for use in mania.

Olanzapine is a potent antimuscarinic, produces dry mouth and constipation. Weaker D2 blockade results in few extrapyramidal side effects and little rise in prolactin levels, but is more epileptogenic than high potency phenothiazines. It causes weight gain and carries a higher risk of impairing glucose tolerance or worsening diabetes as well as elevating serum triglyceride. These metabolic complications have discouraged its use. Incidence of stroke may be increased in the elderly. Agranulocytosis has not been reported with olanzapine. It is metabolized by CYP1A2 and glucuronyl transferase. The t½ is 24–30 hours.

4. *Quetiapine*   This new short-acting (t½ 6 hours) atypical antipsychotic requires twice daily dosing. It blocks 5-HT$_{1A}$, 5-HT$_2$, D2, α_1, α_2 and H$_1$ receptors in the brain, but D2 blocking activity is low: extrapyramidal and hyperprolactinaemic side effects are minimal. However, it is quite sedating (sleepiness is a common side effect), and major portion of daily dose is given at night. Postural hypotension can occur, especially during dose titration. Urinary retention/incontinence are reported in few patients. Weight gain and rise in blood sugar are moderate, and it causes some degree of QTc prolongation, risking arrhythmia only at high doses. Quetiapine has not been found to benefit negative symptoms of schizophrenia, but there is evidence of efficacy in acute mania as well as in bipolar depression, because of which it is frequently selected for maintenance therapy. It is metabolized mainly by CYP3A4; can interact with macrolides, antifungals, anticonvulsants, etc.

5. *Aripiprazole*   This atypical antipsychotic is unique in being a partial agonist at D2 and 5-HT$_{1A}$ receptor, but antagonist at 5-HT$_2$ receptor. The high affinity but low intrinsic activity of aripiprazole for D2 receptor impedes dopaminergic transmission by occupying a large fraction of D2 receptors but activating them minimally. It is not sedating, may even cause insomnia. Extrapyramidal side effects, hyperprolactinaemia and hypotension are not significant. Little tendency to weight gain and rise in blood sugar has been noted. A moderate prolongation of Q-Tc interval occurs at higher doses. Frequent side effects are nausea, dyspepsia, constipation and light-headedness, but not antimuscarinic effects.

Aripiprazole is quite long-acting (t½ ~ 3 days); dose adjustments should be done after 2 weeks treatment. It is metabolized by CYP3A4 as well as CYP2D6; dose needs to be halved in patients receiving ketoconazole or quinidine, and doubled in those taking carbamazepine. Aripiprazole is indicated in schizophrenia as well as mania and bipolar illness. Efficacy is comparable to haloperidol.

6. *Ziprasidone*   Another atypical antipsychotic with combined D2 + 5-HT$_{2A/2C}$ + H$_1$ + α_1 blocking activity. Antagonistic action at 5-HT$_{1D}$ + agonistic activity at 5-HT$_{1A}$ receptors along with moderately potent inhibition of 5-HT and NA reuptake indicates some anxiolytic and antidepressant property as well. Like other atypical antipsychotics, ziprasidone has low propensity to cause extrapyramidal side effects or hyperprolactinaemia. It is mildly sedating, causes modest hypotension and little weight gain or blood sugar elevation. Nausea and vomiting are the common side effects but it lacks antimuscarinic effects. More importantly, a dose-related prolongation of Q-T interval occurs imparting potential to induce serious cardiac arrhythmias, especially in the presence of predisposing factors/drugs.

The t½ of ziprasidone is ~8 hours; needs twice daily dosing. In comparative trials, its

efficacy in schizophrenia has been rated equivalent to haloperidol. It is also indicated in mania.

7. *Amisulpiride* This congener of *Sulpiride* (typical antipsychotic) is categorized with the atypical antipsychotics because it produces few extrapyramidal side effects and improves many negative symptoms of schizophrenia as well. However, it retains high affinity for D2 (and D3) receptors and has low-affinity for 5-HT_2 receptors. Hyperpolactinemia occurs similar to typical neuroleptics. Antidepressant property has also been noted. Amisulpiride is not a sedative. Rather, insomnia, anxiety and agitation are common side effects. Risk of weight gain and metabolic complications is lower, but Q-T prolongation has been noted, especially in predisposed elderly patients. Amisulpiride is absorbed orally and mainly excreted unchanged in urine with a t½ of 12 hours.

Dose: 50–300 mg/day in 2 doses for schizophrenia with predominant negative symptoms. Also for acute psychosis 200–400 mg BD.

SULPITAC, AMIPRIDE, ZONAPRIDE 50, 100, 200 mg tabs.

8. *Zotepine* Another atypical antipsychotic with dopamine D2+D1, 5-HT_2, α_1 adrenergic and histamine H_1 receptor blocking activities. It also inhibits NA reuptake. Like other drugs of the class, it benefits both positive and negative symptoms of schizophrenia, but is rated less effective than clozapine. Extrapyramidal side effects are less prominent than with typical neuroleptics, but more than clozapine. Hyperprolactinemia is noted. Zotepine lowers seizure threshold and incidence of seizures is increased at high doses. Weight gain, hyperglycaemia and dyslipidemia are likely as with clozapine. Common side effects are weakness, headache, and postural hypotension.

Absorption after oral ingestion is good but first pass metabolism is extensive. The elimination t½ is 14 hours. Zotepine is available in India for use in schizophrenia, but does not offer any specific advantage. It has been discontinued in the U.K.

Dose: Initially 25 mg TDS; increase upto 100 mg TDS.
ZOLEPTIL, NIPOLEPT 25, 50 mg tabs.

ADVERSE EFFECTS

Antipsychotics are very safe drugs in single or infrequent doses: deaths from overdose are almost unknown. However, side effects are common and often limit their use.

I. Based on pharmacological actions (dose related)

1. CNS Drowsiness, lethargy, mental confusion; more with low potency typical antipsychotics and some atypical ones like quetiapine and clozapine. Tolerance to sedative effect may develop. Other side effects are increased appetite and weight gain (not with haloperidol); aggravation of seizures in epileptics; even nonepileptics may develop seizures with high doses of some antipsychotics like clozapine and occasionally olanzapine. However high potency, phenothiazines, risperidone, quetiapine aripiprazole and ziprasidone have little effect on seizure threshold.

2. CVS Postural hypotension, palpitation, inhibition of ejaculation (especially with thioridazine) are due to α adrenergic blockade; more common with low potency phenothiazines. Q-T prolongation and cardiac arrhythmias are a risk of overdose with thioridazine, pimozide and ziprasidone. Excess cardiovascular mortality has been attributed to antipsychotic drug therapy.

3. Anticholinergic Dry mouth, blurring of vision, constipation, urinary hesitancy in elderly males (thioridazine has the highest propensity); absent in high potency agents. Dry mouth and constipation is common with olanzapine. Some like clozapine induce hypersalivation despite anticholinergic property, probably due to central action.

4. Endocrine Hyperprolactinemia (due to D2 blockade) is common with typical neuroleptics and risperidone. This can lower Gn levels, but amenorrhoea, infertility, galactorrhoea and gynaecomastia occur infrequently after prolonged treatment. The atypical antipsychotics, except risperidone, do not appreciably raise prolactin levels.

5. Metabolic effects Elevation of blood sugar and triglyceride levels as a consequence of chronic therapy with certain antipsychotics is a major concern now. Low potency pheno-thiazines (CPZ, thioridazine) and some atypical antipsychotics, particularly olanzapine and clozapine have high risk of precipitating diabetes or worsening it. High potency drugs like triflu-perazine, fluphenazine, haloperidol and atypical antipsychotics like risperidone, aripiprazole and ziprasidone have low/no risk. The mechanism of this effect is not clear; may be due to weight gain and/or accentuation of insulin resistance.

Raised triglyceride level is another conse-quence of insulin resistance. Cardiovascular mortality among schizophrenics is higher; increased use of atypical antipsychotics may be a contributory factor.

6. Extrapyramidal disturbances These are the major dose-limiting side effects; more prominent with high potency drugs like fluphenazine, haloperidol, pimozide, etc., least with thioridazine, clozapine, and all other atypical antipsychotics, except higher dose of risperidone. The extrapyramidal effects may be categorized into:

(a) *Parkinsonism* with typical manifesta-tions—rigidity, tremor, hypokinesia, mask like facies, shuffling gait; appears between 1–4 weeks of therapy and persists unless dose is reduced. If that is not possible, one of the anticholinergic antiparkinsonian drugs may be given concurren-tly. Changing the antipsychotic, especially to an atypical agent, may help. Though quite effective, routine combination of the anticholinergic from the start of therapy in all cases is not justified, because they tend to worsen memory and impair intellect, in addition to dry mouth and urinary retention. Amantadine is an alternative. Levodopa is not effective since D2 receptors are blocked.

A rare form of extrapyramidal side effect is perioral tremors 'rabbit syndrome' that generally occurs after a few years of therapy. It often responds to central anticholinergic drugs.

(b) *Acute muscular dystonias* Bizarre muscle spasms, mostly involving linguo-facial muscles —grimacing, tongue thrusting, torticollis, locked jaw; occurs within a few hours of a single dose or at the most in the first week of therapy. It is more common in children below 10 years and in girls, particularly after parenteral adminis-tration; overall incidence is 2%. It lasts for one to few hours and then resolves spontaneously. One of the central anticholinergics, prometha-zine or hydroxyzine injected i.m. clears the reaction within 10–15 min.

(c) *Akathisia* Restlessness, feeling of discom-fort, apparent agitation manifested as a compel-ling desire to move about, but without anxiety, is seen in some patients between 1–8 weeks of therapy: upto 20% incidence. It may be mistaken for exacerbation of psychosis. The mechanism of this complication is not understood; no specific antidote is available. A central anti-cholinergic may reduce the intensity in some cases; but a benzodiazepine like clonazepam or diazepam is the first choice treatment of the motor restlessness. Propranolol is more effective; may be given to non-responsive cases. Most patients respond to reduction in dose of the neuroleptic or changeover to an atypical antipsychotic like quetiapine.

(d) *Malignant neuroleptic syndrome* It occurs rarely with high doses of potent agents. The patient develops marked rigidity, immobility, tremor, hyperthermia, semiconsciousness, fluctuating BP and heart rate; myoglobin may be present in blood. The syndrome lasts 5–10 days after drug withdrawal and may be fatal. The neuroleptic must be stopped promptly and symptomatic treatment instituted. Though, antidopaminergic action of the neuroleptic may be involved in the causation of this syndrome; anticholinergics are of no help. Intravenous dantrolene may benefit. Bromocriptine in large doses has been found useful.

(e) *Tardive dyskinesia* It occurs late in therapy, sometimes even after withdrawal of the

neuroleptic: manifests as purposeless involuntary facial and limb movements like constant chewing, pouting, puffing of cheeks, lip licking, choreoathetoid movements. It is more common in elderly women, and is a manifestation of progressive neuronal degeneration along with supersensitivity to DA. It is accentuated by anticholinergics and temporarily suppressed by high doses of the neuroleptic (this should not be tried except in exceptional circumstances). An incidence of 10–20% has been reported after long term treatment. This reaction is uncommon with clozapine and all other atypical antipsychotics. The dyskinesia may subside months or years after withdrawal of therapy, or may be lifelong. There is no satisfactory solution of the problem.

7. Miscellaneous   *Weight gain* often occurs due to long-term antipsychotic therapy, sugar and lipids may tend to rise. *Blue pigmentation* of exposed skin, *corneal and lenticular opacities, retinal degeneration* (more with thioridazine) occur rarely after long-term use of high doses of phenothiazines.

II. Hypersensitivity reactions   These are not dose related.

1. *Cholestatic jaundice* with portal infiltration; 2–4% incidence; occurs between 2–4 weeks of starting therapy. It calls for withdrawal of the drug; resolves slowly. More common with low potency phenothiazines; rare with haloperidol.

2. *Skin rashes, urticaria, contact dermatitis, photosensitivity* (more with CPZ).

3. *Agranulocytosis* is rare; more common with clozapine.

4. *Myocarditis*   Few cases have occurred with clozapine.

INTERACTIONS

1. Neuroleptics potentiate all CNS depressants —hypnotics, anxiolytics, alcohol, opioids and antihistaminics. Overdose symptoms may occur.
2. Neuroleptics block the actions of levodopa and direct DA agonists in parkinsonism.

3. Antihypertensive action of clonidine and methyldopa is reduced, probably due to central α_2 adrenergic blockade.
4. Phenothiazines and others are poor enzyme inducers—no significant pharmacokinetic interactions occur. Enzyme inducers (barbiturates, anticonvulsants) can reduce blood levels of neuroleptics.

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. They control positive symptoms (hallucinations, delusions, disorganized thought, restlessness, insomnia, anxiety, fighting, aggression) better than negative symptoms (apathy, loss of insight and volition, affective flattening, poverty of speech, social withdrawal). They also tend to restore affective and motor disturbances and help upto 90% patients to lead a near normal life in the society. However, intellect and cognition are little benefited. Some patients do not respond, and virtually none responds completely. They are only symptomatic treatment, do not remove the cause of illness; long-term (even life-long) treatment may be required. Judgement, memory and orientation are only marginally improved. Patients with recent onset of illness and acute exacerbations respond better. The goal of therapy is to relieve symptoms and functionally rehabilitate the patient.

   Choice of drug is largely empirical, guided by the presenting symptoms (it is the target symptoms which respond rather than the illness as a whole), associated features and mood state, and on the type of side effect that is more acceptable in a particular patient. Individual patients differ in their response to different antipsychotics; there is no way to predict which patient will respond better to which drug. The following may help drug selection:
• Agitated, combative and violent—haloperidol, quetiapine, CPZ, thioridazine.

CHAPTER 32

- Withdrawn and apathetic—trifluoperazine, fluphenazine, aripiprazole, ziprasidone.
- Patient with mainly negative symptoms and resistant cases—clozapine is the most effective; alternatives are olanzapine, risperidone, aripiprazole, ziprasidone.
- Patient with mood elevation, hypomania—haloperidol, fluphenazine, quetiapine, olanzapine.
- If extrapyramidal side effects must be avoided—thioridazine, clozapine or any other atypical antipsychotic.
- Elderly patients who are more prone to sedation, mental confusion and hypotension—a high potency phenothiazine, haloperidol or aripiprazole.

Currently, the newer atypical antipsychotics are more commonly prescribed. Though, there is no convincing evidence of higher efficacy, they produce fewer side effects and neurological complications. Moreover, they may improve the negative symptoms as well. They are preferable for long-term use in chronic schizophrenia due to lower risk of tardive dyskinesia. Of the older, typical neuroleptics, the high potency agents are preferred over the low potency ones.

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. The antipsychotic may be continued for months or may be withdrawn gradually after 1–3 weeks when lithium has taken effect. Now, oral therapy with one of the atypical antipsychotics olanzapine/risperidone/aripiprazole/quetiapine is mostly used to avoid extrapyramidal side effects, especially for cases not requiring urgent control.

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. One of the potent drugs is preferred to avoid mental confusion, hypotension and precipitation of seizures. Moreover, low potency drugs (CPZ, thioridazine) have significant antimuscarinic property which may worsen delirium and dementia. Haloperidol, risperidone, ripiprazole or ziprasidone are mostly selected.

General comments   The dose of antipsychotic drugs has to be individualized by titration with the symptoms and kept at minimum. In chronic schizophrenia maximal therapeutic effect is seen after 2–4 months therapy. However, injected neuroleptics control aggressive symptoms of acute schizophrenia over hours or a few days. Combination of two or more antipsychotics is not advantageous. However, a patient on maintenance therapy with a nonsedative drug may be given additional CPZ or haloperidol by i.m. injection to control exacerbations or violent behaviour.

In a depressed psychotic, a tricyclic/SSRI antidepressant may be combined with relatively lower dose of an antipsychotic. One of the atypical agents is mostly used because they are effective in bipolar disorder. Quetiapine is the preferred drug, because it is effective as monotherapy as well. Benzodiazepines may be added for brief periods in the beginning.

Low dose maintenance or intermittent regimens of antipsychotics have been tried in relapsing cases. Depot injections, e.g. fluphenazine/haloperidol decanoate given at 2–4 week intervals are preferable in many cases.

2. Anxiety   Antipsychotics have antianxiety action but should not be used for simple anxiety because of psychomotor slowing, emotional blunting, autonomic and extrapyramidal side effects. Benzodiazepines are preferable. However, low dose of quetiapine, risperidone or olanzepine have been found useful as adjuvants to SSRIs in generalized anxiety disorder. Patients having a psychotic basis for anxiety may be treated with a neuroleptic.

3. 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. Though effective in morning sickness, they should not be used for this condition. They are ineffective in motion sickness: probably because dopaminergic pathway through the CTZ is not involved. With the availability of 5-HT$_3$ antagonists and other antiemetics, use of neuroleptics for control of vomiting has declined.

4. Other uses

(a) *To potentiate hypnotics, analgesics and anaesthetics:* such use is rarely justified now.
(b) *Intractable hiccough* may respond to parenteral CPZ.
(c) *Tetanus* CPZ is an alternative drug to relieve skeletal muscle spasm.
(d) *Alcoholic hallucinosis, Huntington's disease and Gilles de la Tourette's syndrome* are rare indications.

ANTIMANIC AND MOOD STABILIZING DRUGS (Drugs for bipolar disorder)

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.

In the 1960s and 1970s the importance of maintaining a narrow range of serum lithium concentration was realized and unequivocal evidence of its clinical efficacy was obtained. Lithium is a drug of its own kind to suppress mania and to exert a prophylactic effect in bipolar (manic depressive) disorder at doses which have no overt CNS effects. Lithium is established as the standard antimanic and mood stabilizing drug. Over the past 2 decades, several anticonvulsants and atypical antipsychotics have emerged as alternatives to lithium with comparable efficacy.

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. However, relative to Na$^+$ and K$^+$ concentration, the concentration of Li$^+$ associated with therapeutic effect is very low.

(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 phosphatidyl-inositides, which are the source of IP$_3$ and DAG, is reduced (Fig. 32.1). 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. In support of this hypothesis, it has been recently demonstrated that valproate, which has Li$^+$ like effect in mania and bipolar disorder, also reduces intraneuronal
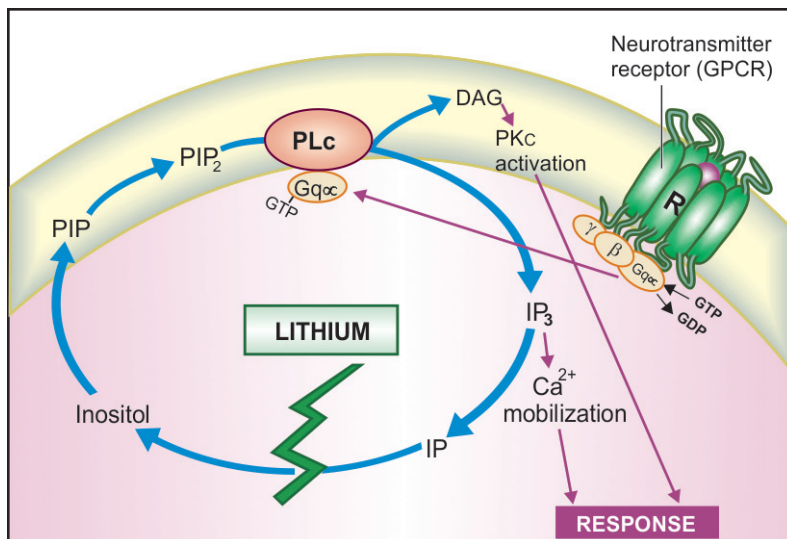
Fig. 32.1: Proposed mechanism of antimanic action of lithium
PIP—Phosphatidyl inositol phosphate; PIP_2—Phosphatidyl inositol bisphosphate;
IP_3—Inositol trisphosphate; IP—Inositol-1-phosphate; PLc—Phospholipase C;
DAG—Diacylglycerol; PKc—Protein Kinase C; Gq—Coupling Gq protein;
R—Neurotransmitter receptor

concentration of inositol in human brain by inhibiting *de novo* inositol synthesis.

Several other mechanisms involving elements of neuronal signalling like PKc, glutamate, arachidonate, etc. have also been proposed to explain lithium action.

2. *Other actions*   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. Majority of Li^+ treated patients remain in a state of compensated euthyroidism, but few get decompensated and become clinically hypothyroid.

Pharmacokinetics and control of therapy

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. Apparent volume of distribution at steady-state averages 0.8 L/kg.

Lithium is handled by the kidney in much the same way as Na^+. Nearly 80% of the filtered Li^+ is reabsorbed in the proximal convoluted tubule. When Na^+ is restricted, a larger fraction of filtered Na^+ is reabsorbed, so is Li^+. After a single dose of Li^+, its urinary excretion is rapid for 10–12 hours, followed by a much slower phase lasting several days. The t½ of the latter phase is 16–30 hours. Renal clearance of lithium is 1/5 of creatinine clearance. On repeated medication, steady-state plasma concentration is achieved in 5–7 days. Levels are higher in older patients and in those with renal insufficiency.

There is marked individual variation in the rate of lithium excretion. Thus, with the same daily dose, different individuals attain widely different plasma concentrations. However, in any

individual the clearance remains fairly constant over time. Since the margin of safety is narrow, monitoring of serum lithium concentration is essential for optimising therapy. Serum lithium level is measured 12 hours after the last dose to reflect the steady-state concentration; 0.5–0.8 mEq/L is considered optimum for maintenance therapy in bipolar disorder, while 0.8–1.1 mEq/L is required for episodes of acute mania. Toxicity symptoms occur frequently when serum levels exceed 1.5 mEq/L.

Peaks in plasma lithium level over and above the steady-state level occur after every dose. Divided daily dosing in 2–3 portions or SR tablet is needed to avoid high peaks, but this causes more polyuria. Lithium is excreted in sweat and saliva as well, and secreted in breast milk. Mothers on lithium should not breastfeed.

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. Overdose symptoms are regularly seen at plasma concentration above 2 mEq/L. In acute intoxication these symptoms progress to muscle twitchings, drowsiness, delirium, coma and convulsions. Vomiting, severe diarrhoea, albuminuria, hypotension and cardiac arrhythmias are the other features.

Treatment It is symptomatic. There is no specific antidote. Osmotic diuretics and sod. bicarbonate infusion promote Li^+ excretion. Haemodialysis is indicated if serum levels are > 4 mEq/L.

5. On long-term use, some patients develop renal diabetes insipidus. Most patients gain some body weight. Goiter has been reported in about 4%. This is due to interference with release of thyroid hormone $\rightarrow$ fall in circulating T_3, T_4 levels $\rightarrow$ TSH secretion from pituitary $\rightarrow$ enlargement and stimulation of thyroid. Enough hormone is usually produced due to feedback stimulation so that patients remain euthyroid. However, few become hypothyroid. Lithium induced goiter and hypothyroidism does not warrant discontinuation of therapy; can be easily managed by thyroid hormone supplementation.
6. Lithium is contraindicated during pregnancy: foetal goiter and other congenital abnormalities, especially cardiac, can occur; the newborn is often hypotonic.
7. At therapeutic levels, Li^+ can cause reduction of T-wave amplitude. At higher levels, SA node and A-V conduction may be depressed, but arrhythmias are infrequent. Lithium is contra-indicated in sick sinus syndrome.

Lithium can cause dermatitis and worsen acne.

Interactions

1. Diuretics (thiazide, furosemide) by causing Na^+ loss promote proximal tubular reabsorption of Na^+ as well as Li^+ $\rightarrow$ plasma levels of lithium rise. Potassium sparing diuretics cause milder Li^+ retention.
2. Tetracyclines, NSAIDs and ACE inhibitors can also cause lithium retention.
3. Lithium reduces pressor response to NA.
4. Lithium tends to enhance insulin/sulfonylurea induced hypoglycaemia.
5. Succinylcholine and pancuronium have produced prolonged paralysis in lithium treated patients.
6. Neuroleptics, including haloperidol, have been frequently used along with lithium without problem. However, sometimes, the combination of haloperidol and lithium produces marked tremor and rigidity. The neuroleptic action appears to be potentiated by lithium.

Use

Lithium is used as its carbonate salt because this is less hygroscopic and less gastric irritant than LiCl. It is converted into chloride in the stomach. Lithium citrate is used in syrup formulations.

LICAB, LITHOSUN 300 mg tab, 400 mg SR tab.

It is generally started at 600 mg/day and gradually increased to yield therapeutic plasma levels; mostly 600–1200 mg/day is required.

1. *Acute mania*   (inappropriate cheerfullness or irritability, motor restlessness, high energy level, nonstop talking, flight of ideas, little need for sleep and progressive loss of contact with reality; sometimes violent behaviour). Though lithium is effective in controlling acute mania, response is slow and control of plasma levels is difficult during the acute phase. Most psychiatrists now prefer to use an atypical antipsychotic orally or by i.m. injection, with or without a potent BZD like clonazepam/lorazepam, and start lithium after the episode is under control. Maintenance lithium therapy is generally given for 6–12 months to prevent recurrences.

2. *Prophylaxis in bipolar disorder*   Lithium has proven efficacy in bipolar disorder: is gradually introduced and maintained at plasma concentration between 0.5–0.8 mEq/L. Such treatment lengthens the interval between cycles of mood swings: episodes of mania as well as depression are attenuated, if not totally prevented. Bipolar disorder is the most common and definite indication of lithium. Risks and benefits of prolonged lithium therapy are to be weighed in individual cases. This depends on the type of bipolar disorder, i.e. *Type I* (mania episodes only or both manic and depressive phases), *Type II* (cycles of hypomania alternating with major depression) or unipolar depression; cycle length and comorbid conditions, concurrent medications, etc. Patients have been maintained on lithium therapy for over a decade. Most cases relapse when lithium is discontinued. Withdrawal, when attempted should be gradual over months.

Recurrent *unipolar depression* also responds to lithium therapy. Combination of antidepressant + lithium is often used initially, and lithium alone is continued in the maintenance phase.

3.   Lithium is being sporadically used in many other *recurrent neuropsychiatric illness*, cluster headache and as adjuvant to antidepressants in resistant nonbipolar *major depression*.

4.   Cancer chemotherapy induced *leukopenia* and *agranulocytosis*: Lithium may hasten the recovery of leukocyte count.

5.   *Inappropriate ADH secretion syndrome*: Lithium tends to counteract water retention, but is not dependable.

ALTERNATIVES TO LITHIUM

Approximately 30% patients of mania and bipolar disorder (especially rapidly cycling cases) show incomplete or poor response to lithium. Many do not tolerate it, or are at special risk of toxicity. In the last two decades, several anticonvulsants and atypical antipsychotics have been extensively evaluated as alternatives to lithium. Strong evidence of efficacy of some of these in different phases of the disorder now exists. In view of the limitations and problems in the use of lithium, use of valproate and some atypical antipsychotics has overtaken that of lithium.

1. *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. Patients with rapid cycling pattern may particularly benefit from valproate therapy. A combination of lithium and valproate may succeed in cases resistant to monotherapy with either drug. Valproate has a favourable tolerability profile, and now its use as prophylactic in bipolar disorder has exceeded that of lithium. Combination of valproate with an atypical antipsychotic has high efficacy in acute mania. *Divalproex*, a compound of valproate, is more commonly used due to better gastric tolerance. Dosage guidelines are the same as for epilepsy.

2. *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. Carbamazepine is less effective than lithium or valproate in acute mania. Moreover, acute mania requires rapidly acting drug, while effective doses of carbamazepine have to be gradually built up. Initiation of therapy with high doses needed for efficacy produce neurotoxicity and are poorly tolerated. Compared to lithium and valproate, efficacy of carbamazepine for long-term prophylaxis of bipolar disorder and suicides is less well established. Nevertheless, it is a valuable alternative/adjunct to lithium. The dose and effective plasma concentration range is the same as for treatment of epilepsy.

3. *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. The tolerability profile of lamotrigine is favourable.

4. *Atypical antipsychotics* Lately, several studies have testified to the efficacy of atypical antipsychotics in acute mania. Olanzapine, risperidone, aripiprazole, quetiapine, with or without a BZD, are now the first line drugs for control of acute mania, except cases requiring urgent parenteral therapy, for which the older neuroleptics are still the most effective. Aripiprazole has recently emerged as the favoured drug for treatment of mania in bipolar I disorder, both as monotherapy as well as adjuvant to lithium or valproate. Maintenance therapy with aripiprazole prevents mania, but not depressive episodes. Lack of metabolic effects, favours its long-term use.

Olanzapine is also approved for maintenance therapy of bipolar disorder. Though both manic and depressive phases are suppressed, it is not considered suitable for long-term therapy due to higher risk of weight gain, hyperglycaemia, etc. Strong evidence of efficacy of quetiapine has emerged in bipolar depression. Combination of an atypical antipsychotic with valproate or lithium has demonstrated high efficacy in acute phases as well as for maintenance therapy of bipolar disorder.

HALLUCINOGENS
(Psychotomimetics, Psychedelics, Psychodysleptics, Psychotogens)

These are drugs which alter mood, behaviour, thought and perception in a manner similar to that seen in psychosis. Many natural products having hallucinogenic property have been discovered and used by man since prehistoric times. A number of synthetic compounds have also been produced. The important ones are briefly described below.

INDOLE AMINES

1. Lysergic acid diethylamide (LSD)
Synthesized by Hofmann (1938) who was working on chemistry of ergot alkaloids, and himself experienced its hallucinogenic effect. It is the most potent psychedelic, 25–50 µg produces all the effects. In addition to the mental effects, it produces pronounced central sympathetic stimulation. Its action appears to involve serotonergic neuronal systems in brain.

2. Lysergic acid amide A close relative of LSD but 10 times less potent; found in morning glory (*Ipomoea violace*) seeds.

3. Psilocybin Found in a Mexican mushroom *Psilocybe mexicana*; it has been used by Red Indian tribals during religious rituals.

4. Harmine It is present in a vine *Banisteriopsis caapi*, found in the Amazon region. The Brazilian natives have used it as a snuff.

5. Bufotenin Isolated from skin of a toad (*Bufo marinus*). It is also found in 'Cohaba Snuff' and in the mushroom *Amanita muscaria*.

The above are all *Indolealkylamines* related chemically to 5-HT. A number of other synthetic derivatives like Dimethyltryptamine (DMT) are also hallucinogenic.

PHENYLALKYL AMINES

Mescaline　From Mexican 'Peyote cactus' *Lophophora williamsi*. It is a low potency hallucinogen used by natives during rituals. It is a phenylalkylamine but does not have marked sympathomimetic effects.

Ecstasy　Methylene dioxy methamphetamine (MDMA, or tenamphetamine) is an amphetamine-like synthetic compound with stimulant and hallucinogenic properties, that has been abused as a recreational and euphoriant drug, especially by college students under the name *'Ecstasy'*. Fear of neurotoxicity has reduced its popularity.

Yaba　This is a combination of methamphetamine with another stimulant methylhexanamine or caffeine. Popular as a 'street drug' in Thailand and Myanmar, it has spread to many countries including India, as a 'party drug' among the youth. Users claim it to be an aphrodisiac and produces a 'high'. The risk of neurotoxicity is similar to amphetamine.

Other synthetic phenylalkylamines with hallucinogenic property are—Dimethoxymethyl amphetamine (DOM) and Methylene dioxyamphetamine (MDA). High doses and repeated use of amphetamine can also cause psychosis.

ARYLCYCLOHEXYL AMINES

Phencyclidine　It is an anticholinergic, which activates σ receptors in brain causing disorientation, distortion of body image, hallucinations and an anaesthetic like state. Ketamine is a closely related compound with lower hallucinogenic potential and is used in anaesthesia. Mixed with drinks, ketamine has been abused as a 'rape drug', because of its fast and strong depressant-amnesic action.

CANNABINOIDS

$^9\Delta$ Tetrahydrocannabinol ($^9\Delta$ THC)　It is the active principle of *Cannabis indica* (Marijuana), which has been the most popular recreational and ritualistic intoxicant used for millennia. Its use has spread worldwide. The following are the various forms in which it is used.

Bhang　the dried leaves—is generally taken by oral route after grinding and making a paste. It acts slowly.

Ganja　the dried female inflorescence—is more potent and is smoked: effects are produced almost instantaneously.

Charas　is the dried resinous extract from the flowering tops and leaves—most potent and is usually smoked along with tobacco; also called 'hashish'.

Cannabis is the drug of abuse having the lowest acute toxicity. Even habitual use is not clearly associated with neurotoxicity or damage to any organ system. Though, personality and psychiatric problems are more common among cannabis users, it is not definite whether such traits led to cannabis use or cannabis caused them. Young abusers may exhibit 'amotivational syndrome', i.e. loss of interest in work or self-improvement activities.

Considerable insight has been obtained recently in cannabinoid pharmacology. Since 1990 two *cannabinoid receptors CB1* (in CNS) and *CB2* (in peripheral tissues) have been identified and cloned. A host of endogenous ligands for the cannabinoid receptors have also been isolated. *Anandamide,* the ethanolamide of arachidonic acid is the principal endocannabinoid synthesized in the brain. The physiological function subserved by central and peripheral cannabinoid system is not clearly known. Endocannabinoids are released by macrophages during haemorrhagic shock and cause fall in BP. However, all actions of cannabis are not mimicked by anandamide.

Cannabis produces potent analgesic, antiemetic, anti-inflammatory and many other pharmacological actions. The crude herb, its active constituents and some synthetic analogues have been tried in a variety of conditions and many potential clinical applications are proposed.

- To ameliorate muscle spasm and pain in multiple sclerosis, and certain dystonias.
- Cancer chemotherapy induced vomiting. The synthetic cannabinoids nabilone and dronabinol ($^9\Delta$ THC) are licenced for this use.
- As a neuronal protective after head injury and cerebral ischaemia.
- To relieve anxiety and migraine.
- To reduce i.o.t. in glaucoma.
- As appetite stimulant.
- As bronchodilator in asthma.

However, the hallucinogenic and psychomotor effects are a limitation; nonhallucinogenic congeners are being investigated.

The hallucinogens, particularly marijuana, produce a dream-like state with disorientation, loss of contact with reality, field of vision may appear to sway and objects distorted like images in a curved mirror, faces may appear grotesque. On closing the eyes an unending series of colourful, very realistic and fantastic images appear to surge; time sense is altered, music appears tangible. Ability to concentrate is impaired, one can read but does not know what he is reading; however, ataxia is not prominent. Many subjects feel relaxed and supremely happy, may laugh uncontrollably (experience a 'high') or may

become sad and weep. With higher doses—panic reactions and sinking sensation are common.

Some degree of tolerance occurs, but *reverse tolerance* is not unusual.

Psychological dependence on hallucinogens may be mild (occasional trips) to marked (compulsive abuse), but physical dependence does not occur. All are drugs of abuse.

Hallucinogens have been rarely used in psychiatry to facilitate conversation and for opening up the inner self in case of withdrawn patients.

☞ PROBLEM DIRECTED STUDY

32.1 A 25-year-male was diagnosed as a case of schizophrenia on the basis of disturbed thinking process, inappropriate talking and behaviour, restlessness, bursts of temper, anxiety, poor self-care, disturbed sleep, delusional beliefs and occasional auditory hallucinations. He was treated with tab. haloperidol 5 mg once daily at bed time. The dose was increased to 7.5 mg daily in the 2nd week and to 10 mg daily in the 3rd week. His symptoms gradually subsided and he appeared more calm and organized. However, in the 5th week his family members reported that his restlessness has reappeared, he keeps pacing around in the room, but is not aggressive or combative. On questioning the patient admitted an uncontrollable urge to move around and that he feels uncomfortable in remaining still. He is not worried or anxious, but has difficulty in falling asleep.

(a) What could be the reason for the motor restlessness? Should the dose of haloperidol be increased or decreased, or should it be changed to another antipsychotic drug?

(b) Should any other drug be given to relieve the condition?

(see Appendix-1 for solution)

Chapter 33 Drugs Used in Mental Illness: Antidepressant and Antianxiety Drugs

Major depression and mania are two extremes of *affective disorders* which refer to a pathological change in mood state. *Major 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, etc. It may be a *unipolar* or a *bipolar disorder* in which cycles of mood swings from mania to depression occur over time. The mood change may have a psychotic basis with delusional thinking or occur in isolation and induce anxiety. On the other hand, pathological anxiety may lead to depression. Anxiety and depression are the leading psychiatric disorders now.

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. Over the past three decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines, and on pre/post-junctional aminergic/cholinergic receptors have become available so that a cogent classification is difficult. The following working classification may be adopted.

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,
    Clomipramine
  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, Atomoxetine

Many other drugs like Protriptyline, Maprotiline, Nafazodone, etc. are marketed in other countries.

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.

Dopamine is degraded equally by both isoenzymes.

Their distribution also differs. Peripheral adrenergic nerve endings, intestinal mucosa and human placenta contain predominantly MAO-A, while MAO-B predominates in certain areas (mainly serotonergic) of brain and in platelets. Liver contains both isoenzymes.

Two hydrazine drugs—*isoniazid* and *iproniazid* were used for tuberculosis in 1951; the latter was especially found to cause disproportionate elevation of mood. Its capacity to inhibit degradation of biogenic amines was soon discovered and was believed to be responsible for the mood elevating action. Its less hepatotoxic congeners like *phenelzine* and

isocarboxazid and some nonhydrazine MAO inhibitors (related to amphetamine) like *tranylcypromine* were used as antidepressants in the 1960s. They inhibited MAO irreversibly and were nonselective for the two isoforms. Because of high toxicity and interactions with foods and other drugs, they have become obsolete.

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. The drugs themselves stay in the body for relatively short periods, but their effects last for 2–3 weeks after discontinuation: they are 'hit and run' drugs. Return of MAO activity depends on synthesis of fresh enzyme; tissue monoamine levels remain elevated long after the drug has been largely eliminated.

Interactions   These drugs inhibit a number of other enzymes as well, and interact with many food constituents and drugs.

(i) *Cheese reaction*   Certain varieties of cheese, beer, wines, pickled meat and fish, yeast extract contain large quantities of tyramine, dopa, etc. In MAO inhibited patients these indirectly acting sympathomimetic amines escape degradation in the intestinal wall and liver → reaching into systemic circulation they displace and release large amounts of NA from transmitter loaded adrenergic nerve endings → *hypertensive crisis*, cerebrovascular accidents. When such a reaction occurs, it can be treated by i.v. injection of a rapidly acting α blocker, e.g. phentolamine. Prazosin or chlorpromazine are alternatives.

(ii) *Cold and cough remedies*   They contain ephedrine or other sympathomimetics—hypertensive reaction can occur.

(iii) *Reserpine, guanethidine, tricyclic antidepressants*   Excitement, rise in BP and body temperature can occur when these drugs are given to a patient on MAO inhibitors. This is due to their initial NA releasing or uptake blocking action.

(iv) *Levodopa*   Excitement and hypertension occur due to increase in biological t½ of DA and NA that are produced from levodopa.

(v) *Antiparkinsonian anticholinergics*   Hallucinations and symptoms similar to those of atropine poisoning occur.

(vi) *Barbiturates, alcohol, opioids, antihistamines*   Action of these drugs is intensified and prolonged. Respiration may fail.

(vii) *Pethidine*   High fever, sweating, excitation, delirium, convulsions and severe respiratory depression have occurred. The most accepted explanation is—
MAO inhibitors retard hydrolysis of pethidine but not its demethylation. Thus, excess of *norpethidine* (normally a minor metabolite—*see* p. 475) is produced which has excitatory actions.

Reversible inhibitors of MAO-A (RIMAs)

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. Clinical trials have shown moclobemide to be an efficacious antidepressant, comparable to TCAs, except in severe cases. It lacks the anticholinergic, sedative, cognitive, psychomotor and cardiovascular adverse effects of typical TCAs and is safer in overdose. This makes it a particularly good option in elderly patients and in those with heart disease.
*Dose:* 150 mg BD–TDS (max 600 mg/day)
RIMAREX, TRIMA 150, 300 mg tabs.

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.

Moclobemide has emerged as a well tolerated alternative to TCAs for mild to moderate depression and for social phobia.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

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

$CH_2CH_2CH_2N{<}^{CH_3}_{CH_3}$

IMIPRAMINE
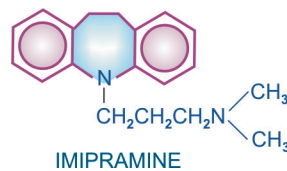
reuptake into neurones. A large number of congeners were soon added and are called *tricyclic antidepressants (TCAs)*.

These older compounds, in addition to uptake blockade have direct effects on adrenergic, cholinergic and histaminergic receptors, and are referred to as '*first generation antidepressants*,' a group which also includes MAOIs.

The subsequently produced *second generation antidepressants* have more selective action on amine uptake; are either *Selective serotonin reuptake inhibitors (SSRIs)*, or *Serotonin and noradrenaline reuptake inhibitors (SNRIs)*, with no direct action on cholinergic/adrenergic/histaminergic receptors, or have some *atypical features*. They have a limited spectrum of action resulting in fewer side effects.

PHARMACOLOGICAL ACTIONS

The most prominent action of TCAs is their ability to inhibit norepinephrine transporter (NET) and serotonin transporter (SERT) located at neuronal/platelet membrane at low and therapeutically attained concentrations.

The TCAs inhibit monoamine reuptake and interact with a variety of receptors *viz.* muscarinic, α adrenergic, histamine H_1, 5-HT_1, 5-HT_2 and occasionally dopamine D2. However, relative potencies at these sites differ among different compounds. The actions of imipramine are described as prototype.

1. 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. The EEG effects of low doses are similar to hypnotics but high doses cause desynchronization. Sedative property varies among different compounds (*see* Table 33.1). The more sedative ones are suitable for depressed patients showing anxiety and agitation. The less sedative or stimulant ones are better for withdrawn and retarded patients.

The TCAs lower seizure threshold and produce convulsions in overdose. Clomipramine and bupropion have the highest seizure precipitating potential. Amitriptyline and imipramine depress respiration in overdose only.

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 (*see* classification above).

Most of the compounds do not inhibit DA uptake, except bupropion. Moreover, amphetamine and cocaine (which are not antidepressants but CNS stimulants) are strong inhibitors of DA uptake. However, it has been proposed that TCAs indirectly facilitate dopaminergic transmission in forebrain that may add to the mood elevating action.

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.

Certain findings indicate that uptake blockade is not directly responsible for the antidepressant action, e.g.

- Uptake blockade occurs quickly but anti-depressant action develops after weeks
- Mianserin is antidepressant but has no uptake blocking action.

Initially the presynaptic α_2 and $5\text{-}HT_1$ autoreceptors are activated by the increased amount of NA/5-HT in the synaptic cleft resulting in decreased firing of locus coeruleus (noradrenergic) and raphe (serotonergic) neurones. After, long-term administration, antidepressants desensitise the presynaptic α_2, $5\text{-}HT_{1A}$, $5\text{-}HT_{1D}$ autoreceptors and induce other adaptive changes in the number and sensitivity of pre and post synaptic NA and/or 5-HT receptors as well as in amine turnover of brain, the net effect of which is enhanced nor-adrenergic and serotonergic transmission. Thus, uptake blockade appears to initiate a series of time-dependent changes that culminate in antidepressant effect.

None of the TCAs, except amoxapine, block DA receptors or possess antipsychotic activity.

2. ANS Most TCAs are potent anticholinergics—cause dry mouth, blurring of vision, constipation and urinary hesitancy as side effect. The anticholinergic potency is graded in Table 33.1.

They potentiate exogenous and endogenous NA by blocking uptake, but also have weak α_1 adrenergic blocking action. Some, e.g. amitriptyline, doxepin, trimipramine have slight H_1 antihistaminic action as well.

3. 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 α_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. The NA potentiating + ACh blocking actions along with direct myocardial depression compound the proarrhythmic potential. Older

patients are more susceptible. The SSRIs, SNRIs and atypical antidepressants are safer in this regard.

Tolerance and dependence

Tolerance to the anticholinergic and hypotensive effects of imipramine-like drugs develops gradually, but antidepressant action is sustained.

Psychological dependence on these drugs is rare, because their acute effects are not pleasant.

There is some evidence of physical dependence occurring when high doses are used for long periods—malaise, chills, muscle pain may occur on discontinuation and have been considered withdrawal phenomena. Gradual withdrawal is recommended, but antidepressants do not carry abuse potential.

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 (~20 L/kg). They are extensively metabolized in liver; the major route for imipramine and amitriptyline is demethylation whereby active metabolites—desipramine and nortriptyline respectively are formed. Both these metabolites predominantly block NA reuptake. Few other TCAs also produce active metabolites. Inactivation occurs by oxidation and glucuronide conjugation. Various CYP isoenzymes like CYP2D6, CYP3A4, CYP1A2 and others metabolise tricylic and related antidepressants. Metabolites are excreted in urine over 1–2 weeks. The plasma t½ of amitriptyline, imipramine and doxepin range between 16–24 hours. The t½ is longer for some of their active metabolites. Because of relatively long t½s, once daily dosing (at bed time) is practicable in the maintenance phase.

An unusual *therapeutic window* phenomenon has been observed, i.e. optimal antidepressant effect is exerted at a narrow band of plasma concentrations (between 50–200 ng/ml of imipramine, amitriptyline, nortriptyline). Both

TABLE 33.1   Comparative properties and preparations of tricyclic and related antidepressants

Drug	Sedation	Anti-muscarinic	Hypotension	Cardiac arrhythmia	Seizure precipitation	Daily dose (mg)	Preparations
Tricyclic antidepressants (TCAs)							
1. Imipramine	+	++	++	+++	++	50–200	DEPSONIL, ANTIDEP 25 mg tab, 75 mg SR cap.
2. Amitriptyline	+++	+++	+++	+++	++	50–200	AMLINE, SAROTENA, TRYPTOMER, 10,25,75 mg tabs.
3. Trimipramine	+++	+++	++	+++	++	50–150	SURMONTIL 10, 25 mg tab.
4. Doxepin	+++	++	++	+++	++	50–150	SPECTRA, DOXIN, DOXETAR 10, 25, 75 mg tab/cap.
5. Clomipramine	++	+++	++	+++	+++	50–150	CLOFRANIL, 10, 25, 50 mg tab, 75 mg SR tab. CLONIL, ANAFRANIL 10, 25 mg tab.
6. Dothiepin (Dosulpin)	++	++	++	++	++	50–150	PROTHIADEN, DOTHIN 25, 75 mg tab.
7. Nortriptyline	+	++	+	++	+	50–150	SENSIVAL, PRIMOX 25 mg tab.
8. Amoxapine	+	+	++	++	++	100–300	DEMOLOX 50, 100 mg tab.
Selective serotonin reuptake inhibitors (SSRIs)							
1. Fluoxetine	±	—	—	—	±	20–40	FLUDAC 20 mg cap, 20 mg/5 ml susp. FLUNIL 10, 20 mg caps; FLUPAR, PRODAC 20 mg cap.
2. Fluvoxamine	±	—	—	—	—	50–200	FLUVOXIN 50, 100 mg tab.
3. Paroxetine	±	±	—	—	—	20–50	XET 10, 20, 30, 40 mg tabs.
4. Sertraline	±	—	—	—	—	50–150	SERENATA, SERLIN, SERTIL 50, 100 mg tabs.
5. Citalopram	—	—	—	—	—	20–40	CELICA 10, 20, 40 mg tabs.
6. Escitalopram	—	—	—	—	—	10–20	ESDEP, FELIZ-S 5, 10, 20 mg tabs.
Serotonin and noradrenaline reuptake inhibitors (SNRIs)							
1. Venlafaxine	—	—	—	±	—	75–150	VENLOR 25, 37.5, 75 mg tabs, VENIZ-XR 37.5, 75, 150 mg ER caps.
2. Duloxetine	—	—	—	—	—	30–80	DELOK, DULANE, DUZAC, 20, 30, 40 mg caps.
Atypical antidepressants							
1. Trazodone	+++	—	±	±	—	50–200	TRAZODAC 25, 50 mg tab, TRAZONIL, TRAZALON 25, 50, 100 mg tabs.
2. Mianserin	++	+	++	+	++	30–100	TETRADEP 10, 20, 30 mg tab, SERIDAC 10, 30 mg tab.
3. Bupropion	–,–	—	—	—	+++	150–300	SMOQUIT 150 mg tab.
4. Mirtazapine	+++	—	±	—	—	15–45	MIRT 15, 30, 45 mg tabs, MIRTAZ 15, 30 mg tab.

below and above this range, beneficial effects are suboptimal.

Wide variation in the plasma concentration attained by different individuals given the same dose has been noted. Thus, doses need to be individualized and titrated with the response, but plasma concentrations are not a reliable guide for adjusting the dose of TCAs.

ADVERSE EFFECTS

Side effects are common with TCAs because of which SSRIs, SNRIs and atypical anti-depressants have become the first line drugs.

1. Anticholinergic: dry mouth, bad taste, constipation, epigastric distress, urinary retention (especially in males with enlarged prostate), blurred vision, palpitation.
2. Sedation, mental confusion and weakness, especially with amitriptyline and more sedative congeners.
3. Increased appetite and weight gain is noted with most TCAs and trazodone, but not with SSRIs, SNRIs and bupropion.
4. Some patients receiving any antidepressant may abruptly 'switch over' to a dysphoric-agitated state or to mania. Most likely, these are cases of bipolar depression, the other pole being unmasked by the antidepressant. Patients receiving higher doses, especially of TCAs, are at greater risk than those receiving lower doses and SSRIs or bupropion.
5. Sweating (despite antimuscarinic action) and fine tremors are relatively common.
6. Seizure threshold is lowered—fits may be precipitated, especially in children. Bupropion, clomipramine, amoxapine have greater propensity, while desipramine, SSRIs and SNRIs are safer in this regard.
7. Postural hypotension, especially in older patients. It is less severe with desipramine-like drugs and insignificant with SSRIs/SNRIs.
8. Sexual distress: especially delay or interference with erection, ejaculation and occasionally with orgasm.

9. Cardiac arrhythmias, especially in patients with ischaemic heart disease. Arrhythmias may be responsible for sudden death in these patients. Amitriptyline and dosulpin are particularly dangerous in overdose; higher incidence of arrhythmia is reported with them.
10. Rashes and jaundice due to hypersensitivity are rare. Mianserin is more hepatotoxic.

Acute poisoning Poisoning with TCAs is frequent; usually self-attempted by the depressed patients, and may endanger life. Manifestations are:

Excitement, delirium and other anticholinergic symptoms as seen in atropine poisoning, fol-lowed by muscle spasms, convulsions and coma. Respiration is depressed, body temperature may fall, BP is low, tachycardia is prominent. ECG changes and ventricular arrhythmias are common.

Treatment is primarily supportive with gastric lavage, respiratory assistance, fluid infusion, maintenance of BP and body temperature. Aci-dosis must be corrected by bicarbonate infusion.

Diazepam may be injected i.v. to control convulsions and delirium. Most important is the treatment of cardiac arrhythmias, for which propra-nolol/lidocaine may be used. The class IA and IC antiarrhythmics and digoxin themselves depress cardiac conduction; are therefore contraindicated.

INTERACTIONS

1. TCAs potentiate directly acting *sympathomi-metic amines* (present in cold/asthma remedies). Adrenaline containing local anaesthetic should be avoided. However, TCAs attenuate the action of indirect sympathomi-metics (ephedrine, tyramine).
2. TCAs abolish the antihypertensive action of *guanethidine* and *clonidine* by preventing their transport into adrenergic neurones.
3. TCAs potentiate *CNS depressants*, including alcohol and antihistaminics.
4. *Phenytoin, phenylbutazone, aspirin and CPZ* can displace TCAs from protein binding sites and cause transient overdose symptoms.

5. *Phenobarbitone* competitively inhibits as well as induces imipramine metabolism. Carbamazepine and other enzyme inducers enhance metabolism of TCAs.

6. SSRIs inhibit metabolism of several drugs (*see* later) including TCAs—dangerous toxicity can occur if the two are given concurrently.

7. By their anticholinergic property, TCAs delay gastric emptying and retard their own as well as other drug's absorption. However, *digoxin* and *tetracyclines* may be more completely absorbed. When used together, the anticholinergic action of neuroleptics and TCAs may add up.

8. *MAO inhibitors*—dangerous hypertensive crisis with excitement and hallucinations has occurred when given with TCAs.

Amoxapine   This tetracyclic compound is unusual in that it blocks dopamine D2 receptors in addition to inhibiting NA reuptake. It is chemically related to the antipsychotic drug loxapine and has mixed antidepressant + neuroleptic properties—offers advantage for patients with psychotic depression. Risk of extrapyramidal side effects is also there. Seizures (including status epilepticus) occur in its overdose.

Reboxetine   This is a newer selective NA reuptake blocker with weak effect on 5-HT reuptake. Antimuscarinic and sedative actions are minimal. It appears to produce fewer side effects and may be safer in overdose than the older TCAs. Usual side effects are insomnia, palpitation, dry mouth, constipation, sexual distress and urinary symptoms.

Dose: 4 mg BD or 8 mg OD.
NAREBOX 4, 8 mg tab.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

The major limitations of TCAs (first generation antidepressants) are:

• Frequent anticholinergic, cardiovascular and neurological side effects.

• Relatively low safety margin. They are hazardous in overdose; fatalities are common.

• Lag time of 2–4 weeks before antidepressant action manifests.

• Significant number of patients respond incompletely and some do not respond.

To overcome these shortcomings, a large number of newer (second generation) antidepressants have been developed since 1980s. The most significant of these are the SSRIs and SNRIs which selectively inhibit membrane associated SERT or both SERT and NET. Though, some patients may not respond even to these drugs, the efficacy of second generation antidepressants is rated higher than older TCAs and RIMAs. Some patients not responding to one type of drug may respond to another type. More importantly the newer drugs have improved tolerability, both in therapeutic dose as well as in overdose. It has been claimed that certain drugs (bupropion, venlafaxine, mirtazapine) have faster onset of antidepressant action, but this has not been unequivocally established.

The relative safety and better acceptability of SSRIs has made them 1st line drugs in depression and allowed their extensive use in anxiety, phobias, OCD and related disorders. The SSRIs produce little or no sedation, do not interfere with cognitive and psychomotor function or produce anticholinergic side effects. They are devoid of α adrenergic blocking action—postural hypotension does not occur, making them suitable for elderly patients. They have practically no seizure precipitating propensity and do not inhibit cardiac conduction—overdose arrhythmias are not a problem. Prominent side effects are gastrointestinal; all SSRIs frequently produce nausea (due to 5-HT$_3$ receptor stimulation), but tolerance develops over time. Loose motions are due to 5-HT uptake blockade in the gut and activation of 5-HT receptors on enteric plexus neurones. Weight gain is not a problem with SSRIs, but they more commonly interfere with ejaculation or orgasm. A new constellation of mild side effects, *viz.* nervousness, restlessness, insomnia, anorexia, dyskinesia and headache is associated with them, but patient acceptability is good. Increased incidence of

epistaxis and ecchymosis has been reported, probably due to impairment of platelet function. Gastric blood loss due to NSAIDs may be increased by SSRIs.

The SSRIs inhibit drug metabolizing iso-enzymes CYP2D6 and CYP3A4: elevate plasma levels of TCAs, haloperidol, clozapine, terfena-dine, astemizole, warfarin, β blockers, some BZDs and carbamazepine. '*Serotonin syndrome*' manifesting as agitation, restlessness, rigidity, hyperthermia, delirium, sweating, twitchings followed by convulsions can be precipitated when any serotonergic drug (e.g. MAOIs, tramadol, pethidine) is taken by a patient receiving SSRIs. Some degree of tolerance to antidepressant action of SSRIs has been noted in few patients after months of use. Discontinuation reaction consisting of paresthesias, bodyache, bowel upset, agitation and sleep disturbances occurs in some patients. However, risk of switching over to hypomania during treatment is less with SSRIs than with TCAs.

Some authorities now consider SSRIs to be more effective antidepressants than TCAs. However, some patients not responding to SSRIs may respond to TCAs. The converse is also true, and there is no way to predict which patient will respond to which drug. Because of freedom from psychomotor and cognitive impairment, SSRIs are preferred for prophylaxis of recurrent depression (should be combined with lithium/valproate). Metaanalysis of comparative trials has shown no significant difference in efficacy among individual SSRIs, but there are pharma-cokinetic differences and incidence of particular side effects differs somewhat.

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. It has been approved for use in children 7 years or older for depression and OCD on the basis of similar efficacy and side effect profile as in adults, but should be given to children only when psychotherapy fails. Agitation and dermatological

reactions are more frequent than other SSRIs. Because of slower onset of antidepressant effect, it is considered less suitable for patients needing rapid effect, but is more appropriate for poorly compliant patients. Its stimulant effect could worsen patients showing agitation.

Fluvoxamine   It is a shorter-acting SSRI with a t½ of 18 hours and no active metabolite, which has been specifically recommended for genera-lized anxiety disorder and OCD, rather than for depression. Relatively more nausea, dyspepsia, flatulence, nervousness and discontinuation reactions have been reported with fluvoxamine.

Paroxetine   Another short acting SSRI (t½ 20 hours) which does not produce active metabolite. A higher incidence of g.i. side effects, sexual distress, agitation and discontinuation reaction than with other SSRIs has been noted.

Sertraline   This SSRI has gained popularity, because in clinical trials fewer patients stopped sertraline due to side effects. Efficacy in juvenile depression has been demonstrated, and it is recommended for anxiety and post-traumatic stress disorder (PTSD) as well. Drug interactions due to inhibition of CYP isoenzymes are less likely to occur with this SSRI. Its plasma t½ is 26 hours and it produces a still longer-lasting active metabolite.

Citalopram   This SSRI shares with sertraline a lower propensity to cause drug interactions. Its t½ is 33 hours and no active metabolite is known. However, few deaths due to overdose of citalopram are on record, because of which it is to be avoided in patients likely to attempt suicide. Citalopram is the preferred SSRI for mood disorders in premenstrual syndrome.

Escitalopram   It is the active S(+) enantiomer of citalopram, effective at half the dose, with similar properties. Side effects are milder and safety is improved.

Dapoxetine   A SSRI which has been developed and is being promoted for delaying premature ejaculation, a property common to many SSRIs

and some TCAs. Dapoxetine acts rapidly and can be taken 1 hour before sexual intercourse. Combined with behavioural therapies, it has been found to help many sufferers. Side effects are nausea, vomiting, loose motions, headache, dizziness and occasionally insomnia.

Dose: 60 mg taken 1 hour before intercourse; older patients 30 mg.

SUSTINEX, DURALAST, KUTUB 30 mg, 60 mg tabs.

Other uses of SSRIs   The SSRIs are now 1st choice drugs for OCD, panic disorder, social phobia, eating disorders, premenstrual dysphoric disorder and PTSD. They are also being increasingly used for anxiety disorders, body dysmorphic disorder, compulsive buying, klepto-mania and premature ejaculation. Elevation of mood and increased work capacity has been reported in postmyocardial infarction and other chronic somatic illness patients. Thus, SSRIs are being used to improve outlook on life and to feel good, even in apparently nondepressed patients. Wisdom of such use though is questionable.

SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS (SNRIs)

1. 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. Trials have shown it to be as effective antidepressant as TCAs and may work in some resistant cases. A faster onset of action is claimed. 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.

2. Duloxetine   A newer SNRI similar to venla-faxine. It is neither sedative, nor anticholinergic, nor antihistaminic, nor α blocker. Side effects,

including g.i. and sexual problems are milder, but some agitation, insomnia and rise in BP can occur. Antidepressant efficacy is comparable to TCAs. Duloxetine is also indicated in panic attacks, diabetic neuropathic pain, fibromyalgia and stress urinary incontinence in women (because it increases urethral tone).

ATYPICAL ANTIDEPRESSANTS

1. Trazodone   It is the first atypical anti-depressant; less efficiently blocks 5-HT uptake and has prominent α adrenergic and weak $5-HT_2$ antagonistic actions. The latter may contribute to its antidepressant effect, which nevertheless is modest. It is sedative but not anticholinergic, causes bradycardia rather than tachycardia, does not interfere with intracardiac 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 and it has benefited cases of OCD. Inappropriate, prolonged and painful penile erection (priapism) occurs in few recipients resulting in impotence in a fraction of these. The α_1 adrenergic blocking property has been held responsible for this effect as well as for postural hypotension. In general, trazodone is infrequently used now in depression.

2. Mianserin   It is unique in not inhibiting either NA or 5-HT uptake; but blocks presynaptic α_2 receptors thereby increasing release and turnover of NA in brain which may be respon-sible for the antidepressant effect. Antagonistic action at $5-HT_2$, $5-HT_{1c}$ as well as H_1 receptors has also been shown. It is a sedative—relieves associated anxiety and suppresses panic attacks. While anticholinergic and cardiac side effects are less prominent, it has caused seizures in over-dose. However, overdose fatality is low. Reports of blood dyscrasias and liver dysfunction have restricted its use.

3. Mirtazapine   This antidepressant acts by a novel mechanism, *viz*. blocks α_2 auto- (on NA neurones) and hetero- (on 5-HT neurones) receptors enhancing both NA and 5-HT release. The augmented NA further increases firing of

serotonergic raphe neurones *via* α_1 receptors. Selective enhancement of antidepressive 5-HT_1 receptor action is achieved by concurrent blockade of 5-HT_2 and 5-HT_3 receptors which are held responsible for some of the adverse effects of high serotonergic tone. Accordingly, it has been labelled as "*noradrenergic and specific serotonergic antidepressant*" (NaSSA). It is a H_1 blocker and quite sedative, but not anticholinergic or antidopaminergic. Efficacy in mild as well as severe depression is reported to be comparable to TCAs, and given once daily at bed time, it is particularly suitable for those with insomnia. Increased appetite and weight gain is frequent. Sexual dysfunction is not a problem with mirtazapine.

4. Bupropion This inhibitor of DA and NA uptake has excitant rather than sedative property. It is metabolized into an amphetamine like compound which can cause presynaptic release of DA and NA. A sustained-release formulation is marketed as an aid to smoking cessation. In clinical trials it has been found to yield higher smoking abstinence and quitting rates than placebo and equivalent to nicotine replacement. Bupropion may be acting by augmenting the dopaminergic reward function. Better results are obtained when it is combined with nicotine patch. The nicotine withdrawal symptoms were less severe in bupropion recipients. However, long-term efficacy is not known, and it can cause insomnia, agitation, dry mouth and nausea, but not sexual side effects. Seizures occur in over dose and in predisposed patients due to lowering of seizure threshold. The dose of 150 mg BD should not be exceeded. It is contraindicated in eating disorders and in bipolar illness. Bupropion is infrequently used to treat depression; may be added to a SSRI.

5. Tianeptine This antidepressant is reported to increase rather than inhibit 5-HT uptake, and is neither sedative nor stimulant. It has shown efficacy in anxiodepressive states, particularly with psychosomatic symptoms, as well as in endogenous depression. Side effects are dry mouth, epigastric pain, flatulence, drowsiness/insomnia, tremor and bodyache.

Dose: 12.5 mg BD–TDS; STABLON 12.5 mg tab.

6. Amineptine Like tianeptine it enhances 5-HT uptake, and has antidepressant property. It produces anticholinergic side effects including tachycardia, confusion and delirium. Postural hypotension, conduction disturbances and arrhythmias can occur, especially in patients with heart disease.

Dose: 100 mg BD at breakfast and lunch. SURVECTOR 100 mg tab.

7. Atomoxetine It is unrelated to tricyclic antidepressants, but is a selective NA reuptake inhibitor. It is approved only for treatment of attention deficit hyperactivity disorder (ADHD), and is described in Ch. 35.

USES

1. *Endogenous (major) depression:* The aim is to relieve symptoms of depression and restore normal social behaviour. The tricyclic and related antidepressants are of proven value. Response takes at least 2–3 weeks to appear, full benefits take still longer. Choice of a particular drug for an individual patient depends on the secondary properties (sedative, anticholinergic, hypotensive, cardiotoxic, seizure precipitating, etc.) as described above. The SSRIs are currently used as first choice for their better tolerability, safety and may be higher efficacy as well. The SNRIs and newer atypical agents also offer some advantages. The only antidepressants clearly shown to be effective in juvenile depression are fluoxetine and sertraline. The TCAs are mostly used as alternatives in non-responsive cases or in those not tolerating the second generation antidepressants. Substituting a drug with a different pattern of aminergic action often succeedes in non-responsive cases. However, few patients fail any antidepressant. Moclobemide is a well tolerated option for mild to moderate depression, especially suited for elderly and cardiac patients. However, antidepressants are not the answer to every grief, loss, set back and other sad events that are part of life, but the less toxic and more patient-friendly SSRIs/SNRIs/atypical antidepressants are now more readily prescribed for depressive illness.

After a depressive episode has been controlled, continued treatment at maintenance doses (about 100 mg imipramine/day or equivalent) for months is recommended to prevent relapse. Discontinuation of the antidepressant may be attempted after 6–12 months. Long-term therapy may be needed in patients who tend to relapse. ECT may be given in the severely depressed, especially initially while the effect of antidepressants is developing, because no antidepressant has been clearly demonstrated to act fast enough to prevent suicide. The TCAs or SSRIs must be combined with lithium/valproate/lamotrigine for bipolar depression, and not used alone due to risk of switching over to mania.

Combination of one of the SSRIs with an atypical antipsychotic (such as olanzapine, aripiprazole or quetiapine) is also accepted as a treatment option for bipolar depression.

2. *Obsessive-compulsive and phobic states:* The SSRIs, particularly fluoxamine, are the drugs of choice due to better patient acceptability. TCAs, especially clomipramine, are highly effective in OCD and panic disorders: more than 25% improvement occurs in OCD rating scale and panic attacks are reduced in >75% patients. SSRIs and TCAs also reduce compulsive eating in *bulimia*, and help patients with *body dysmorphic disorder, compulsive buying* and *kleptomania,* though these habits may not completely die.

3. *Anxiety disorders:* Antidepressants, especially SSRIs, exert a delayed but sustained beneficial effect in many patients of *generalized anxiety disorder;* may be used along with a short course of BZDs to cover exacerbations. SSRIs have also proven helpful in *phobic disorders*, sustained treatment of *panic attacks* and in *post-traumatic stress disorder.*

4. *Neuropathic pain:* Amitriptyline and other TCAs afford considerable relief in diabetic and some other types of chronic pain. Amitriptyline reduces intensity of post-herpetic neuralgia in ~50% patients. The SSRIs are less effective in these conditions. Duloxetine, a SNRI, is now a first line drug for diabetic neuropathy, fibromyalgia, etc. Other drugs useful in neuropathic pain are pregabalin or gabapentin. Combination of duloxetine + pregabalin may work if monotherapy is not satisfactory.

5. *Attention deficit-hyperactivity disorder (ADHD) in children:* TCAs with less depressant properties like imipramine, nortriptyline and amoxapine are now first line drugs in this disorder, comparable in efficacy to amphetamine-like drugs, with the advantage of less fluctuating action and fewer behavioural side effects. Atomoxetine is a NA reuptake inhibitor unrelated to both TCAs as well as amphetamine, which is used specifically in ADHD.

6. *Premature ejaculation:* It refers to repeated occurrences of ejaculation before or shortly after penetration, or with minimal sexual stimulation. It is a very common sexual complaint, which is often interpreted as sexual weakness; can cause considerable distress and dissatisfaction in the patient as well as in his partner. Sometimes the subject has unreasonable expectations about the optimal/desirable length of intercourse.

Most SSRIs and some TCAs, especially clomipramine have the common property of delaying and in some cases inhibiting ejaculation (this itself can cause sexual distress). The primary treatment of premature ejaculation is counselling and behavioural therapy, but this can be supplemented by drugs. Dapoxetine is a SSRI which has been specifically introduced for this purpose. It acts rapidly; 60 mg taken 1 hour before intercourse has helped many subjects. Clomipramine 10–25 mg three times a day is a slow acting drug which needs to be taken regularly for maximum benefit. For on demand use, 25 mg may be taken 6 hours before sex.

7. *Enuresis:* In children above 5 years, imipramine 25 mg at bedtime is effective, but bed wetting may again start when the drug is stopped. Eldery subjects with bed wetting have also benefited.

8. *Migraine:* Amitriptyline has some prophylactic value, especially in patients with mixed headaches.

9. *Pruritus*: Some tricyclics have antipruritic action. Topical doxepin has been used to relieve itching in atopic dermatitis, lichen simplex, etc. NOCTADERM 5% cream.

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. Some degree of anxiety is a part of normal life. Treatment is needed when it is disproportionate to the situation and excessive. Some psychotics and depressed patients also exhibit pathological anxiety.

Cardiac neurosis (unfounded fear of heart disease—palpitation, functional precordial pain); g.i. neurosis (fixation on bowel movement, distention, eructation, reflux, acidity); social anxiety (fear of being observed and evaluated by others); obsessive-compulsive disorder (OCD), post-traumatic stress disorder and various forms of phobias are some specific types of anxiety disorders.

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. The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They:

1. Have no therapeutic effect to control thought disorder of schizophrenia.
2. Do not produce extrapyramidal side effects.
3. Have anticonvulsant property.
4. Produce physical dependence and carry abuse liability.
5. Do not selectively block conditioned avoidance response in animals.

CLASSIFICATION

1. *Benzodiazepines*   Diazepam
Chlordiazepoxide
Oxazepam
Lorazepam, Alprazolam

2. *Azapirones*   Buspirone, Gepirone, Ispapirone
3. *Sedative antihistaminic*   Hydroxyzine
4. β *blocker*   Propranolol

In addition to the above drugs, antidepressants, especially the SSRIs and SNRIs are effective in OCD, phobias, panic and many types of severe generalized anxiety disorders.

BENZODIAZEPINES

The pharmacology of benzodiazepines (BZDs) as a class is described in Ch. 29.

Some members have a slow and prolonged action, relieve anxiety at low doses without producing significant CNS depression. They have a selective taming effect on aggressive animals and suppress induced aggression. They also suppress the performance impairing effect of punishment. In contrast to barbiturates, they are more selective for the limbic system and have proven clinically better in both quality and quantity of improvement in anxiety and stress-related symptoms.

At antianxiety doses, cardiovascular and respiratory depression is minor.

Because anxiety is a common complaint and is a part of most physical and mental illness, and because the BZDs—

- have little effect on other body systems
- have lower dependence producing liability than barbiturates and other sedatives; withdrawal syndrome is milder and delayed due to their long half lives
- are relatively safe even in gross overdosage,

they are presently one of the widely used class of drugs. Potent BZDs like lorazepam and clonazepam injected i.m. have adjuvant role in the management of acutely psychotic and manic patients.

BZDs act primarily by facilitating inhibitory GABAergic transmission, but other additional mechanisms of action have been suggested. Higher doses induce sleep and impair performance.

Adverse effects of BZDs noted in their use as hypnotics are described in Ch. 29. *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. Rashes are uncommon. Some women fail to ovulate while on regular use of BZDs. The major constraint in their long-term use for anxiety disorders is their potential to impair mental functions and to produce dependence.

Differences between individual BZDs recommended for anxiety are primarily pharmacokinetic: choice of one over the other is largely empirical.

1. 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, and has been the commonest BZD used to cover alcohol withdrawal. Its t½ is 6–12 hours, but active metabolites are produced which extend the duration of action. Its anticonvulsant action is weak.
Daily dose: 25–100 mg; LIBRIUM 10, 25 mg tabs; EQUILIBRIUM 10 mg tab.

2. Diazepam   It is quickly absorbed; produces a brief initial phase of strong action followed by prolonged milder effect due to a two phase plasma concentration decay curve (distributive phase t½ 1 hr, elimination phase t½ 20–30 hours). The biological effect t½ is still longer due to production of active metabolites. It is preferred in acute panic states and anxiety associated with organic disease.
Daily dose: 5–30 mg; VALIUM, PLACIDOX 2, 5, 10 mg tabs; CALMPOSE 5, 10 mg tab, 2 mg/5 ml Syr.

3. Oxazepam   It is slowly absorbed; being relatively polar, its penetration in brain is also slow. The plasma t½ is about 10 hours. It is metabolized only by glucuronide conjugation, therefore no active metabolite is produced.

Duration of action is relatively shorter making it preferable for the elderly and in those with liver disease. It has been used mainly in short lasting anxiety states.
Daily dose: 30–60 mg in 2–3 divided portions; SEREPAX 15, 30 mg tab.

4. Lorazepam   Has slow oral absorption. Being less lipid-soluble than diazepam, its rate of entry in brain is slower. The plasma t½ is shorter (10–20 hours); no active metabolite is produced, since it is directly conjugated with glucuronic acid, and is suitable for older patients. However, it is quite sedative and capable of producing marked amnesia when injected i.v. Injection site complications are minor. Therefore, it is the only BZD recommended for i.m. use. It has been preferred for short lasting anxiety states, panic, OCD and tension syndromes, as well as for psychosomatic diseases and for i.v. use in status epilepticus.
Daily dose: 1–6 mg; LARPOSE, ATIVAN 1, 2 mg tab. CALMESE 1, 2 mg tabs, 4 mg/2 ml inj.

5. Alprazolam   A high potency anxiolytic BZD which in addition has some mood elevating action in mild depression. As such, it is particularly useful in anxiety associated with depression. Good response has been obtained in panic disorders with severe anxiety and autonomic symptoms. Its plasma t½ is about 12 hours, but an active metabolite is produced. Alprazolam is also used as hypnotic. When administered daily as anxiolytic, some patients experience anxiety in between doses, which may be obviated by employing sustained release tablet. Withdrawal symptoms may be more marked on discontinuation than with other BZDs.
Dose: 0.25–1.0 mg TDS; upto 6 mg/day in panic disorder; ALPRAX 0.25, 0.5, 1.0 mg tabs., 0.5, 1.0, 1.5 mg SR tabs; ALZOLAM 0.25, 0.5, 1.0 mg tabs; 1.5 mg SR tab, ALPROCONTIN 0.5, 1.0, 1.5 mg CR tabs. RESTYL 0.25, 0.5, 1.0 mg tabs, RESTYL-SR 0.5, 1.0, 1.5 mg SR tabs.

OTHER ANTIANXIETY DRUGS

Buspirone   It is the first azapirone, a new class of antianxiety drugs, distinctly different from BZDs. Buspirone:

- Does not produce significant sedation or cognitive/functional impairment.
- Does not interact with BZD receptor or modify GABAergic transmission.
- Does not produce tolerance or physical dependence.
- Does not suppress BZD or barbiturate withdrawal syndrome.
- Has no muscle relaxant or anticonvulsant activity.

Buspirone relieves mild-to-moderate generalized anxiety, but is ineffective in severe cases, in those showing panic reaction and in OCD. The therapeutic effect develops slowly; maximum benefit may be delayed up to 2 weeks. The mechanism of anxiolytic action is not clearly known, but may be dependent on its selective partial agonistic action on 5-HT$_{1A}$ receptors. By stimulating presynaptic 5-HT$_{1A}$ autoreceptors, it reduces the activity of dorsal raphe serotonergic neurones. Antagonistic action at certain postsynaptic 5-HT$_{1A}$ receptors has also been demonstrated. After chronic treatment, adaptive reduction in cortical 5-HT$_2$ receptors may occur. 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; (bioavailability <5%), one metabolite is active and excretion occurs both in urine and faeces; t½ is 2–3.5 hrs. 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. Though most patients on buspirone remain alert, those operating machinery/motor vehicles should be cautioned.

Dose: 5–15 mg OD–TDS:

ANXIPAR, BUSPIN, BUSCALM 5, 10 mg tab.

Hydroxyzine   An H$_1$ antihistaminic with sedative, antiemetic, antimuscarinic and spasmolytic properties. It is claimed to have selective anxiolytic action, but the accompanying sedation is quite marked. Hydroxyzine may be used in reactive anxiety or that associated with marked autonomic symptoms.

Due to antihistaminic and sedative property, it is useful in pruritus and urticaria.
Daily dose 50–200 mg;
ATARAX 10, 25 mg tab, 10 mg/5 ml syr, 25 mg/2 ml inj.

β Blockers (*see* Ch. 10)

Many symptoms of anxiety (palpitation, rise in BP, shaking, tremor, gastrointestinal hurrying, etc.) are due to sympathetic overactivity, and these symptoms reinforce anxiety. Propranolol and other nonselective β blockers help anxious patients troubled by these symptoms, by cutting the vicious cycle and provide symptomatic relief. They do not affect the psychological symptoms such as worry, tension and fear, but are valuable in acutely stressful situations (examination fear, unaccustomed public appearance, etc.). They may be used for performance/situational anxiety or as adjuvant to BZDs. The role of β blockers in anxiety disorders is quite limited.

TREATMENT OF ANXIETY

Anxiety is a universal phenomenon, and to experience it in appropriate circumstances is the normal response. It may serve to enhance vigilance and drive. However, if anxiety symptoms are frequent and persist in a severe form, they are a cause of distress/suffering and markedly impair performance. Anxiety should be treated with drugs only when excessive and disabling in its own right.

The established drugs are BZDs which act quickly, while buspirone and SSRIs/SNRIs act only after chronic treatment. The BZDs should be used in the smallest possible dose. The dose has to be found out for each patient by titration with symptoms of anxiety. Acute anxiety states generally respond better than chronic anxiety. The drug should be withdrawn as soon as it is no longer required. However, when large doses have been used for longer periods, withdrawal should be gradual. Long-term use of BZDs is of questionable merit due to cognitive impairment and risk of dependence.

The usual practice is to give 1/2 to 2/3 of the daily dose at bed time to ensure good nightly

rest; the remaining is divided in 2–3 doses given at day time. Though the t½ of BZDs used in anxiety are longer, divided day time doses or SR tab. are required to avoid high peaks.

Buspirone is a nonsedating alternative to BZDs for chronic treatment of less severe forms of generalized anxiety. The SSRIs and SNRIs are now extensively used in most forms of chronic anxiety disorders, but are not good for acute anxiety. They produce a delayed but often gratifying response and can be combined with BZDs. The SSRIs are now drugs of choice for social anxiety, OCD, eating disorders and PTSD in which BZDs, though effective, carry abuse potential on long-term use.

Panic attacks are initially treated with a rapidly acting BZD (e.g. diazepam, alprazolam), but BZDs are not suitable for long-term therapy. SSRIs and duloxetine are the drugs of choice for sustained treatment, which in the initial few weeks may be supplemented by continuing the BZD. Valproate is an alternative to SSRIs. Phobic disorders are mostly treated by a SSRI, such as paroxetine, fluvoxamine or sertraline. In situational phobias, propranolol may be added as and when required. Gabapentin has been used as alternative to SSRI.

Patients with hypertension, peptic ulcer, ulcerative colitis, irritable bowel syndrome, gastroesophageal reflux, thyrotoxicosis, angina pectoris are often given low doses of BZD in addition to specific therapy, though anxiety may not be a prominent manifestation.

Fixed dose combination of tranquillizers with vitamins has been banned.

☞ PROBLEM DIRECTED STUDY

33.1 A businessman aged 35 years suffered loss and his employees left. He became very depressed and stopped taking interest in the business. Gradually he stopped going out and withdrew socially. He felt guilty, worthless and tired all the time, lost interest in pleasure and sex, stopped eating properly and had disturbed sleep. When he showed no sign of recovery even after 3 months, the family members consulted a doctor, who diagnosed him to be a case of major depression and prescribed—

Tab Sertraline 50 mg twice a day, and a multivitamin.

The family members brought him back after one week and complained that there was no improvement. On questioning the patient revealed that he felt more restless, had nausea, pain in upper abdomen, headache and no desire to eat.

(a) What could be the reason for no improvement in the depressive symptoms? Is the choice of drug inappropriate? Does the medication needs to be changed, dose increased or decreased? Should another drug be added at this stage?

(see Appendix-1 for solution)

Chapter 34 Opioid Analgesics and Antagonists

Algesia (pain) is an ill-defined, unpleasant bodily sensation, usually evoked by an external or internal noxious stimulus.

Analgesic A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.

Pain is a warning signal, primarily protective in nature, but causes discomfort and suffering; may even be unbearable and incapacitating. It is the most important symptom that brings the patient to the physician. Excessive pain may produce other effects—sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in BP, tachypnoea. Analgesics relieve pain as a symptom, without affecting its cause. They are used when the noxious stimulus (evoking the pain) cannot be removed or as adjuvants to more etiological approach to pain. Analgesics are divided into two groups, *viz.*

A. Opioid/narcotic/morphine-like analgesics.

B. Nonopioid/non-narcotic/aspirin-like/antipyretic or antiinflammatory analgesics (described in Ch. 14).
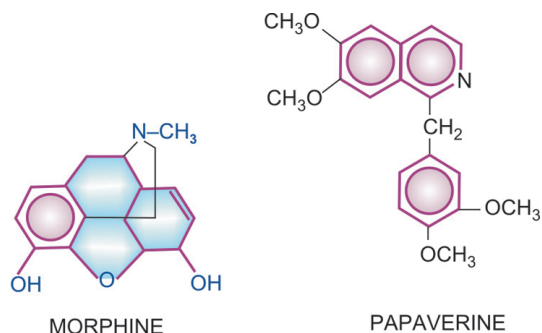
OPIOID ANALGESICS

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

Phenanthrene derivatives
Morphine (10% in opium)
Codeine (0.5% in opium)
Thebaine (0.2% in opium), (Nonanalgesic)

Benzoisoquinoline derivatives
Papaverine (1%) ⎤ Nonanalgesic
Noscapine (6%) ⎦

MORPHINE   PAPAVERINE

Opium has been known from the earliest times. It is mentioned in the Eber's papyrus (1500 BC), in the writings of Theophrastus (300 BC) and Galen (2nd century AD). Opium eating became a social custom in China in the 18th century. Serturner, a pharmacist, isolated the active principle of opium in 1806 and named it *'morphine'* after the Greek god of dreams *Morpheus*. In the last century a large number of semisynthetic and synthetic compounds have been developed with morphine-like, antagonistic and mixed agonistic-antagonistic properties.

Compounds that are derived from opium or are chemically related to morphine are called '*opiates*', while all those having morphine-like action, irrespective of chemical nature, are called '*opioids*'. Accordingly, pethidine, endorphins, etc. are opioids, but not opiates.

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. Nociceptive pain arising from stimulation of peripheral pain receptors is relieved better than neuretic pain (such as trigeminal neuralgia) produced by inflammation of or damage to neural structures. The associated reactions to intense pain (apprehension, fear, autonomic effects) are also dampened. Suppression of pain perception is selective, without affecting other sensations or producing proportionate generalized CNS depression (contrast general anaesthetics).

Perception of pain and the emotional component (anxiety, fear, suffering, distress) induced by it are both altered so that pain is no longer as unpleasant or distressing, i.e. the patient tolerates pain better. The analgesic action of morphine has both spinal and supraspinal components. Intrathecal injection of morphine has been shown to cause segmental analgesia without affecting other modalities. 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. The action appears to be exerted through interneurones which are involved in the 'gating' of 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. Action at supraspinal sites in medulla, periaqueductal gray matter, limbic and cortical areas may alter processing and interpretation of pain impulses. 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. Simultaneous action at spinal and supraspinal sites greatly amplifies the analgesia.

A *peripheral action* of opioids on small primary afferent terminals in skin or deeper structures, attenuating their sensitization following tissue injury has also been demonstrated. This may play a role in the analgesic action of morphine in conditions like burns and trauma.

(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. In the absence of pain or apprehension, these are generally appreciated as unpleasant by normal people. However, patients in pain or anxiety, and especially addicts, perceive it as pleasurable floating sensation: refer it as 'high'. Rapid i.v. injection by addicts gives them a 'kick' or 'rush' which is intensely pleasurable—akin to orgasm. Thus, one has to learn to perceive the *euphoric* effect of morphine.

The pleasurable and reinforcing effects of μ opioid agonists (morphine-like) appear to involve a separate set of neuronal mechanisms than those involved in analgesia and sedation. The euphoric effects are most likely mediated by DA release in nucleus accumbance, whereas κ agonists (nalorphine like) inhibit DA release and produce aversion. The μ opioid receptors appear to inhibit the inhibitory GABAergic neurones, thereby facilitating DA release in nucleus accumbens. Inhibition of NA release in locus ceruleus by opioids is implicated in their action to allay apprehension and fear.

(d) *Respiratory centre*   Morphine depresses respiratory centre in a dose dependent manner; rate and tidal volume are both decreased. However, analgesic dose in an otherwise healthy individual produces no cognizable respiratory depression, but it may be marked in the presence of other sedatives, cardiopulmonary/liver/kidney disease, etc. Death in morphine poisoning is due to respiratory failure. Neurogenic, hypercapnoeic and later hypoxic drives to the respiratory centre are suppressed in succession. In addition, there is indifference to breathing: apnoeic patient may breath if commanded.

(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.

Morphine stimulates:

(a) *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.

(b) *Edinger Westphal nucleus* of III nerve is stimulated producing miosis. No miosis occurs on topical application of morphine to the eye, since this is a central action. Morphine produces this effect by inhibiting the GABAergic interneurone which tonically inhibits the Edinger-Westphal nucleus. Mydriasis occurs in some species like cats. Another ocular effect is a decrease in intraocular tension.

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

(d) *Certain cortical areas and hippocampal cells* are stimulated. Muscular rigidity and immobility is consistently manifested at high doses (especially on i.v. injection). This resembles catalepsy seen in rats and mice. Morphine lowers seizure threshold. Convulsions may occur in morphine poisoning. The proconvulsant action has been ascribed to inhibition of GABA release by hippocampal interneurones. Morphine causes excitation instead of sedation in an occasional individual. Species like cat, lion, horse, sheep and cow are uniformly excited and show hyperthermia.

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 (these are under predominant inhibitory control). The sex hormone and cortisol levels are lowered. Some degree of tolerance may develop to this effect, but heavy abusers often suffer loss of libido, impotence, menstrual irregularities and infertility. Clinical hypocorticism is unusual. Morphine can release ADH and reduce urine volume.

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

There is a shift of blood from pulmonary to systemic circuit due to greater vasodilatation in the latter. Therapeutic doses cause little change in the BP of recumbent normovolaemic patient. Postural hypotension and fainting do occur due to venodilatation and impairment of vascular reflexes. Morphine has little direct effect on heart; rate generally decreases due to stimulation of vagal centre, but may increase reflexly if the BP falls. Cardiac work is consistently reduced due to decrease in peripheral resistance, imparting anti-ischaemic property to morphine. Intracranial tension tends to rise as a consequence of CO_2 retention leading to cerebral vasodilatation.

4. GIT The enteric plexus neurones and g.i. mucosa are rich in opioid receptors. Morphine exerts marked effect on g.i. motility as well as on fluid dynamics across g.i. mucosa. Constipation is a prominent feature of morphine action. Several factors contribute:
(a) Action directly on intestines and in the CNS increases tone and segmentation but decreases propulsive movements. Tone of duodenum and colon may be increased to the level of spasm.
(b) Spasm of pyloric, ileocaecal and anal sphincters.
(c) 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. Absorption of fluid is increased due to stasis. (d) Central action causing inattention to defecation reflex.

No tolerance develops to this action: addicts remain chronically constipated.

5. Other smooth muscles

(a) *Biliary tract*   Morphine causes spasm of sphincter of Oddi → intrabiliary pressure is increased several fold → may cause biliary colic. This action is only partly counteracted by atropine but more completely by opioid antagonist naloxone and direct smooth muscle relaxants like nitrates.

(b) *Urinary bladder*   Tone of both detrusor and sphincter muscle is increased → urinary urgency and difficulty in micturition. Contractions of ureter are also increased.

(c) *Uterus*   The action is clinically insignificant, may slightly prolong labour.

(d) *Bronchi*   Morphine releases histamine (due to its bulky basic molecule; the mechanism is nonimmunological), which can cause broncho-constriction. This is of no consequence in normal individuals, but can be dangerous in asthmatics.

6. ANS
Morphine causes mild hyperglycaemia due to central sympathetic stimulation. It has weak anticholinesterase action.

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 (more potent than morphine on μ opioid receptors), 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. However, small amounts persist in the body due to enterohepatic circulation.

ADVERSE EFFECTS

1. *Side 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 (especially in elderly male) are other side effects. BP may fall, especially in hypovolaemic patient and if he/she walks about.

2. *Idiosyncrasy and allergy*   Allergic reactions manifesting as urticaria, swelling of lips occur infrequently. Anaphylactoid reaction is rare. A local reaction at injection site and generalized itching may occur due to histamine release.

3. *Apnoea of the newborn*   This may occur when morphine is given to the mother during labour. The blood-brain barrier of the foetus is undeveloped, morphine attains higher concentration in foetal brain than in that of mother. Naloxone 10 μg/kg injected in the umbilical cord is the treatment of choice.

4. *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. Manifestations are extensions of the pharmacological action.

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 (*see* p. 483). Due to short duration of action, naloxone should be repeated every 1–4 hours, according to the response.

5. *Tolerance and dependence* High degree of tolerance can be developed to morphine and related opioids if the drug is used repeatedly. It is partly pharmacokinetic (enhanced rate of metabolism), but mainly pharmacodynamic (cellular tolerance). Tolerance is exhibited to most actions, but not to constipating and miotic actions. Addicts tolerate morphine in grams: lethal dose is markedly increased. Patients in intense pain are relatively tolerant to depressant effects. Cross tolerance among opioids is of high degree. Morphine tolerant subjects are partially cross tolerant to other CNS depressants as well.

Morphine produces pronounced psychological and physical dependence, its abuse liability is rated high. Recently the NMDA antagonists and nitric oxide synthase inhibitors have been found to block morphine tolerance and dependence in animals. Thus, the analgesic action of morphine can be dissociated from tolerance and dependence which contribute to its abuse. Concern about abuse has been a major limitation in the use of morphine, but appropriate medical use of morphine seldom progresses to dependence and abuse. Morphine abuse is higher among medical and paramedical personnel because they have easier access to the drug.

Earlier, morphine addicts tended to be from the middle age group, but now younger individuals are also opting for it. Opium eating has been prevalent among natives in the orient.

Withdrawal of morphine is associated with marked drug-seeking behaviour. Physical manifestations of abstinence are—lacrimation, sweating, yawning, anxiety, fear, restlessness, gooseflesh, mydriasis, tremor, insomnia, abdominal colic, diarrhoea, dehydration, rise in BP, palpitation and rapid weight loss. Delirium and convulsions are not a characteristic feature (contrast barbiturates) and are seen only occasionally. Cardiovascular collapse and fatality are rare if supportive measures are instituted.

Opioid antagonists (naloxone, nalorphine) precipitate acute withdrawal syndrome in the dependent subject. In the more severely dependent, even 0.2 mg of naloxone can precipitate marked withdrawal.

Treatment: consists of withdrawal of morphine and substitution with oral methadone (long-acting, orally effective) followed by gradual withdrawal of methadone. However, relapse rate among postaddicts is high. Long-term methadone maintenance and other techniques using agonist-antagonistic drugs are also employed.

PRECAUTIONS AND CONTRAINDICATIONS

Morphine is a drug of emergency, but due care has to be taken in its use.
1. Infants and the elderly are more susceptible to the respiratory depressant action of morphine.
2. It is dangerous in patients with respiratory insufficiency (emphysema, pulmonary fibrosis, cor pulmonale); sudden deaths have occurred. Morphine accentuates sleep apnoea; hypoxic brain damage can occur.
3. Bronchial asthma: Morphine can precipitate an attack by its histamine releasing action. A high potency opioid with lower histamie releasing potential (e.g. fentanyl) should be used, if unavoidable, in an asthmatic.

4. Head injury: morphine is contraindicated in patients with head injury. Reasons are—

- By retaining CO_2, it increases intracranial tension which will add to that caused by head injury itself.
- Even therapeutic doses can cause marked respiratory depression in these patients.
- Vomiting, miosis and altered mentation produced by morphine interfere with assessment of progress in head injury cases.

5. Hypotensive states and hypovolaemia exaggerate fall in BP due to morphine.

6. Undiagnosed acute abdominal pain: morphine can aggravate certain conditions, e.g. diverticulitis, biliary colic, pancreatitis. Inflamed appendix may rupture. Morphine can be given after the diagnosis is established. Pentazocine, buprenorphine are less likely to aggravate biliary spasm.

7. Elderly male: chances of urinary retention are high.

8. Hypothyroidism, liver and kidney disease patients are more sensitive to morphine.

9. Unstable personalities: are liable to continue with its use and become addicted.

Interactions

Phenothiazines, tricyclic antidepressants, MAO inhibitors, amphetamine and neostigmine potentiate morphine and other opioids, either by retarding its metabolism or by a pharmacodynamic interaction at the level of central neurotransmitters.

Morphine retards absorption of many orally administered drugs by delaying gastric emptying.

Dose: 10–50 mg oral, 10–15 mg i.m. or s.c. or 2–6 mg i.v.; 2–3 mg epidural/intrathecal; children 0.1–0.2 mg/kg. i.m. or s.c.

MORPHINE SULPHATE 10 mg/ml inj; MORCONTIN 10, 30, 60, 100 mg continuous release tabs; 30–100 mg BD; RILIMORF 10, 20 mg tabs, 60 mg SR tab.

CLASSIFICATION OF OPIOIDS

1. *Natural opium alkaloids:* Morphine, Codeine

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

Many others like—Hydromorphone, Oxymorphone, Hydrocodone, Oxycodone are not used in India.

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

Many others like—Levorphanol, Dextromoramide, Dipipanone, Alfentanil, Sufentanil, Remifentanil are not available in India.
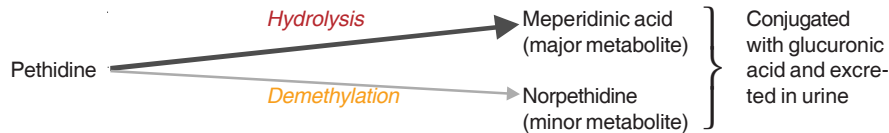
1. Codeine It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine. It is less potent than morphine (1/10th as analgesic), also less efficacious; is a partial agonist at μ opioid receptor with a low ceiling effect. The degree of analgesia is comparable to aspirin (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 (*see* p. 220). 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 (*see* Ch. 48). 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.

2. Pholcodeine, Ethylmorphine They have codeine like properties and have been used mainly as antitussive (*see* p. 220); claimed to be less constipating.

3. 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,

Pethidine →(Hydrolysis)→ Meperidinic acid (major metabolite)

Pethidine →(Demethylation)→ Norpethidine (minor metabolite)

Conjugated with glucuronic acid and excreted in urine

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.

4. 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 μ 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. After i.m. injection, the onset of action is more rapid but duration is shorter (2–3 hours).

3. It does not effectively suppress cough.

4. Spasmodic action on smooth muscles is less marked—miosis, constipation and urinary retention are less prominent.

Pethidine is believed to induce less biliary spasm than morphine; traditionally preferred in cholecystitis/biliary colic. However, there is no objective evidence to support this belief. One study* in patients undergoing cholecystectomy found pethidine to raise common bile duct pressure 14% more than equianalgesic dose of morphine.

5. 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.

6. Tachycardia (due to antimuscarinic action) occurs instead of bradycardia.

7. It causes less histamine release and is safer in asthmatics.

8. It has local anaesthetic action: corneal anaesthesia is seen after systemic doses.

9. 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.

* *See* Lee F and Cundiff D; *Arch Intern. Med.* **158**, (1998), 2399.

Side effects These are similar to morphine except those mentioned above. Some atropinic effects (dry mouth, blurred vision, tachycardia) may be noted in addition.

Overdose of pethidine produces many excitatory effects—tremors, mydriasis, hyperreflexia, delirium, myoclonus and convulsions. This is due to accumulation of *norpethidine* which has excitant effects. Renal failure patients given repeated doses of pethidine are prone to experience similar effects.

Nonselective MAO inhibitors interfere with hydrolysis but not with demethylation of pethidine—norpethidine is produced in excess and excitement occurs. Pethidine injected in patients receiving a selective serotonin reuptake inhibitor (SSRI) may produce the 'serotonin syndrome' (*see* p. 461) by enhancing 5-HT release.

Tolerance and physical dependence develop slowly with pethidine. Probably due to its shorter duration of action, body functions get time to recover. For the same reason withdrawal syndrome develops more rapidly. Autonomic disturbances are less marked during pethidine withdrawal, than after morphine withdrawal.

Use Pethidine is primarily used as an analgesic (substitute of morphine) and in preanaesthetic medication, but not for cough or diarrhoea. It has also been used to control shivering during recovery from anaesthesia or that attending i.v. infusions. Conventional antihistaminics, NSAIDs and corticosteroids augment this effect of pethidine. Potential adverse effects due to accumulation of norpethidine limit its utility in patients who require repeated dosing. It is the preferred opioid analgesic during labour, because at equianalgesic doses neonatal respiratory depression is less marked, but still significant.

CHAPTER 34

Dose: 50–100 mg i.m., s.c. (may cause irritation, local fibrosis on repeated injection). It is occasionally given orally or i.v.
PETHIDINE HCL 100 mg/2 ml inj; 50, 100 mg tab.

5. Fentanyl A pethidine congener, 80–100 times more potent than morphine, both in analgesia and respiratory depression. In analgesic doses it produces few cardiovascular effects. Cardiac contractility and heart rate are only marginally reduced, and it has less propensity to release histamine. Because of high lipid solubility, it enters brain rapidly and produces peak analgesia in 5 min after i.v. injection. The duration of action is short: starts wearing off after 30–40 min due to redistribution, while elimination t½ is ~4 hr. In the injectable form it is almost exclusively used in anaesthesia (*see* p. 384). Transdermal fentanyl has become available for use in cancer/terminal illness or other types of chronic pain for patients requiring opioid analgesia. Buccal use is possible, but not oral.
DUROGESIC transdermal patch delivering 12 µg/hr, 25 µg/hr, 50 µg/hr, 75 µg/hr or 100 µg per hour; the patch is changed every 3 days.

6. Methadone A synthetic opioid, chemically dissimilar but pharmacologically very similar to morphine. It has analgesic, respiratory depressant, emetic, antitussive, constipating and biliary actions similar to morphine.

The most important feature of methadone is high oral : parenteral activity ratio (1 : 2) and its firm binding to tissue proteins. In single doses it is only slightly more potent than morphine and has comparable duration of action (4–6 hours on i.m. injection), but it cumulates in tissues on repeated administration—duration of action is progressively lengthened due to gradual release from these sites; plasma t½ on chronic use is 24–36 hours. Plasma protein binding is 90% and it is metabolized in liver, primarily by demethylation and cyclization. Metabolites are excreted in urine. Rifampin and phenytoin can cause withdrawal symptoms to appear in methadone dependent subjects by inducing its metabolism.

Because of slow and persistent nature of action, sedative and subjective effects are less intense. It is probably incapable of giving a 'kick'. The abuse potential is rated lower than morphine. Tolerance develops more slowly, probably due to progressive filling of tissue stores. Withdrawal syndrome is of gradual onset, taking 1–2 days after discontinuation, is prolonged and less severe.

Methadone has been used primarily as substitution therapy for opioid dependence: 1 mg of oral methadone can be substituted for 4 mg of morphine, 2 mg of heroin and 20 mg of pethidine. Another technique is *methadone maintenance* therapy in opioid addicts— sufficient dose of methadone (10–40 mg/day) is given orally over long term to produce high degree of tolerance so that pleasurable effects of i.v. doses of morphine or heroin are not perceived and the subject gives up the habit.

Methadone can also be used as an analgesic for the same conditions as morphine; dose 2.5–10 mg oral or i.m. but not s.c. It is occasionally employed as antitussive.
METHADONE 5mg/ml and 10mg/ml syr; 5, 10, 20, 40 mg tabs (for maintenance therapy of opioid dependence).
PHYSEPTONE 10 mg inj, 2 mg/5 ml linctus.

7. Dextropropoxyphene It is chemically related to methadone but is quite similar in analgesic action and in side effects to codeine, except that it is a poor antitussive, probably less constipating, and nearly half as potent as codeine, with a lower oral : parenteral activity ratio. It is metabolized in liver; t½ is variable (4–12 hours). Delirium and convulsions have occurred in overdose. The demethylated metabolite of propoxyphene has a longer t½ (>24 hours), accumulates on repeated dosing and is cardiotoxic. The abuse liability is similar to or lower than codeine.

Dextropropoxyphene (60–120 mg) is used as a mild oral analgesic. It is marketed only in combination with paracetamol ± other drugs; but the contribution of dextropropoxyphene to the analgesic effect of the combination is questionable. The cardiac toxicity of its demethylated metabolite and seizures are dangerous in overdose. The toxicity is only partly antagonized

by naloxone. Because of reported fatalities and no clear advantage of the combinations over paracetamol alone, such preparations have been withdrawn in the UK and Europe, a warning has been put on the labels in the US, but they are quite popular in India, probably due to the perceived addictive potential of codeine.

PARVODEX 60 mg cap: PARVON, PROXYVON, WALAGESIC: dextropropoxyphene 65 mg + paracetamol 400 mg cap; WYGESIC, SUDHINOL 65 mg + paracetamol 650 mg cap.

8. Tramadol This centrally acting analgesic is an atypical opioid which relieves pain by opioid as well as additional mechanisms. Its affinity for μ opioid receptor is low, while that for κ and δ is very low. Unlike other opioids, it inhibits reuptake of NA and 5-HT, increases 5-HT release, and thus activates monoaminergic spinal inhibition of pain. Its analgesic action is only partially reversed by the opioid antagonist naloxone.

Injected i.v. 100 mg tramadol is equianalgesic to 10 mg i.m. morphine. Oral bioavailability of tramadol is good (oral: parenteral dose ratio is 1.4). The $t\frac{1}{2}$ is 5–6 hours and effects last for 4–6 hrs. Tramadol causes less respiratory depression, sedation, constipation, urinary retention and rise in intrabiliary pressure than morphine. It is well tolerated; side effects are dizziness, nausea, sleepiness, dry mouth, sweating and lowering of seizure threshold. Haemodynamic effects are minimal. Tramadol should not be given to patients taking SSRI therapy because of risk of 'serotonin syndrome' (*see* p. 461).

Tramadol is indicated for mild-to-moderate short-lasting pain due to diagnostic procedures, injury, surgery, etc, as well as for chronic pain including cancer pain, but is not effective in severe pain. Little tendency to dose escalation by chronic users is seen and abuse potential is low.

Dose: 50–100 mg oral/i.m./slow i.v. infusion (children 1–2 mg/kg) 4–6 hourly.

CONTRAMAL, DOMADOL, TRAMAZAC 50 mg cap, 100 mg SR tab; 50 mg/ml inj in 1 and 2 ml amps.

USES (Of morphine and its congeners)

1. *As analgesic* Opioid analgesics are indicated in severe pain of any type. However, they only provide symptomatic relief without affecting the cause. Pain may be valuable for diagnosis; should not be relieved by a potent analgesic unless proper assessment of the patient has been done. Indiscriminate use of opioids can be hazardous. On the other hand, inadequate dose or reluctance to use an opioid for a patient in distress is equally deplorable.

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. It should be given promptly in myocardial infarction to allay apprehension and reflex sympathetic stimulation. Opioids, especially pethidine, have been extensively used for obstetric analgesia, but one must be prepared to deal with the foetal and maternal complications.

Adequate use of morphine (even i.v.) is indicated in an emergency. It may prevent neurogenic shock and other autonomic effects of excruciating pain such as that of crush injuries. Patients in severe pain require higher doses of opioids and tolerate them without manifesting toxicity. There is considerable individual variability in the response to opioids. They should not be restricted in case of pain of terminal illness (cancer pain), but for other chronic conditions, due consideration must be given to their addicting liabilities. Neuropathic pain responds less predictably to opioid analgesics, while pregabalin, amitriptyline, duloxetine are the major drugs for such pain.

Epidural (2–3 mg) or intrathecal (0.2 mg) injection of morphine produces segmental analgesia lasting ~12 hour without affecting other sensory, motor or autonomic modalities. It is being used for surgical analgesia in abdominal, lower limb and pelvic operations as well as for labour, postoperative, cancer and other intractable pain. Respiratory depression occurs after a delay due to ascent of the opioid through the subarachnoid space to the respiratory centre. Use of fentanyl in place of morphine produces faster analgesia and reduces the risk of respiratory depression because of greater uptake of fentanyl by nerves at the site of injection.

Patient controlled analgesia (PCA) is an attractive technique of postoperative pain control in which the patient himself regulates the rate of i.v. fentanyl infusion according to intensity of pain felt.

Transdermal fentanyl is a suitable option for chronic cancer and other terminal illness pain. The patch produces analgesia after ~12 hr, but then blood levels of fentanyl and intensity of analgesia remain fairly uniform if the patch is changed every 3 days. For severe chronic pain continuous opioid analgesia with a long-acting preparation works better than a short-acting opioid given intermittently. Rescue short-acting opioid is to be added to the continuous analgesia for 'breakthrough pain'.

For milder pain, e.g. toothache, headache, arthralgia, etc., aspirin-like analgesics are preferred. When they are not effective—codeine/dextropropoxyphene may be used orally, either alone or in combination with aspirin-like drug. The combination enhances the ceiling analgesia. For majority of painful conditions, especially more severe and longerlasting pain, a NSAID may be combined with the opioid. This helps to enhance analgesia while keeping the opioid dose low.

2. *Preanaesthetic medication*   Morphine and pethidine are used in few selected patients (*see* p. 386).

3. *Balanced anaesthesia and surgical analgesia*   Fentanyl, morphine, pethidine, alfentanil or sufentanil are an important component of anaesthetic techniques (*see* p. 384).

4. *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 overactivity. However, they should not be used as anxiolytics or to induce sleep.

5. *Acute left ventricular failure (cardiac asthma)* Morphine injected i.v. affords dramatic relief by—
(a) Reducing preload on heart due to vaso-dilatation 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.

Morphine is also indicated to relieve pulmonary edema due to infarction of lung, but not due to irritant gases. It is contraindicated in bronchial asthma.

6. *Cough*   Codeine or its substitutes are widely used for suppressing dry, irritating cough (*see* Ch. 16).

7. *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 antidiarrhoeals. The risk and benefits of their use are detailed in Ch. 48.

OPIOID RECEPTORS

Morphine and other opioids exert their actions by interacting with specific receptors present on neurones in the CNS and in peripheral tissues. Chemical modification of morphine structure has yielded a number of compounds which have a complex pattern of morphine-like and other agonistic and antagonistic actions that cannot be explained on the basis of a single opioid receptor. Radioligand binding studies divided the opioid receptors into three types (μ, κ, δ); which have been cloned, mapped and studied with modern techniques. Each has a specific pharmacological profile and pattern of anatomical distribution in the brain, spinal cord and peripheral tissues (mainly gut, blood vessels, heart, lungs and immune cells). Subtypes of μ and κ receptor have been identified. The proposed functional role of the 3 types of opioid receptors is listed in Table 34.1.

Opioid ligands can interact with different opioid receptors as agonists, partial agonists or

TABLE 34.1	Actions ascribed to different types of opioid receptors		
μ (mu)	**κ (kappa)**	**δ (delta)**	
Analgesia (supraspinal μ_1 + spinal μ_2)	Analgesia (spinal κ_1) (supraspinal-κ_3)	Analgesia (spinal + affective component of supraspinal)	
Respiratory depression (μ_2)	Respiratory depression (lower ceiling)	Respiratory depression	
Sedation	Dysphoria, psychotomimetic	Affective behaviour	
Euphoria	Miosis (lower ceiling)	Reinforcing actions	
Miosis	Sedation	Reduced g.i. motility	
Muscular rigidity	Physical dependence (nalorphine type)	Proconvulsant	
Reduced g.i. motility (μ_2)	Reduced g.i. motility		
Physical dependence (morphine type)			

competitive antagonists. The overall pattern of effect of a particular agent depends not only on the nature of its interaction with different opioid receptors, but also on its relative affinity for these, e.g. morphine is an agonist on μ, κ and δ receptors, but its affinity for μ receptors is much higher than that for the other two. The effects, therefore, are primarily the result of μ receptor activation.

The nature and intensity of action of complex action opioids and antagonists are summarized in Table 34.2.

μ receptor The μ receptor is characterized by its high affinity for morphine. It is the major receptor mediating actions of morphine and its congeners. Endogenous ligands for μ receptor—peptides called *Endomorphins 1 and 2*, have only recently been found in mammalian brain. They produce biological effects ascribed to μ receptor. Other opioid peptides *viz.* β-endorphin, enkephalins and dynorphins bind to μ receptor with lower affinity. *β-funaltrexamine* is a relatively selective but irreversible μ antagonist. High density of μ receptors has been detected in periaqueductal gray, thalamus, nucleus tractus solitarious, nucleus ambiguus and area postrema.

Two subtypes of μ receptor have been proposed:
μ_1: Has higher affinity for morphine, mediates supraspinal analgesia and is selectively blocked by naloxonazine.
μ_2: Has lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipating action.

CHAPTER 34

TABLE 34.2	Nature of interaction of opioid ligands with the three major types of opioid receptors, along with equivalent analgesic doses			
Ligand	μ (mu)	κ (kappa)	δ (delta)	Analgesic* dose (mg)
1. Morphine	Ago. (St)	Ago. (W)	Ago. (W)	10
2. Nalorphine	Anta. (St)	Ago. (M)	—	—
3. Pentazocine	P.Ago., Anta. (W)	Ago. (M)	—	30–60
4. Butorphanol	P.Ago (W)	Ago. (St)	—	1–3
5. Buprenorphine	P.Ago	Anta. (M)	—	0.3–0.4
6. Naloxone	Anta. (St)	Anta. (M)	Anta. (W)	—
7. Naltrexone	Anta. (St)	Anta. (St)	Anta. (W)	—
8. Met/Leu enkephalin	Ago. (M)	—	Ago. (St)	—
9. β-Endorphin	Ago. (St)	—	Ago. (St)	—
10. Dynorphin A, B	Ago. (W)	Ago. (St)	Ago. (W)	—

* Equivalent single parenteral analgesic dose.
Ago—Agonist; Anta.—Antagonist
P. Ago—Partial agonist: have lower efficacy, though affinity (potency) may be high.
St—Strong action; M—Moderate action; W—Weak action (low affinity).

κ receptor This receptor is defined by its high affinity for ketocyclazocine and dynorphin A; the latter is considered to be its endogenous ligand. *Norbinaltorphimine* is a selective κ antagonist. Two subtypes of κ receptor κ_1 and κ_3 are functionally important. Analgesia caused by κ agonists is primarily spinal (through κ_1 receptor). However, κ_3 receptors mediate lower ceiling supraspinal analgesia. Other κ actions are listed in Table 34.1.

δ receptor This receptor has high affinity for leu/met enkephalins which are its endogenous ligands. The δ mediated analgesia is again mainly spinal (δ receptors are present in dorsal horn of spinal cord). The limbic areas are rich in δ receptors, suggesting role of these receptors in the affective component of supraspinal analgesia, reinforcing actions and dependence. The proconvulsant action is more prominent in δ agonists. Myenteric plexus neurones express high density of δ receptors, which mediate reduced g.i. motility. *Naltrindole* is a selective δ antagonist.

It thus appears that μ and δ receptor responses are quite similar, but those exerted through κ receptor are distinct. In certain areas κ actions are antagonistic to μ actions.

The σ (sigma) receptor is no longer considered an opioid receptor, because it is neither activated by morphine nor blocked by naloxone. However, certain opioids, e.g. pentazocine, butorphanol and many unrelated compounds (including the hallucinogens phencyclidine) bind to σ receptors. Certain naloxone insensitive effects of pentazocine like drugs, e.g. dysphoria, psychotomimetic action, tachycardia, mydriasis are believed to be mediated by σ receptors.

Opioid receptor transducer mechanisms All 3 types of opioid receptors (μ, κ, δ) have been cloned; all are GPCRs located mostly on prejunctional neurones. They generally exercise inhibitory modulation by decreasing release of the junctional transmitter (Fig. 34.1). As such, various monoaminergic (NA, DA, 5-HT), GABA, glutamate (NMDA/AMPA) pathways are intricately involved in opioid actions.

Opioid receptor activation reduces intracellular cAMP formation and opens K^+ channels (mainly through μ and δ receptors) or suppresses voltage gated N type Ca^{2+} channels (mainly κ receptor). These actions result in neuronal hyperpolarization and reduced availability of intracellular $Ca^{2+} \rightarrow$ decreased neurotransmitter release by cerebral, spinal, and myenteric neurones (e.g. glutamate from primary nociceptive afferents). However, other mechanisms and second messengers may also be involved, particularly in the long-term.

COMPLEX ACTION OPIOIDS AND OPIOID ANTAGONISTS

1. *Agonist-antagonists (κ analgesics)*
   Nalorphine, Pentazocine, Butorphanol

2. *Partial/weak μ agonist + κ antagonist*
   Buprenorphine

3. *Pure antagonists*
   Naloxone, Naltrexone, Nalmefene

Clinically, the agonist-antagonist (agonist at one opioid receptor, antagonist at another) and partial/weak agonist (low intrinsic activity) opioids are analgesics of limited efficacy equivalent to low doses of morphine. They cause low ceiling respiratory depression and have lower abuse potential. However, in only few situations they have proven to be advantageous over the full μ receptor agonists. Their clinical utility is rather limited.

1. Nalorphine It is N-allyl-normorphine; was the first opioid antagonist introduced in 1951 which could reverse morphine action. Later it was found to have agonistic action on κ receptor as well, producing lower ceiling analgesia. It is not used clinically because of dysphoric and psychotomimetic effects.

2. Pentazocine It is the first agonist-antagonist to be used as an analgesic. It has weak μ antagonistic and more marked κ agonistic actions. The profile of action is similar to morphine; important differences are:

(a) Analgesia caused by pentazocine is primarily spinal (κ_1) and has a different character than that caused by morphine. Parenterally 30 mg pentazocine = 10 mg morphine; but ceiling effect
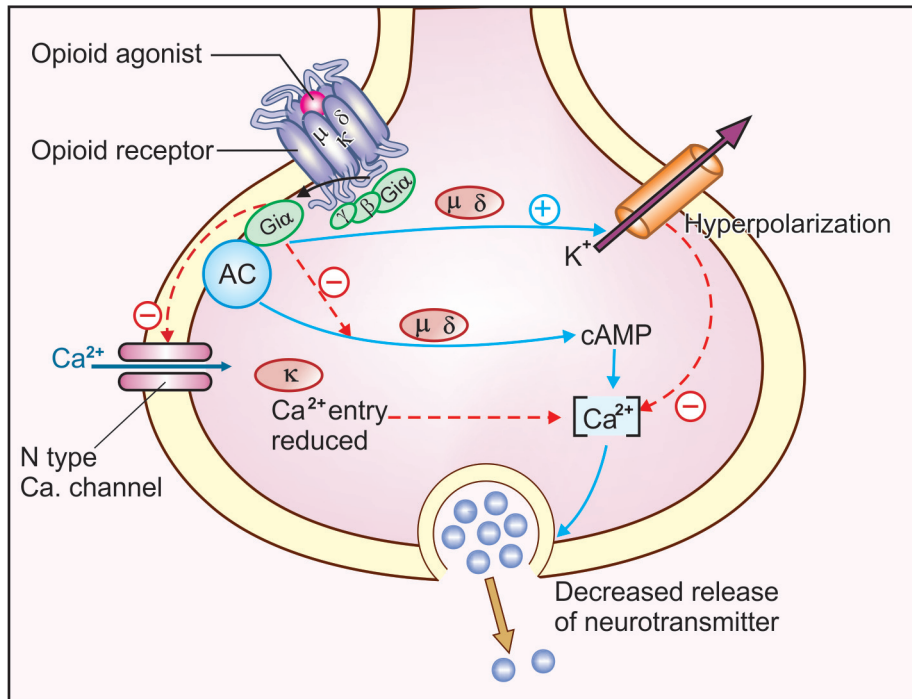
Fig. 34.1: Opioid receptor transducer mechanisms
AC-Adenylyl cyclase; Gi-coupling protein; cAMP-Cyclic AMP

is lower, i.e. at higher doses proportionate increase in analgesia does not occur.

(b) Sedation and respiratory depression is 1/3 to 1/2 of morphine at lower doses, and has a lower ceiling, does not increase much beyond 60 mg dose.

(c) Tachycardia and rise in BP are produced at higher doses due to sympathetic stimulation. This may increase cardiac work; better avoided in coronary ischaemia and myocardial infarction.

(d) Biliary spasm and constipation are less severe.

(e) Vomiting is less frequent. Other side effects are sweating and lightheadedness.

(f) Subjective effects are pleasurable (morphine-like) at lower doses: recognised by post-addicts as an opiate. However, as dose is increased, these become unpleasant (nalorphine-like at > 60 mg i.m.) and psychotomimetic effects (κ, σ mediated) appear.

Tolerance, psychological and physical dependence to pentazocine develops on repeated use. Withdrawal syndrome has features of both morphine and nalorphine abstinence, but is milder in intensity. 'Drug seeking' occurs. Abuse liability is rated lower than morphine.

Injected in morphine dependent subjects, it precipitates withdrawal. The μ receptor antagonistic action is 1/5th as potent as nalorphine which is not enough to be useful in morphine poisoning. In pentazocine dependent subjects, naloxone precipitates withdrawal, but at higher doses.

Pharmacokinetics and use Pentazocine is effective orally, though considerable first pass metabolism occurs; oral: parenteral ratio is 1 : 3.

It is oxidized and glucuronide conjugated in liver and excreted in urine. Plasma t½ is 3–4 hours, duration of action of a single dose is 4–6 hours.

Oral dose: 50–100 mg, efficacy like codeine.

Parenteral dose: 30–60 mg i.m., s.c., may cause local fibrosis on repeated injection due to irritant property.

FORTWIN 25 mg tab., 30 mg/ml inj., FORTSTAR, SUSEVIN 30 mg/ml inj; FORTAGESIC pentazocine 15 mg+paracetamol 500 mg tab.

Pentazocine is indicated for postoperative and moderately severe pain in burns, trauma, fracture, cancer, etc. Though abuse liability is low, frequent side effects and potential for dysphoric/psychotomimetic effect limits its utility in chronic (cancer) pain.

3. Butorphanol   It is a κ analgesic, similar to but more potent than pentazocine (butorphanol 2 mg = pentazocine 30 mg). Likewise, analgesia and respiratory depression have a lower ceiling than morphine. Sedation, nausea, cardiac stimulation and other side effects are similar to pentazocine, but subjective effects are less dysphoric. Psychotomimetic effects are not prominent (it is a weaker σ agonist at higher doses). BP is not increased.

Postaddicts recognize butorphanol as a barbiturate rather than opiate and mostly dislike it. However, it produces physical dependence; withdrawal can be precipitated by high dose of naloxone, but the syndrome is mild. The abuse potential of butorphanol is low. The most outstanding feature is that butorphanol can neither substitute for, nor antagonize morphine. This shows its very weak interaction with μ receptors.

It has been used in a dose of 1–4 mg i.m. or i.v. for postoperative and other short-lasting (e.g. renal colic) painful conditions, but should be avoided in patients with cardiac ischaemia. The t½ and duration of action is similar to morphine.

BUTRUM 1 mg/ml, 2 mg/ml inj.

4. Buprenorphine   It is a synthetic thebaine congener, highly lipid-soluble μ analgesic that is 25 times more potent than morphine but with lower intrinsic activity and ceiling effect. The onset of action is slower and duration longer. After a single dose, analgesia lasts for 6–8 hours; but with repeated dosing, duration of action increases to ~24 hours due to accumulation in tissues. Certain other effects last still longer.

Sedation, vomiting, miosis, subjective and cardiovascular effects are similar to morphine, but constipation is less marked. Postural hypotension is prominent. Respiratory depression (and analgesia) exhibit ceiling effect. It substitutes for morphine at low levels of morphine dependence, but precipitates withdrawal in highly morphine dependent subjects, reflecting its partial agonistic action at μ receptors. Antagonistic action on κ receptor has also been detected.

Lower degree of tolerance and physical as well as psychological dependence develops with buprenorphine on chronic use. Its withdrawal syndrome resembles that of morphine, but is delayed for several days, is milder and longer lasting. 'Drug seeking' is present. Abuse liability is rated lower than morphine.

Naloxone (high dose) can prevent buprenorphine effect, but does not reverse it when given afterwards; does not precipitate buprenorphine withdrawal; probably because of more tight binding of buprenorphine to opioid receptors.

Buprenorphine has good efficacy by sublingual route, is highly plasma protein bound and remains in tissues for several days; terminal t½ is 40 hours. It is mostly excreted unchanged in bile and finds its way out of the body in faeces.

Dose: 0.3–0.6 mg i.m., s.c. or slow i.v., also sublingual 0.2–0.4 mg 6–8 hourly.

NORPHIN, TIDIGESIC 0.3 mg/ml inj. 1 and 2 ml amps. 0.2 mg sublingual tab; BUPRIGESIC, PENTOREL 0.3 mg/ml inj in 1, 2 ml amp.

Use: Buprenorphine is indicated for long-lasting painful conditions requiring an opioid analgesic, e.g. cancer pain. It has also been recommended for premedication, postoperative pain, in myocardial infarction and in the treatment of morphine dependence.

Buprenorphine is not suitable for use during labour, because if respiratory depression occurs in the neonate, it cannot be effectively reversed by naloxone.

Nalbuphine, Meptazinol and *Dezocine* are other agonist-antagonist opioids introduced in some countries.

PURE OPIOID ANTAGONISTS

1. Naloxone   It is N-alylnor-oxymorphone and a competitive antagonist on all types of opioid receptors. However, it blocks μ receptors at much lower doses than those needed to block κ or δ receptors. It is devoid of any kind of agonistic activity even at high doses (20 times μ blocking dose). No subjective or autonomic effects are produced in individuals who have not received an opioid. No physical/psychological dependence or abstinence syndrome has been observed.

Injected intravenously (0.4–0.8 mg) it promptly antagonizes all actions of morphine: analgesia is gone, respiration is not only normalized but stimulated—probably due to sudden sensitization of respiratory centre to the retained CO_2, or it may be a manifestation of acute withdrawal; pupils dilate. However, sedation is less completely reversed.

At 4–10 mg dose it also antagonizes the agonistic actions of nalorphine, pentazocine, etc., but the dysphoric and psychotomimetic effects of some of them are incompletely suppressed. The naloxone insensitive component is believed to be mediated through σ receptors.

Actions of buprenorphine are prevented but not effectively reversed by naloxone, because it fails to displace buprenorphine that has already bound to the opioid receptors.

Naloxone 0.4 mg i.v. precipitates morphine withdrawal in dependent subjects: the syndrome lasts for 2–3 hours; 5 mg or more is required to precipitate nalorphine and pentazocine withdrawal.

Naloxone also blocks the actions of endogenous opioid peptides (*see* below). These peptides have been implicated in a variety of physiological functions; it is surprising that naloxone does not produce hyperalgesia or other effects in normal individuals. However, it has been found to render those individuals more susceptible to pain who normally have high tolerance. It blocks *placebo, acupuncture* and *stress-induced analgesia,* showing involvement of endogenous opioid peptides in these responses. Naloxone partly antagonizes respiratory depression produced by certain nonopioids, e.g. N_2O, diazepam as well.

Naloxone is inactive orally because of high first pass metabolism in liver. Injected i.v. it acts in 2–3 min. The primary pathway of metabolism is glucuronidation. Plasma t½ is 1 hour in adults and 3 hours in newborns.

Adverse effects of naloxone are uncommon; may include rise in BP and pulmonary edema. NARCOTAN 0.4 mg in 1 ml (adult) and 0.04 mg in 2 ml (infant) amps; NALOX, NEX 0.4 mg inj.

Use   Naloxone is the drug of choice for morphine poisoning (0.4–0.8 mg i.v. every 2–3 min: max 10 mg) and for reversing neonatal asphyxia due to opioid use during labour (10 μg/kg in the cord). It is also used to treat overdose with other opioids and agonist-antagonists (except buprenorphine).

Other possible clinical applications of naloxone are:
- To reverse respiratory depression due to intraoperative use of opioids: 0.1–0.2 mg i.v. (this dose usually preserves analgesia in the postoperative period).
- It has also been tried as an adjunct to intraspinal opioid analgesia: reverses respiratory depression without abolishing pain relief.
- Diagnosis of opioid dependence—precipitates withdrawal in dependent subjects.
- It also partially reverses alcohol intoxication.
- Naloxone has been found to elevate BP in endotoxic or hypovolaemic shock, stroke and spinal injury. In these conditions injection of morphine worsens cardiovascular status. Opioid peptides are believed to be involved in the pathogenesis. However, the value of naloxone compared to conventional therapy is uncertain.

2. Naltrexone   It is chemically related to naloxone and is another pure opioid antagonist, that is devoid of subjective and other agonistic effects, but very high doses have caused unpleasant feelings in some individuals. It is more potent than naloxone. Naltrexone differs from naloxone in being orally active and having a long duration of action (1–2 days) which makes it suitable for 'opioid blockade' therapy of postaddicts: 50 mg/day is given orally so that if the subject takes his/her usual shot of the opioid, no subjective effects are produced and the craving subsides. Alcohol craving is also reduced by naltrexone,

and it is approved for prevention of relapse of heavy drinking (*see* p. 393). Nausea is a common side effect; another is headache. High doses can cause hepatotoxicity.

NALTIMA 50 mg tab.

3. Nalmefene This pure opioid antagonist lacks hepatotoxicity of naltrexone, has higher oral bioavailability and is longer acting.

Methyl naltrexone This derivative of naltrexone does not penetrate the blood-brain barrier, but effectively blocks peripheral action of μ opioids. It is being used to reverse constipation in cancer patients receiving chronic opioid analgesia and in those taking methadone maintenance therapy.

ENDOGENOUS OPIOID PEPTIDES

In the mid 1970s, with herculean efforts, a number of peptides having morphine-like actions were isolated from mammalian brain, pituitary, spinal cord and g.i.t. These peptides are active in very small amounts, their actions are blocked by naloxone, and they bind with high affinity to the opioid receptors. There are 3 distinct families of opioid peptides. Each is derived from a specific large precursor polypeptide.

1. Endorphins β-endorphin (β-END) having 31 amino acids is the most important of the endorphins. It is derived from Pro-opio-melanocortin (POMC) which also gives rise to γ-MSH, ACTH and two lipotropins. β-END is primarily μ agonist, but also has δ action.

2. Enkephalins Methionine-enkephalin (met-ENK) and leucine-enkephalin (leu-ENK) are the most important. Both are pentapeptides. The large precursor peptide *proenkephalin* has 4 met-ENK and 1 leu-ENK residues. The two ENKs have a slightly different spectrum of activity; while met-ENK has equal affinity for μ and δ sites, leu-ENK prefers δ receptors.

3. Dynorphins Dynorphin A and B (DYN-A, DYN-B) are 8–17 amino acid peptides derived from *prodynorphin* which contains 3 leu-ENK residues also. DYNs are more potent on κ receptors, but also activate μ and δ receptors.

Distribution of the 3 families of peptides is summarized below:

1. *POMC* (limited distribution)	–	Arcuate nucleus which sends projections to limbic areas and medulla.
	–	Anterior pituitary (modulates hormone release).
	–	Pancreatic islets (modulates insulin, glucagon release).
2. *Proenkephalin* (wide distribution)	–	Pain areas in spinal cord, trigeminal nucleus, periaqueductal grey matter.
	–	Affective areas in limbic system, locus coeruleus and cortex.
	–	Medulla (autonomic functions).
	–	Median eminence of hypothalamus (neuro-endocrine control).
	–	Adrenal medulla, gastric and intestinal glands.
3. *Prodynorphin*	–	Wide distribution roughly parallel to proenkephalin, but in distinct neurones of the same area.

Receptor selectivity of the 3 major opioid peptide families may be graded as:

Opioid peptide	Relative receptor selectivity
β-Endorphin	$\mu > \delta \gg \kappa$
Enkephalin (Met/Leu)	$\delta \geq \mu \gg \kappa$
Dynorphin A,B	$\kappa \gg \mu = \delta$

The opioid peptides constitute an endogenous opioid system which normally modulates pain perception, mood, hedonic (pertaining to pleasure) and motor behaviour, emesis, pituitary hormone release and g.i.t. motility, etc.

β-END injected directly into the brain is 20–40 times more potent analgesic than morphine. Its primary localization in hypothalamus and pituitary and its long t½ prompts that it has a *neurohormone* function which modulates the release of other hormones. β-END decreases LH, FSH release and increases GH, prolactin release. Naloxone has opposite effects on the levels of these hormones—suggesting that the system is constitutively active.

The wide distribution of ENKs and DYNs along with their short t½ suggests that they function as *neuromodulator* or *neurotransmitter*. They appear to regulate pain responsiveness at spinal and supraspinal levels. Naloxone blocks placebo, acupuncture and stress-induced analgesia, suggesting the involvement of opioid peptides in

these responses. Opioid peptides also appear to participate in regulation of affective behaviour and autonomic function.

A novel opioid peptide Nociceptin/orphanin FQ (N/OFQ) has been isolated from mammalian brain. It is localized in cortex, hippocampus, spinal cord and certain sensory sites; is believed to play a role in stress response, reward and reinforcing actions, learning and memory. The N/OFQ receptor, is now called *Nociceptin opioid peptide (NOP)* receptor. At certain sites, N/OFQ can act as an 'antiopioid' through the NOP receptor. In the pain control mechanisms, N/OFQ appears to play both opioid-like as well as antagonistic roles, depending on the site and the basal state of pain.

Morphine and other opioids act as exogenous agonists on some of the receptors for these peptides. This has given an explanation for the existence of specific receptors in the body for exogenous substances like morphine. Morphine itself has now been detected in mammalian brain.

☞ PROBLEM DIRECTED STUDY

34.1 A boy aged 14 years is brought to the hospital emergency with crush injury of both lower legs. An eye witness who brought the boy told that a bus had run over his legs about 20 min. ago. The legs were crushed but he had not bled much. He also told that initially the boy was shrieking in pain, but had fainted on way to the hospital. Preliminary examination reveals that the patient is in a semiconscious state, looks pale, the pulse is fast, low volume and collapsing. Both legs have sustained multiple fractures, the skin and soft tissues have lacerated from which blood is oozing, but there is no active bleeding. There is no apparent head injury.

(a) Should any medicine be administered immediately, before even completing a thorough physical examination? If so, which drug, by what route, and why?

(see Appendix-1 for solution)

CNS STIMULANTS

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

The CNS stimulants mostly produce a generalized action which may, at high doses, result in convulsions. Given below is a working classification based primarily on the clinical use, because clearcut differences do not exist.

CLASSIFICATION

1. *Convulsants* Strychnine, Picrotoxin, Bicuculline, Pentylenetetrazol (PTZ).
2. *Analeptics* Doxapram
3. *Psychostimulants* Amphetamines, Methylphenidate, Atomoxetine, Modafinil, Armodafinil, Pemoline, Cocaine, Caffeine.

Many other drugs are capable of causing CNS stimulation as side effect or at high doses.

I. 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. It has been labelled as a spinal convulsant because the dose producing convulsions is the same in spinal animals as in intact animals; actually it stimulates the whole cerebrospinal axis.

Strychnine acts by blocking *post-synaptic* inhibition produced by the inhibitory transmitter glycine. One of the sites that has been clearly demonstrated is the Renshaw cell-motoneurone junction in the spinal cord through which inhibition of antagonistic muscles is achieved. Due to loss of synaptic inhibition, any nerve impulse becomes generalized, resulting in apparent excitation and convulsions.

There are no valid uses of strychnine now. Accidental poisonings, especially in children, do occur. Treatment of poisoning is similar to that of status epilepticus (*see* Ch. 30).

2.   Picrotoxin   Obtained from 'fish berries' of East Indies *Anamirta cocculus.* It is a potent convulsant—convulsions are clonic, spontaneous and asymmetrical. The convulsions are accompanied by vomiting, respiratory and vasomotor stimulation. Though regarded as a medullary stimulant, it has little selectivity in site of action.

Picrotoxin acts by blocking *presynaptic* inhibition mediated through GABA. However, it is not a competitive antagonist; does not act on GABA receptor itself, but on a distinct site and prevents Cl¯ channel opening (*see* p. 403). Diazepam, which facilitates GABAergic transmission, is the drug of choice for picrotoxin poisoning. Picrotoxin has no therapeutic indication now.

3.   Bicuculline   This synthetic convulsant has picrotoxin-like actions. It is a competitive $GABA_A$ receptor (intrinsic Cl¯ channel receptor) antagonist, while $GABA_B$ receptor (G-protein coupled receptor) is insensitive to it. It is only a research tool.

4.   Pentylenetetrazol (PTZ, Metrazol, Leptazol)   It is a powerful CNS stimulant, believed to be acting by direct depolarization of central neurones. However, it has also been shown to interfere with GABAergic inhibition—may be acting in a manner analogous to picrotoxin.

Low doses cause excitation, larger doses produce convulsions which are similar in pattern to those caused by picrotoxin. Antagonism of PTZ induced convulsions is an established method of testing anticonvulsant drugs in laboratory animals (*see* Ch. 30).

II. ANALEPTICS (Respiratory stimulants)

These are drugs which stimulate respiration and can have resuscitative value in coma or fainting. They do stimulate respiration in subconvulsive doses, but margin of safety is narrow; the patient may get convulsions while still in coma. Mechanical support to respiration and other measures to improve circulation are more effective and safe.

The role of analeptics in therapeutics is very limited. Situations in which they may be employed are:
(a) As an expedient measure in hypnotic drug poisoning untill mechanical ventilation is instituted.
(b) Suffocation on drowning, acute respiratory insufficiency.
(c) Apnoea in premature infant.
(d) Failure to ventilate spontaneously after general anaesthesia.
However, the overall utility of analeptics is dubious.

Doxapram   It acts by promoting excitation of central neurones. At low doses it is more selective for the respiratory centre than other analeptics. Respiration is stimulated through carotid and aortic body chemoreceptors as well. Falling BP rises. Continuous i.v. infusion of doxapram may abolish episodes of apnoea in premature infant not responding to theophylline. Other uses: *see* above.

Dose: 40–80 mg i.m. or i.v.; 0.5–2 mg/kg/hr i.v. infusion.
CAROPRAM 20 mg/ml in 5 ml amp.

Reflex stimulation Smelling ammonia or a drop of alcohol in the nose may be enough for hysterical fainting; analeptics should not be used.

III. PSYCHOSTIMULANTS

These drugs have predominant cortical action; their psychic effects are more prominent than those on medullary vital centres.

1. 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. Their pharmacology and uses are described in Ch. 9.

2. 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 considered superior to amphetamine for attention deficit hyperkinetic disorder (ADHD) because it causes lesser tachycardia and growth retardation. Behaviour and learning ability are improved in 3 out of 4 treated children. It can also be used for concentration and attention defect in adults, and for narcolepsy, but should not be employed to treat depression, dementia, obesity or to keep awake.

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.
Dose: Adults 5–10 mg BD; children 0.25 mg/kg/day initially, increased up to 1 mg/kg/day if needed.
RETALIN 5, 10, 20, 30 mg tab.

3. Atomoxetine This is a selective NA reuptake inhibitor, unrelated to amphetamine as well as to imipramine, which does not enhance DA release in the brain, and is neither a CNS stimulant nor an antidepressant. However, it has been found to improve attention span and behaviour in ADHD. It is indicated in children >6 years and in adults with concentration and attention problems.

Atomoxetine is absorbed orally, hydroxylated by CYP2D6 and excreted in urine, mainly as glucuronide. While majority of individuals are extensive metabolizers (EM), few are poor metabolizers (PM) due to polymorphism of CYP2D6. Inhibitors of CYP2D6 like fluoxetine, paroxetine, quinidine increase concentration and toxicity of atomoxetine. It should not be given with MAO inhibitors and is contraindicated in glaucoma.
Dose: 0.5 mg/kg/day in the morning, may be increased upto 1.2 mg/kg/day and split into morning and afternoon doses. Adults 40 mg OD, max 100 mg/day.
ATTENTROL 10, 18, 25, 40 mg caps AXEPTA 18, 25 mg caps.

Atomoxetine is relatively well tolerated, does not produce agitation, seizures, dependene or arrhythmias. Common side effect is dyspepsia, anorexia and other abdominal symptoms. Others are sleep disturbances, mood swings, emotional lability, rarely suicidal thoughts and hepatotoxicity. Growth retardation is possible in children.

4. Modafinil This newer psychostimulant is popular with night-shift (call centre) workers and other professionals who want to improve alertness and keep awake. It is claimed to increase attention span and improve accuracy that has been compromized by fatigue and sleepiness. Although, modafinil has been shown to inhibit NA and DA uptake as well as alter junctional concentration of glutamate and GABA, its actual mechanism of action is not known. The approved indications are day-time sleepiness due to narcolepsy, sleep-apnoea syndrome and shift-work disorder (SWD). It has also been found to reduce euphoria produced by cocaine and to suppress cocaine withdrawal symptoms; is being evaluated as a drug to prevent relapse of cocaine dependence.

The most common side effects are insomnia and headache. Others are nausea, dyspepsia, dizziness, confusion, amnesia, personality disorders, tremors and hypertension. Dependence is a possibility on long-term use.

Modafinil is absorbed within 2–4 hours of oral administration, and is eliminated with a t½ of 15 hours.

Dose: 100–200 mg morning and afternoon for day-time sleepiness due to narcolepsy or sleep-apnoea syndrome; or 200 mg 1 hour before starting night-shift work.
MODALERT, PROVAKE 100, 200 mg tabs.

Armodafinil A congener of modafinil which has been recently approved for improving wakefulness in patients with obstructive sleep apnoea (OSA), SWD and narcolepsy.

5. Pemoline Though chemically unrelated, pemoline has CNS stimulant actions similar to those of methylphenidate. Sympathomimetic and CVS actions are insignificant. Pemoline has been used in ADHD, narcolepsy and excessive day-time sleepiness, with benefits and side effects similar to methylphenidate. However, because of slow onset of action and hepatotoxicity, it has been discontinued in USA, and is not available in India.

6. Cocaine (*see* Ch. 26)

7. Caffeine
Out of the three naturally occurring methylxanthines, only caffeine is used as a CNS stimulant. Its pharmacological actions are described in Ch. 16 along with those of theophylline.

Pharmacokinetics Caffeine has poor water solubility; is rapidly but irregularly absorbed after oral administration. It is < 50% bound to plasma proteins, distributed all over the body, and nearly completely metabolized in liver by demethylation and oxidation. Metabolites are excreted in urine; plasma t½ is 3–6 hours in adults.

Adverse effects Toxic effects of caffeine are extensions of its pharmacological actions. Caffeine poisoning is rare, and it is less toxic than theophylline.

Gastric irritation, nausea and vomiting may occur as side effects.

Excitatory and motor effects such as nervousness, insomnia, agitation, muscular twitching, rigidity, rise in body temperature, delirium and convulsions are produced at toxic doses.

Tachycardia, occasionally extrasystoles occur at high doses.

Caffeine is to be avoided in peptic ulcer patients. It is not contraindicated in gout because it is not converted in the body to uric acid. Moderate coffee drinking does not contribute to development of hypertension.

Uses

1. In analgesic mixture: caffeine benefits headache probably by allaying fatigue and boredom. It has no analgesic action of its own.
2. Migraine: Caffeine is used in combination with ergotamine for treatment of migraine attack. It appears to benefit by augmenting constriction of cranial vessels and by enhancing absorption of ergotamine from the g.i.t.
3. Apnoea in premature infants: as alternative to theophylline (*see* Ch. 16).

Caffeine is available only in combined formulations with ergotamine or analgesics in tablets.
CAFERGOT: Caffeine 100 mg + ergotamine 1 mg tab.
MICROPYRIN: Caffeine 20 mg + aspirin 350 mg tab.

Tonics containing caffeine are banned in India.

COGNITION ENHANCERS
(Cerebroactive drugs)

These are a heterogenous group of drugs developed for use in dementia and other cerebral disorders. They do elicit pharmacological effects, but widely different mechanisms of action are claimed. Therapeutic benefits are limited, and at the best, short-lasting.

Dementia Refers to acquired global impairment of intellect, memory and personality (cognitive functions) in the absence of gross clouding of consciousness or motor involvement. Memory, capacity to solve problems of day to day living, performance of learned motor skills, social skills and control of emotions are primarily affected.

Alzheimer's disease (AD) A progressive neurodegenerative disorder which affects older individuals and is the most common cause of dementia. It may progress to a totally vegetative state. Atrophy of cortical and subcortical areas is associated with deposition of β-amyloid protein in the form of extracellular senile (amyloid) plaques and formation of intracellular neurofibrillary tangles. These abnormal proteins accumulate mostly due to reduced clearance, but in some cases, due to overproduction, and cause neuronal damage. There

is marked cholinergic deficiency in the brain, though other neurotransmitter systems, especially glutamate and neuro-peptide, are also affected.

The indications of cognition enhancers include:
1. Alzheimer's disease (AD) and multi-infarct dementia (MID).
2. Mild cognitive impairment (MCI) or 'common symptoms' of the elderly; dizziness and episodic memory lapses.
3. Mental retardation in children, learning defects, attention deficit disorder.
4. Transient ischaemic attacks (TIAs), cerebro-vascular accidents, stroke.
5. Organic psychosyndromes and sequelae of head injury, ECT, brain surgery.

Apart from some cholinergic activators and glutamate antagonist introduced lately, the above therapeutic field is barren and commercially highly profitable. A variety of drugs have been briskly promoted by manufacturers and wishfully prescribed by physicians. The mechanism by which they are believed to act are:
1. Increasing global/regional cerebral blood flow (CBF)
2. Direct support of neuronal metabolism.
3. Enhancement of neurotransmission.
4. Improvement of descrete cerebral functions, e.g. memory.

All cerebroactive drugs are tested for their vaso-dilator activity. The basic assumption has been that improvement in cerebral circulation is pos-sible, real and therapeutically useful. However, precise measurements have shown that in many cases such claims are merely expectations. In stroke a global vasodilator effect may even be harmful by worsening cerebral edema and inducing 'steal' phenomenon, i.e. diversion of blood flow to non-ischaemic areas to the detriment of ischaemic area. Cerebral blood flow is reduced in AD, but this is probably a conse-quence of loss of neurones and not its cause.

The cerebroactive drugs may be grouped into:

a. *Cholinergic activators:*
   Tacrine, Rivastigmine, Donepezil, Galantamine

b. *Glutamate (NMDA) antagonist:*
   Memantine

c. *Miscellaneous cerebroactive drugs:*
   Piracetam, Pyritinol (Pyrithioxine), Dihydro-ergotoxine (Codergocrine), Citicoline, Piribedil, Ginkgo biloba.

1. Cholinergic activators Since brain ACh levels are markedly reduced and cholinergic neurotransmission is the major sufferer in AD, various approaches to augment brain ACh have been tried. Precursor loading with choline or lecithin have failed because there is no shortage of these substrates in the brain. Cholinergic agonists (arecoline, bethanechol, oxotremorine) and conventional anticholinesterases (anti-ChEs) like physostigmine produce symptom improve-ment, but at the cost of marked peripheral side effects. Over the past two decades 4 cerebro-selective antiChEs have been introduced and 3 are widely used in AD.

Tacrine It is the first centrally acting anti-ChE to be introduced for AD. In clinical trials tacrine produced significant improvement in memory, attention, praxis, reason and language. However, it does not alter the course of underlying disease process. Frequent side effects and hepatotoxicity have restricted its use.

Rivastigmine This carbamate derivative of physostigmine inhibits both AChE and BuChE, but is more selective for the G1 isoform of AChE that predominates in certain areas of the brain. Rivastigmine is highly lipid-soluble—enters brain easily. Greater augmentation of cholinergic transmission in brain is obtained with mild peripheral effect. The carbamyl residue intro-duced by rivastigmine into AChE molecule dissociates slowly resulting in inhibition of cerebral AChE for upto 10 hours despite the 2 hr plasma t½ of the drug.

In clinical trials an average of 3.8 point improvement in Alzheimer's Disease Assessment Scale (ADAS-cog) has been obtained compared to placebo. Other symptoms like apathy, delu-sions, hallucinations and agitation also improve, but to a lesser extent. Disease progression is briefly slowed or is not affected. Peripheral cho-linergic side effects are mild. It has not produced liver damage. Rivastigmine is indicated in mild-to-moderate cases of AD, but not in advanced disease.

Dose: Initially 1.5 mg BD, increase every 2 weeks by 1.5 mg/day upto 6 mg/BD.
EXELON, RIVAMER 1.5, 3, 4.5, 6.0 mg caps.

Donepezil This cerebroselective and reversible anti-AChE produces measurable improvement in several cognitive as well as non-cognitive (activities of daily living) scores in AD, which is maintained at least upto 2 years. The benefit is ascribed to elevation of ACh level in the cortex, especially in the surviving neurones that project from basal forebrain to cerebral cortex and hippocampus. Therapeutic doses produce only weak peripheral AChE inhibition: cholinergic side effects are mild. Because of long t½ (~70 hr), donepezil is administered once daily at bed time; a distinct advantage over rivastigmine and galantamine which need twice daily dosing. Moreover, it can be used even in relatively severe case of AD. Donepezil is generally well tolerated and is not hepatotoxic.
Dose: 5 mg OD HS (max 10 mg OD);
DONECEPT, DOPEZIL, DORENT 5, 10 mg tabs.
Oral dispersible tablets of donepezil have also been approved for the benefit of patients who have problem in swallowing the regular tablet.

Galantamine It is a natural alkaloid which selectively inhibits cerebral AChE and has some direct agonistic action on nicotinic receptors as well. Galantamine has produced cognitive and behavioural benefits in AD which are comparable to rivastigmine and donepezil. It is well tolerated, but needs twice daily dosing.
Dose: 4 mg BD (max 12 mg BD)
GALAMER 4, 8, 12 mg tabs.

There is now firm evidence that rivastigmine, donepezil and galantamine afford similar, but modest symptomatic benefit in AD. Cognitive decline is slowed or halted for a short time, but not prevented. Their side effects, mostly g.i. smptoms, muscle pain and weird dreams, are also comparable among the three. There is now some evidence to support their use in MCI and non-Alzheimer dementia as well.

2. Memantine This new NMDA receptor antagonist, related to amantadine (that is also a NMDA antagonist), has been found to slow the functional decline in moderate-to-severe AD, but benefit in milder disease are unclear. It appears to block excitotoxicity of the transmitter glutamate in a noncompetitive and use-dependent manner. Beneficial effects have also been noted in parkinsonism.

Memantine is better tolerated than anti-AChEs used in AD. Side effects are constipation, tiredness, headache, dizziness, and drowsiness. It is indicated in moderate-to-severe AD, either to replace anti-AChEs or to supplement them. Memantine can be used for other types of dementia as well.
Dose: Initially 5 mg OD, increase gradually upto 10 mg BD; stop if no clinical benefit in 6 months.
ADMENTA, MENTADEM 5, 10 mg tabs, ALMANTIN 5 mg tab.

3. Piracetam This cyclic GABA derivative has no GABA-like activity and has been called 'nootropic' meaning a drug that selectively improves efficiency of higher telencephalic integrative activities.

Piracetam is not a vasodilator, does not affect total/regional CBF, but may reduce blood viscosity. In India and some other countries it has been promoted for cognitive impairment and dementia in the elderly as well as for mental retardation in children for over 30 years. However, a Cochrane Database review (2004) has concluded that published data does not support such use. Some later studies have demonstrated a neuroprotective effect of piracetam during coronary bypass surgery, and that it may benefit cognitive disorders of cerebrovascular and traumatic origin. In the UK, it is approved for adjunctive treatment of cortical myoclonus, but is not recommended for children. It is not approved in the USA.

Side effects are minor: gastric discomfort, nervousness, excitement, insomnia, dizziness and skin rash.
Dose: 0.8–1 g TDS oral; children 20 mg/kg BD–TDS; 1–3 g i.m. 6 hourly in stroke/head injury.
NORMABRAIN, NEUROCETAM, NOOTROPIL 400, 800 mg cap, 500 mg/5 ml syr., 300 mg/ml inj.

4. Pyritinol (Pyrithioxine) Pyritinol consists of two pyridoxine molecules joined through a disulfide bridge, but has no vit B$_6$ activity. It is claimed to activate cerebral metabolism by selectively increasing glucose transport across blood-brain barrier and improving regional blood flow in ischaemic brain areas. It has been promoted for:
- Sequelae of cerebrovascular accidents, head injury, prolonged anaesthesia.
- Infants and children with developmental disorders of CNS, delayed milestones.
- Concentration and memory defects, senility, organic brain syndromes.

However, therapeutic benefit, if any, is uncertain.

ENCEPHABOL 100, 200 mg tab. 100 mg/5 ml suspension; 200 mg dry powder with 2 ml solvent for i.v. infusion.

Dose: 100–200 mg TDS, children 50–100 mg TDS orally; 200–400 mg every 4–6 hours (max. 1 g/day) has been given i.v. for recovery from cerebral hypoxia due to cardiac arrest, anaesthesia, brain operations and stroke.

Side effects: Only mild g.i. upset was noted initially. Later skin rashes, itching and taste disturbances (attributable to the disulfide moiety) have been reported. It has been withdrawn in some countries.

5. Dihydroergotoxine (Codergocrine): It is a semi-synthetic ergot alkaloid having α adrenergic blocking property; claimed to increase cerebral blood flow selectively. It is believed to act by protecting altered brain metabolism. In a dose of 1.0–1.5 mg TDS oral/sublingual or 0.3 mg i.m. OD, it has been recommended for MCI and dementia, but therapeutic valve is not established.

HYDERGINE 1 mg tab, 0.3 mg/ml inj. CERELOID 1 mg tab.

Side effects: flushing, headache, nasal congestion, postural hypotension, g.i. disturbances and rashes.

6. Piribedil: It is a dopaminergic agonist claimed to improve memory, concentration, vigilance, giddiness and tinnitus in the elderly due to circulatory insufficiency, but benefit is unsubstantiated. Minor efficacy in parkinsonism has also been reported. Side effects are mild g.i. complaints.

Dose: 50 mg OD, BD; TRIVASTAL LA 50 mg tab.

7. Citicoline It is a compound derived from choline and cytidine, that is involved in biosynthesis of lecithin. Citicoline is believed to improve cerebral function by increasing blood flow to the brain and enhancing cerebral metabolism. Some studies have demonstrated short-term improvement in memory and behaviour in cerebrovascular disorders, but there is little evidence of clear-cut benefit. In the absence of effective medicines and under promotional pressure, citicoline is being commonly prescribed for impaired brain function due to ischaemic stroke, parkinsonism, head injury, etc.

Dose: 0.5–1 g/day i.m. or i.v. inj, 200–600 mg/day oral in divided doses.

CITILIN, CITINOVA 500 mg tab, 500 mg/2 ml inj, STROLIN 500 mg tab.

8. Ginkgo biloba The dried extract of this Chinese plant contains a mixture of ginkgoflavon glycosides (e.g. ginkgolide B) which have PAF antagonistic action. Since PAF has been implicated in cerebral thrombosis and infarcts, it is professed that *G. biloba* will prevent cerebral impairment in cerebrovascular insufficiency. It has been promoted for a variety of cognitive and behavioural disorders in the elderly, but a Cochrane metaanalysis (2007) concluded that *G. biloba* produced slight overall improvement in cognitive performance. However, most trials were small and results were inconsistant.

Side effects are mild upper g.i.t. symptoms, and increased risk of bleeding.

Dose: 40–80 mg TDS for a minimum period of 4 weeks; GINKOCER, BILOVAS, GINKOBA 40 mg tab.

☞ PROBLEM DIRECTED STUDY

35.1 A 75-year-old man was brought with a history of progressive functional decline, so much so that he now needs to be looked-after all the time. He misplaces his daily need articles, forgets what he said few minutes ago, is unable to perform simple calculations, mixes up what happened today and what happened yesterday, has poor control of emotions, but vision, hearing and other sensations are well preserved, and there is no gross ataxia. He was diagnosed to be having moderately advanced Alzheimer's disease and was prescribed Tab Donepezil 5 mg at bed time daily. After one week, his son reported that while his mental and functional state is unchanged, he has developed pain in abdomen, muscle ache, loud eructations, loose motion and is refusing to take the medicine.

(a) What could be the reason for no improvement in the mental and functional state of the patient? Are the new symptoms due to the medication? Should the drug be stopped, changed or another one added at this stage? What alternative drug could be used?

(see Appendix-1 for solution)