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. dopa-minergic 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*
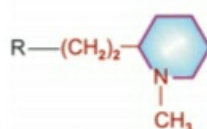   Clozapine   Aripiprazole
   Risperidone   Ziprasidone
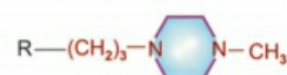   Olanzapine   Amisulpiride
   Quetiapine   Zotepine

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, psychomotor 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 aminoacid (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.

SECTION 7

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-HT₂ 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-HT₂ as well as α adrenergic blockade. It is quite sedating, moderately potent anticholinergic, but paradoxically induces hypersalivation. Significant H₁ 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-HT₂ receptor blockade. In addition it has high affinity for α₁, α₂ and H₁ receptors: blockade of these may contribute to efficacy as well as side effects like postural hypotension. 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.

- 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
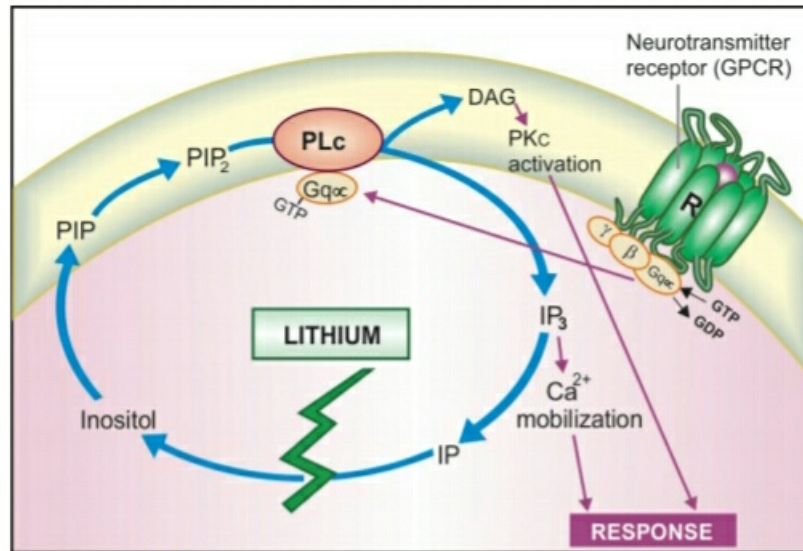
Fig. 32.1: Proposed mechanism of antimanic action of lithium
PIP—Phosphatidyl inositol phosphate; PIP₂—Phosphatidyl inositol bisphosphate;
IP₃—Inositol trisphosphate; IP—Inositol-1-phosphate; PLc—Phospholipase C;
DAG—Diacylglycerol; PKc—Protein Kinase C; Gq—Coupling Gq protein;
R—Neurotransmitter receptor

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 → fall in circulating T$_3$, T$_4$ levels → TSH secretion from pituitary → 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 contraindicated 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$^+$ → 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 admited 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)