CHAPTER

1

General Psychopharmacology

HISTORY

The age of psychopharamcology probably began with the introduction of chlorpromazine in the early 1950s. Before neuroleptics, there were other chemical treatments of psychoses, such as the continuous sleep treatment introduced by *hypnotics* (1920s) and insulin *'shock' treatment* (by German psychiatrist, Sakel in 1930s). In 1931, two Indian researchers reported a new Indian drug for insanity and high blood pressure, *'Rauwolfia serpentina'* one of the active ingredients of which is reserpine. In 1952, Delay and Deniker (French researchers) reported the usefulness of chlorpromazine for treating schizophrenia. They coined the term *'Neuroleptic'*, meaning "that which takes the neuron" to describe the action of this type of drug. Neuroleptics are also called major tranquillizers, antipsychotic drugs, antischizophrenic drugs and ataractics. Chlorpromazine was, however, first synthesized by Charpentier in 1950. Laborit, a French Surgeon, who impressed with its use in surgery (it potentiated the effects of anaesthetics and induced *'artificial hibernation'*) suggested its use in psychiatry. Courvosier et al identified a large number of actions of chlorpromazine and hence it was given the trade name—largactyl. In 1958, Janssen (in Belgium) synthesized and tested, haloperidol (a butyrophenone) as an antischizophrenic compound.

History of Psychopharmacology

Hippocrates	—	Herbal remedies for mental illness
Fisher (1903)		Synthesized first barbiturate
Sen and Bose (1931)	—	Used Rauwolfia extract in major psychosis
Bernthsen (1883)	—	Synthesized chlorpromazine
Charpentier (1950)	—	Described properties of chlorpromazine
Delay, Deniker and Harl (1952)	—	Use of chlorpromazine to treat certain psychotic symptoms and coined term *'neuroleptic'*
Cade (1949)	—	Lithium
Zeller (1952)	—	Described Iproniazid (a MAO inhibitor) as an antidepressant

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Janssen et al (1958)	—	Synthesized a large number of butyrophenones
Divry et al (1958)	—	Described properties of a number of butyrophenones
Kuhn (1957)	—	Described properties of impramine
Haflinger and Schindler (1957)	—	Synthesized imipramine
Sternbach	—	Discovery of chlordiazepoxide
Cohen (1960s)	—	Described properties of chlordiazepoxide
Hoffer and Osmond (1954)	—	Megavitamin therapy (niacin + vit. C + pencillin)
Hald et al (1948)	—	Disulfiram (antabuse)
Ferguson (1956)	—	Calcium carbide cause reaction-like antabuse
Taylor et al (1964)	—	Metronidazole causes antabuse like reactions
Osterman et al (1959)	—	Chlormethiazole (use in alcohol withdrawal symptom)

The groups of drugs discussed in this chapter are:

1. Antipsychotic drugs (neuroleptics)
2. Anti-Parkinsonian drugs
3. Antidepressants
4. Antiaggressive drugs
5. Disulfiram
6. Lithium
7. Hypnosedative drugs
8. CNS stimulants
9. Anticonvulsants
10. Cerebral activators

I. Antipsychotic Drugs (Neuroleptics)

The drugs used to calm down the patients suffering from psychotic symptoms or illness without causing hypnosis or anaesthesia are known as antipsychotic transquillisers. They are also called major tranquillizers or neuroleptics or antischizophrenic drugs or ataractics. The word 'antipsychotics' is most appropriate. The term 'neuroleptic' means drug which produces both extrapyramidal and antipsychotic effects, (but there are drugs, e.g. clozapine, olanzapine which do not produce extrapyramidal effects).

Classification

- Phenothiazines
  - *With dimethylaminopropyl side chain*
    Chlorpromazine
    Trifluopromazine
  - *Piperidine side chain*
    Thioridazine
    Mesoridazine

  - *Piperazine side chain*
    Trifluoperazine
    Fluphenazine
    Perphenazine
    Prochlorperazine
- **Butyrophenone derivatives:** Haloperidol, trifluperidol
- **Thioxanthene derivatives:** Thiothixene, chlorprothixene
- **Diphenylbutypiperidines:** Pimozide, penfluridol, fluspirilene
- **Indole derivatives:** Molindone
- **Rauwolfia alkaloids:** Reserpine
- **Miscellaneous compounds:** Clozapine, olanzapine, risperidone, raclapride, amisulpride, remoxipride, sertindole, quetiapine, ziprasidone, paliperidone, aripiprazole, iloperidone, asenapine, blonanserin, lurasidone.

Further classification has been discussed in **Table 1.1**.

Pharmacological actions of antipsychotics are described with chlorpromazine as an example.

TABLE 1.1. Selected antipsychotic drugs' dosages

Class/Generic name	*Trade name*	*Dose equivalent (mg)*	*Usual daily oral dose (mg)*	*Parenteral single dose (mg)*
I. Phenothiazines				
a. Aliphatic				
i. Chlorpromazine hydrochloride	Chlorpromazine	100	200–600 (up to 2000 mg)	25–100 (IM)
ii. Triflupromazine hydrochloride	Siquil	26–30	50–150 (up to 400)	60–150 (IM)
b. Piperazine				
i. Trifluoperazine	Espazine Trinicalm Neocalm, Trazine	2.4–3.2	5–40	1–2 (IM)
ii. Fluphenazine hydrochroide	Anatensol	1.1–1.3	2.5–10	2–5
iii. Fluphenazine decanoate	Prolinate Anatensol Fludecon	0.61	10 mg of oral fluphenazine = 12.5–25 mg/ 2 weeks of fluphenazine decanoate	25–50 (IM every 2–4 weeks)
iv. Flupenthixol	Fluanxol	8	3–18	—
v. Flupenthixol decanoate	Fluanxol Spenzo	0.50	10 mg of oral = 10–20 mg every 2–4 weeks	20–40 mg (IM every 2–4 weeks)

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Class/Generic name	*Trade name*	*Dose equivalent (mg)*	*Usual daily oral dose (mg)*	*Parenteral single dose (mg)*
vi. Prochlorperazine	Stemetil	15	45–150	20–30 (IM)
vii. Thioproperazine	Majeptil	5	15–45	—
viii. Perphenazine	(Trilafon)	8.4–9.6	16–64	5–10
ix. Acetophenazine maleate	(Tindal)	22–24	60	—
c. Piperidine				
i. Thioridazine hydrochloride	Ridazine Mellaril Thioril Sycoril	90–104	200–600	—
ii. Mesoridazine besylate	(Serentil)	50–62	150	25–175 (IM)
II. Butyrophenones				
i. Haloperidol	Halopidol Senorm Serenace	1.1–2.1	2–12	2–5 (IM or IV)
ii. Haloperidol decanoate	Senorm LA	10 mg/day oral halopheridol = 100–200 mg/4 weeks of decanoate		
III. Thioxanthenes				
i. Chlorprothixene	(Taractan)	36–52	75–200	75–200
ii. Thiothixene	(Navane)	3.4–5.4	6–30	4 (IM)
IV. Diphenylbutyl piperidines				
i. Pimozide	Mozep, orap	—	2–10	—
ii. Penfluridol	Flurilept, penridol	3.5	20–60 (every week)	—
V. Dibenzoxazepine				
Loxapine	Loxapac	10	20	12.5–50 (IM)
VI. Indole derivates				
Molindone hydrochloride	(Moban) (Lidone)	5.1–6.9	15–60	—
VII. Dibenzodiazepine				
Clozapine	Lozapin Sizopin	—	200–900	—

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Class/Generic name	*Trade name*	*Dose equivalent (mg)*	*Usual daily oral dose (mg)*	*Parenteral single dose (mg)*
Olanzapine	Oleanz, oliza, tolaz, olanex	—	5–20	10–20 mg (IM) 210, 300 mg, 405 mg (IM, Depot)
VIII. Substituted benzamides				
Amisulpiride	Amazeo, sulpitac soltus	—	200–800	—
Levosulpride	Levazeo Levipride	—	200–300	—
Risperidone	Sizodon Risdone Respidon	—	2–14	—
Ziprasidone	Zipsydon	—	80–160	—
Paliperidone	Palido-OD Palip-XR Paliris	—	6–12	—
Iloperidone	Ilosure	—	12–24	—
Lurosidone	Latuda	—	40–160	—
IX. Rauwolfia alkaloids				
Reserpine +	Serpasil	—	—	2.5–5 (IM)
X. Newer ones				
Aripiprazole	Arip, arzu	—	10–30	—
Perospirone	(Lullan)	—	12–48	—
Quetiapine	Quitipin, qutan	—	100–800	—
Asenapine	Asenapt	—	10–20 (SL)	—
Blonanserin	Elicia	—	8–24	—
Zotepine	Sirilept	—	75–150	—
Cariprazine	Carispec	—	1.5–6	—
Names in the brackets indicate drugs still not marketed in India.				

A. CNS

- **Psychomotor effects** (on behaviour and motor activity).
  - *Sedation:* They decrease agitation, anxiety, aggression, especially in psychotic patients without affecting wakefulness. They produce sedation which does not progress to anaesthesia. Dysphoria is rather seen.
  - *Antipsychotic effect:* It appears after several weeks but sedative effect appears early during treatment. In schizophrenia, antipsychotics improve thought disorder, blunted affect, withdrawal, autistic behaviour, hallucinations, etc.

- *Vigilance:* They impair vigilance but not intellect (barbiturates impair both).
- *Motor activity:* Antipsychotic drugs may reduce spontaneous motor activity and produce catalepsy. There may also be reduction in conditioned response before the reduction in unconditioned response.
- *Seizure threshold:* They may lower the seizure threshold and may precipitate epilepsy. However, they protect the animals against audiogenic seizures. They are effective against convulsions caused by tetanus but not against strychnine induced.

- **Effects on Different Areas of CNS**
  - *Hypothalamus:* Hypothernia, depressed sham rage and central sympathoplegia (diminished hypertensive response, miosis and failure of ejaculation), inhibition of endocrine function, [decreased adrenocorticotropic hormone (ACTH), enhanced proclatin release, decreased gonadotrophins].
  - *Basal ganglia:* They increase the spontaneous firing of dopaminergic, neurones and cause Parkinsonian like syndrome.
  - *Brain stem:* In therapeutic doses, these drugs produce little effect on the respiratory centre:
    - Depression of vasomotor reflexes mediated through brainstem.
    - Depression of chemoreceptor trigger zone (antiemetic effect) except thioridazine but they do not inhibit emesis induced by stimulation of nodose ganglia, irritation of gastrointestinal tract (GIT) or by vestibular stimuli.
    - Reduction in electron encephalography (EEG) arousal response to auditory stimuli but not to direct electrical stimulation of recticular formation. These drugs may stimulate the reticular formation thus increasing its filtering activity which decreases the reponsiveness to stimuli.
  - *Spinal cord.* Interneuronal blockage by supraspinal action.
  - *EEG:* Slowing of EEG and increase in theta waves.

Mechanism of action of antipsychotics: Blockage of dopamine receptors in caudate nucleus and the limbic system. The blockage of dopamine receptors (D2 receptor) in the mesolimbic system, thus resulting in increased dopamine turnover rate, produce antipsychotic effect. The blockage of dopamine receptors, resulting in increased dopamine turnover rate in caudate nucleus produce Parkinsonism like syndrome, which can be countered by anti-Parkinsonian drugs (See **Table 1.2**).

B. Peripheral Nerves: They have got local anesthetic action.

C. Autonomic Mediators and Autocoids: Adrenergic blocking, anticholingeric, ganglion blocking and antiserotonin effect.

D. CVS: Hypotension (due to inhibition of centralized-mediated pressor reflexes, adrenergic blocking action and direct action and blood vessels), antifibrillatory action (due to quinidine like action, alpha adrenergic blocking action and local anaesthetic effect) tachycardia (due to hypotention), atropine like action and a response to protection against circulatory shock and electrocardiogram (ECG) changes (increased PR interval, increased QT interval, increased QRS complex and blunting of T-wave).

E. Miscellaneous: Antioedema action and potentiation of a number of analgesics and central depressants.

TABLE 1.2. Pharmacologic basis of clinical effects of antipsychotic drugs

Neuroreceptor effect	*Therapeutic effect*	*Side effect*
D_2	Antipsychotic	EPS, TD, hyperprolactinemia
D_1, D_3, D_4, D_5	Antipsychotic	Cognitive showing (bradyphrenia).
$5HT_{2A}$	Antipsychotic, negative symptoms, mood symptoms	Nausea Ameliorates, EPS, sexual dysfunction
$5HT_{25}$		Weight gain
$5HT_3$	Nausea	
$5HT_{1A}$	Mood symptoms, cognitive symptoms	
$5HT_{6,7}$	Antipsychotic	
$NE_{\alpha 1,2}$	Antipsychotic, negative symptoms, mood symptoms	Cardiovascular, hypotension, sedation, sialorrhea
Muscarinic		Dry mouth, constipation, blurred vision, memory impairment, ameliorates EPS
Histaminic (H1)		Sedation
GABA		Lowers seizure threshold

NE: norepinephrine; GABA: gamma aminobutyric acid

TABLE 1.3. Effects of some atypical antipsychotic drugs on receptors

	Aripiprazole (A)	*Olanzapine (O)*	*Risperidone (R)*	*Ziprasidone (Z)*	*Quetiapine (Q)*	*Clozapine (C)*	*Haloperidol (H)*
D_1	265	31	430	525	455	85	210
D_2	0.45	11	4	5	160	126	0.7
D_3	0.8	49	10	7	340	473	2
D_4	44	27	9	32	1600	35	3
$5HT_{1A}$	4.4	10000	210	3	2800	875	1100
$5HT_{2A}$	3.4	4	0.5	0.4	295	16	45
$5HT_{2C}$	15	23	25	1	1500	16	10000
α_1	57	19	0.7	10	7	7	6
H_1	61	7	20	47	11	6	440
M_1	10000	1.9	10000	1000	120	1.9	1500

ATYPICAL ANTIPSYCHOTICS

Effects of these drugs are given in **Tables 1.3, 1.4 and 1.5**.

Pharmacokinetics: For dosage see **Table 1.1**

Phenothiazines and related antipsychotics are well-absorbed after oral as well as parenteral adminsttration. After absorption, they are rapidly distributed in all body tissues. The various metabolic pathways of chlorpromazine are:

- Hydroxylation (at position 3 and 7) and subsequent conjugation (with glucuronic acid). 7-hydroxy chlorpromazine is an active metabolite.

TABLE 1.4: Pharmacodynamics of atypical antipsychotic (in comparison to haloperidol)

	*A**	*O**	*R**	*Z**	*Q**	*C**	*H**
T_{max} (hr)	3–5	5	1.5	6–8	1.5	3	1–2
Protein binding	99	93	90	9	83	95	90
T ½ (hr)	75	30	20	7	6–7	12	20
Potency (mg)	6	4	1	20	80	50	2
Starting dose (mg)	10–15	5–10	2	40	25–50	25–50	5–10
Dose range (mg)	10–15	15–30	2–6	80–160	300–800	300–600	5–20
Maximum dose (mg)	30	40	8	160	1000	900	100
Dosing frequency	OD	OD	OD-BD	BD	BD-TD	OD-BD	BD

*Names as given in **Table 1.3**.

TABLE 1.5: Side Effects of atypical antipsychotic (as compared to haloperidol)

Effects	*A**	*O*	*R*	*Z*	*Q*	*C*	*B*	*H*
EPS	0 to ±	± to +	0 to ±	0 to ±	0 to ±	0 to ±	±/+	+++
Dose related EPS	±	+	++	+	±	0	+	+++
Prolactin elevation	±	+	++	+	+	+	±	+++
Anticholinergic effects	±	+	±	+	+	+++	±	±
Hypertension	±	+	++	+	++	+++	±	+
Sedation	±	++	+	+	++	+++	±	+
QT prolongation	0 to ±	+	±	++	+	++	O/+	±
Weight gain	+	+++	++	+	+	+++	±	+
Total cholesterol and triglycerides	–	–	–	–	–	–	–	–
Glucose intolerence	±	+++	+	±	+	+++	+	+

0 = None, ± = Minimal, + = Mild, ++ = Moderate, +++ = Severe, ↓ = Decrease, ↑ = Increase.
*Names as given in Table 1.3; B: Blonanserin

- Sulfoxide formation (chlorpromazine sulfoxide).
- Subsequent demethylation results in formation of desdimethyl chlorpromazine sulfoxide and desmonomethyl chlorpromazine sulfoxide.
- Dehalogenation results in formation of promazine.

Excretion: It is excreted in the urine as well in the bile (which undergoes enterohepatic circulation). More than half the drug excreted in the urine is in the form of metabolites (*which may be detected even 6 months after discontinuing the drug*).

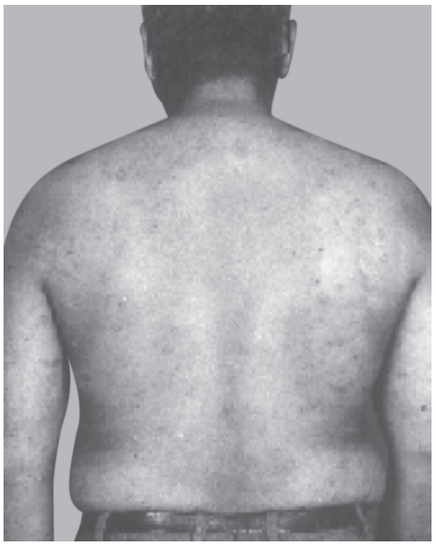

Fig. 1.1: Clozapine-induced lichenoid skin eruptions

Therapeutic window: Many antipsychotics tend to be ineffective if their blood levels are below the window and if the blood levels are higher than the window, they are again ineffective and there are signs of toxicity.

Adverse effects: The antipsychotic drugs have a high therapeutic index (wide safety margin). Their adverse effects, probable mechanism of action and treatment are given in **Tables 1.6** and **1.7**.

Indications

- **Psychiatric Indications**
  - Functional Psychoses
    - Schizophrenia (control of acute attack as well as maintenance).
    - Mania.
    - Schizoaffective psychosis (especially schizomania).
    - Psychotic symptoms in Major depression.
    - Agitation in depression and other disorders.
    - Infantile autism and Pervasive developmental disorder.
  - Organic Psychoses
    - Delirium (in low doses).
    - *Dementia* (if there are psychotic features).
    - *Postictal psychosis* (drugs with no or minimal effect on seizure threshold are preferred e.g. haloperidol, pimozide, trifluoperazine) or *interictal psychosis* (occurring in between attacks of epilepsy).

TABLE 1.6: Adverse effectts of antipsychotic drugs and management

Type	*Side effect*	*Mechanism of action*	*Management*
A. Extrapyramidal side effects	1. Acute dystonia (commonly opisthotonus or torticollis, oculogyric crisis)	Dopaminergic receptor (D_2) blockade in striatal system	Antiparkinsonian anticholinergics, benzodiazepines, rarely methylphenidate, caffeine, barbiturate induced sleep, sodium benzoate (Sometimes change in medication, or lowering dose)
	2. Akathisia (verbal or motor restlessness)	Dopaminergic receptor (D_2) blockade in striatal system	Benzodiazepines, beta-blockers or antiparkinsonian (sometimes lowering dosage, stopping or changing mediaction)
	3. Parkinsonian symptoms (pseudo-Parkinsonism (akinesia, rigidity, tremors)	Dopaminergic receptor (D_2) blockade in Striatal system	Benzodiazepines, beta-blockers or anti-Parkinsonian (amantadine may also be used)
	4. Rabbit syndrome (chewing type movements as of a rabbit)	Dopaminergic receptor (D_2) blockade in striatal system	Benzodiazepines, beta-blockers or anti-Parkinsonian (sometimes, lowering dosage, stopping or changing medication)
	5. Tardive dyskinesia [buccolinguo laryngo-(D_2) masticatory dyskinesia] (risk more in elderly, females, brain damage, increased dose and duration of therapy, use of anti-Parkinsonians)	Post-synaptic dopamine receptor supersensitivity (Noradrenergic hyperactivity) Not reported with clozapine, Olanzapine, etc. (an antipsychotic drug without extrapyramidal side effects)	Prevention best. Use newer atypical drugs—clozapine, olanzapine, risperidone medications, e.g. cholinergics tetrabenazine (physiostigmine, lecithin, choline, arecholine, deanol), reserpine, levodopa, benzodiazepines, lithium, valproate, baclofan, progabide, GABA, muscimol L-tryptophan, propranolol, etc. and lastly the neuroleptics
	6. Neuroleptic malignant syndrome	Not known	Dantrolene (1 mg/kg up to 10 mg/kg/day), bromocriptine, levodopa, anticholinergics, ECT
B. Other neurological side effects	1. Seizures	Decreased seizure threshold	Use drugs with no or minimal effect on seizure threshold (e.g. haloperidol, pimozide, trifluoperazine)

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Type	*Side effect*	*Mechanism of action*	*Management*
	2. Sedation	Blockade of α-adremergic receptors	Use butyrophenones or pimozide; give single dose at night (gradually tolerance devlops)
	3. Depression (pseudodepression)	Blockade of catecho-leamine receptors (noradrenergic and serotoninergic) in brain	Rule out pseudo-Parkinsonism (or add anti-Parkinsonian drugs)
	4. Hallucinosis	Not known (sedation is an important factor)	Decrease dose of drug or change to one with minimum sedation of decrease the dose of anti-Parkinsonian drugs
	5. Increased salivation (with clozapine)	Not known	Use anti-Parkinsonian or stop drugs
	6. Torpor	DA, α-adreregic, other, receptors blocked	Use new atypical drugs, e.g. olanzapine, clozapine
	7. Neuroleptic induced deficit syndrome	DA, α-adreregic, other, receptors blocked	Use new atypical drugs, e.g. olanzapine, clozapine
C. Autonomic side effects a. Anticholinergic	1. Dry mouth	Blockade of muscarinic cholinergic receptors	Rinsing of mouth with water (avoid candy as caries may result) pilocarpine (2%) tolerance develops
	2. Constipation	Blockade of muscarinic cholinergic receptors	Laxatives; change in diet; usually tolerance develops
	3. Urinary retention	Blockade of muscarinic cholinergic receptors	Rule out benign hypertrophy of prostate. Bethanecholine (25–50 mg tid) or catheteri-zation tolerance develops. Stop anticholinergic anti-Parkinsonian or change antipsychotic
	4. Cycloplegia	Blockade of muscarinic cholinergic receptors	Usually none. Sometimes pilocarpine (2%)
	5. Mydriasis	Blockade of muscarinic cholinergic receptors	Usually none. Sometimes pilocarpine (2%)
	6. Anticholinergic delirium	Blockade of muscarinic cholinergic receptors	Physostigmine [1–2 mg (IM)] Diazepam, use neuroleptics with minimal anticholinerrgic effects and stop anticholin-ergic antiparkinsonians
	7. Cholinergic crises	Blockade of muscarinic cholinrgic receptors	Atropine

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Type	*Side effect*	*Mechanism of action*	*Management*
	8. Tachycardia	Blockade of muscarinic cholinergic receptors	Start in low dose. Prefer neuroleptics such as haloperiodol
b. Adrenergic blockage	1. Orthostatic hypotension	Blockade of α_1-adrenergic receptors	Usually none, change in posture gradual, raise bed end, plasma expanders
	2. Impaired ejaculation and impotence	Blockade of α_1-adrenergic receptors	Decrease dose or change drug
c. Combined	Temperature dysregulation.	Both antimuscarinic and α_1-adrenergic blockade	Stop drug if hyperthermia, adequate fluids, avoid exertion
D. Allergic a. Hepatic	Cholestatic jaundice	Hypersensitivity reaction	Stop drug, benign course, suppportive care, change drug
b. Dermatological (See **Fig. 1.1**)	1. Maculopapular skin eruptions	Hypersensitivity reaction	Discontinue drug and add antihistaminic, e.g. diphenhydramine. Start drug from another class of antipsychotics (e.g. haloperidol)
	2. Photodermatitis (more with chlorpromazine)	Not known	Avoid sunlight. Use barrier creams (para-aminobenzoic acid)
	3. Contact dermatitis (more with chlorpromazine)	Hypersensitivity	Avoid contact symptomatic (antihistaminics)
c. Haematological	1. Transient leucopenia and agranulocytosis (common with chlorpromazine and clozapine)	Idiosyncratic reaction	Stop drug, treat infection, add drug from another class (e.g. haloperidol)
	2. Rarely thrombocytopenic purpura, hemolytic	Idiosyncratic reaction	Stop drug, treat infection, add drug from another class (e.g. haloperidol)
	3. Blue gray metallic discolouration	Idiosyncratic reaction	Change drug
E. Metabolic and endocrinal side effects	1. Galactorrhoea (with or without amenorrhea)	Dopaminergic blockade in hypothalamus leading to hyper-prolactinemia	Change drug, quetiapine, olanzapine better, amantadine
	2. Gynaecomastia	Dopaminergic blockade in hypothalamus leading to hyper-prolactinemia	Change drug, amantadine

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Type	*Side effect*	*Mechanism of action*	*Management*
	3. Weight gain (not with molindone)	Not known	Dietary control, exercise, change drug
	4. Decreased libido Priapism (especially with chlorpromazine, thioridazine)	Pituitary gonadotrophins and testosterone decrease. Also anticholinergic, anti-adrenergic (α_1) effects	Reduce dose or change drug
F. Cardiac	1. ECG changes	Anticholinergic effect	ECG monitoring change drug
	2. Sudden death Subictal discharges Respiratory depression	Ventricular fibrillation Start in low dose	Monitor vital signs
G. Ocular	1. Granular deposits in cornea	Not known (? Allergic)	Careful follow up Change drug
	2. Pigmentary retinopathy (with thioridazine)	Not known Extrapyramidal signs	Not use thioridazine above 500 mg/day for prolonged period
H. Pregnancy	First trimester	(Dopamine receptor blockade in foetus) Increased fetal death Risk or teratogenesis	Avoid drug in first trimester (especially haloperidol) Use ECT
I. Antipsychotic withdrawal syndrome		Abrupt withdrawal results in increased dopaminergic noradrenergic, cholinergic and serotinergic effects	Gradually taper off. Continue anti-Parkinsonian for 2–3 days more
The equivalent doses of various commonly antipsychotic drugs are:			
Chlorpromazine Trifluoperazine Fluphenazine decanoate (depot) Fluphenazine enanthate (depot) Haloperidol Thioridazine Thiothixene Loxapine		500 mg 14 mg 3.05 mg 3.35 mg 8 mg 485 mg 44 mg 87 mg	

- *Drug-induced psychosis* (e.g. haloperidol in amphetamine-induced psychosis, pimozide in alcohol induced paranoid states, etc.).
- *Drug withdrawal states* (e.g. haloperidol in delirium tremens, etc.).

– Neuroses
- Severe intractable anxiety (low doses).
- Obsessive compulsive neurosis (e.g. haloperidol in low doses).
- Monosymptomatic hypochondriasis (e.g. pimozide).
- Secondary hypochondriasis (if secondary to schizophrenia).

TABLE 1.7: Determinants and prevention of adverse effects of phenothiazines

Type of reactions	*Determining factors*	*Precautions or treatment*
Adverse behavioural effects		
• Oversedation	Dose : Individual tolerance	Small initial doses; avoid dangerous tasks early
• Impaired psychomotor function.		
• Restlessness, excitement, insomnia, bizarre dreams	Patient personality, type of drug	Conventional sedative or hypnotic drug may be added
• Aggravation of schizophrenic symptoms Toxic-confusional state	Parient with insight, somatic complaints Dose; age	Consider a nonphenothiazine tranquilizer Stop the drug
Toxic effects on central nervous system		
• Extrapyramidal syndromes (Parkinsonian syndrome, dystonic reactions, akathisia)	Dose; age; genetic predisposition	Anticholingeric or antihistaminic drugs; reduce dose
• Seizures	Dose; prior brain damage	Reduce dose; possibly add sodium valproate
• Electroencephalographic slowing, paroxysmal and focal	Dose; duration of treatment, individual susceptibility	Be sure to tell EEG reader of drug history
• Disturbed body temperature (hypo and hyperthemia)	Ambient temperature; mid brain disorder	Avoid extreme temperatures; treat hyperthermia as heat stroke is managed
• Respiratory depression such as electric convulsive therapy	Usually combined with other caused	Use a smaller shock (low voltage)
• Various neurologic syndromes	Dose; previous brain damage	Stop drug
Toxic effects on autonomic nervous system		
• Hypertensive crisis	Parenteral administration; age	Never give drug intravenously; levarterenol intravenously
• Tachycardia, blurred vision, aggravation of glaucoma, paralytic ileus, fecal impaction, bladder paralysis	Predominant anticholingeric effects	Reduce dose or stop drug; cholingeric drug mechanical aids
• Nasal congestion	Sympathetic depression	
• Inhibition of ejaculation	Adrenergic blockade	Reassurance
Allergic or toxic reactions	First four weeks; uncommon (0.5%).	Stop drug; wait
• Cholestatic jaundice	Follows cholestatic jaundice; rare.	Might try corticosteroids early in course
• Xanthomatous biliary cirrhosis	Usually, first 12 weeks; rare; elderly	Stop drug wait; use antibiotic as needed
• Agranulocytosis in women	Avoid transfusions or corticosteroids	
• Eosinophilia	Early in course	No harm Stop drug may switch to another.
• Thrombopenic or nonthrombopenic purpura	Unusual	
• Dermatoses, contact dermatitis, photosensitivity	Early in course	Stop drug

Contd...

Contd...

Type of reactions	*Determining factors*	*Precautions or treatment*
Metabolic or endocrine effects		
• Weight gain	Hypothalamic effect	Small rations
• Edema	Increased antidiuretic hormone secretion	Wait
• Lactation, gynecomastia, menstrual irregularities	Estrogenic effect	Reassurance
• False pregnancy test	Urinary metabolite	Use immunologic tests
• Impotency in men, increased libido in women	Estrogenic effect	Reassurance
Miscellaneous		
• Unexpected deaths	Dose; previous brain damage or seizures	Completely unpredictable; watch doses is known seisures patients
• Hypostatic pneumonia; trophic ulcers	Age; neglect	Adequate nursing care
• Anaesthetic complications	Blocked pressor reflexes	Stop drug prior to elective surger
• Local imflammation, gangrene	At injection site or perivenous leakage	Avoid parenteral drug when possible
• Electrocardiographic abnormalities	Vagolytic, quinidine-like effects	Uncertain
• Potentiation of other drugs, alcohol	Dose	Avoid polypharmacy; warm patient
• Teratogenic effects	Phocomelia with trifluoperazine; not established	Avoid drugs in fertile or pregnant women as much as possible
• Pigmentary retinopathy	Toxic doses	Keep dose under 800 mg daily of thioridazine
• Melanin pigmentation; corneal and lens deposits	Chlorpromazine 2 years or more; high dose	Switch to 'low dose' piperazine derivation

  - Attention deficit disorder with hyperactivity.
  - Tic disorder, e.g. Gilles de la Tourette's syndrome (especially haloperidol).
  - Conduct disorders (aggressive, destructive) in children.
- **Medical Uses**
  - Huntington's chorea (e.g. haloperidol).
  - Nausea and vomiting, if central in origin.
  - Intractable cough.
  - To help patients to regain lost weight, e.g. anorexia nervosa.
  - For relieving tension and emotional distress in physical illness.
  - For relief of pain and distress in inoperable cases of secondary carcinoma.
  - Preanaesthetic medication.
  - Neuroleptanaesthesia (droperidol with fentanyl).
  - *Hyperpyrexia* to induce hypothermia.
  - *Ecclampsia* as a constituent of lytic cocktail (chlorpromazine + promethazine + pethidine).
  - Heat stroke.
  - *Pruritus.*

Contraindications and precautions. They are given in **Table 1.8**.

– In pigeons, tricyclic antidepressants increase the pecking response whereas chlorpromazine decreases the same.

TABLE 1.8: Contraindications and special precautions required for various drugs

Drug group	*Contraindications*	*Special precautions*
1. Major tranquilizers	Depression, subcortical brain damage (Parkinsonism); impaired hepatic functions; blood dyscrasias, circulatory collapse, coma	Use carefully in patients receiving other CNS depressant drugs, may lower seizure threshold, may disturb heat regulation, may produce hypotention, avoid in severe cardiovascular disorders. Butyrophenones may reduce the effectiveness of oral anticoagulants
2. Minor tranquilizers	Hypersensitivity, myasthenia gravis, acute congestive glaucoma, pulmonary insufficiency, chronic psychoses	Cardiorespiratory insufficiency, hepatic or renal dysfunction, with other CNS depressants
3. Antidepressants	Hypersensitivity, heart block, narrow angle glaucoma, severe liver disease	Cardiovascular disease, epilepsy, hyperthyroidism, glaucoma, urinary retention, renal or hepatic dysfunctions, use of other CNS depressants or anticholinergic drugs, suicidal tendencies
4. Stimulants	Heart disease, hypertention, tics, stereotypies, schizophrenia, anxiety states, hypersensitivity	Hepatic disease, mentally-retarded children, depression, chronic use, cerebrovascular or cardiac disease, glaucoma, urinary retention, anticoagulant therapy
5. Anticonvulsants		
a. Carbamazepine	Bone marrow depression, hepatic insufficiency, pregnancy and lactation	
b. Phenobarbitone	Acute intermittent porphyria, attention deficit disorder. Chronic pain; use with other CNS depressants, Petit mal epilepsy	Impaired hepatic, renal, cardiac or pulmonary functions, anticoagulant therapy, chronic use
c. Phenytoin, valproate		Impaired hepatic function, barbiturates enhance its metabolism, while anticoagulants, INH, disulfiram and phenylbutazone increase its levels
d. Succimides	Grand mal epilepsy	Blood dyscrasias, hepatic, and renal insufficiency
6. Lithium carbonate	Addison's disease; heart failure; severe renal insufficiency, thyroid dysfunction	Dehydration or decreased salt intake, diuretic therapy, impaired renal function, pyrexia, electro-convulsive therapy
7. Central anticholinergics	Glaucoma; urinary retention, paralytic ileus, heart disease	Psychosis, pyrexia, hepatic or renal insufficiency

– Unlike chlorpromazine, they antagonise reserpine induced depression and sedation.
– They cause drowsiness (amitriptyline and doxepin cause maximum).
– These drugs make the depressive ideation dull but do not cause euphoria.
– In a *normal* person, they cause unpleasant sedation, drowsiness and unhappiness.

Pharmacokinetics: Imipramine is well absorbed from the GIT. After oral administration, plasma level rises slowly. However, excretion is rapid. Half-life is 12 hours. It is metabolised by:

– Demethylation forming desipramine which is an active metabolite.
– Hydroxylation at 2 position, followed by conjugation.
– N-oxidation forming imipramine N-oxide.

Amitriptyline is metabolised by demethylation to be followed by conjugation.

A very large proportion of the drug is protein bound. With regular administration of tricyclic antidepressants, a constant blood level is achieved usually by 2 to 3 weeks (may take upto 4 weeks). Some antidepressants such as nortriptyline, protriptyline have a therapeutic window.

Drug Interactions

Drug		Interaction
1. Tricyclic antidepressants (TCA)	:	Increased anticholinergic side effects. Increased absorption and plasma levels of TCA Increased chances of seizures. Danger signs—blurred vision or 30% decrease from normal QRS or PR intervals.
2. MAO inhibitors	:	Increased levels of phenothiazines (therefore decreased metabolism).
3. Lithium carbonate	:	Decreased peak plasma concentration of chlorpromazine. Increased blood sugar levels. Reports of severe neurotoxicity with haloperidol.
4. Benzodiazepines	:	Increased sedative effect.
5. Ethyl alcohol	:	Increased CNS depression Decreased concentration of phenothiazines (therefore, alcohol is enzyme inducer).
6. Barbiturates	:	Same as for alcohol.
7. Amphetamines	:	Effect of amphetamines in CNS is neutralized (due to inhibition of 'amine unptake pump')
8. Antihypertensives Reserpine, methyldopa, propranolol, guanethidine	:	Additive hypotensive effect (if guanethidine given before) Decreased neuronal uptake of guanethidine.
9. Levodopa	:	Decrease in therapeutic effect of levodopa.
10. Succinylcholine	:	Increased muscle relaxant effect.

		Increased neuromuscular blockade effect of succinylcholine (due to inhibition of serum and erythrocytic cholinesterase).
11. Antidiabetics	:	Phenothiazines antagonises hypglycemic effects of oral hypoglycemics and insulin (due to activation of adrenergic mechanism).
12. Oral anticoagulants	:	Increased prothrombin time.
13. Antacids	:	Decreased absorption of phenothiazines.
14. Corticosteroids	:	Increased absorption of phenothiazines (due to decreased gut motility).
15. Digoxin	:	— same —
16. Coffee, tea, fruit juice, milk	:	Decreased absorption of antipsychotics.
17. Smoking	:	Increased metabolism of phenothiazines (due to enzyme induction by nicotine).
18. Penicillin and heparin injections	:	They precipitate if chlorpromazine added.
19. Antidiuretic hormone	:	Drug-induced syndrome of inappropriate ADH secretion.
20. Disulfiram	:	Decreased blood levels of phenothiazine (due to enzyme induction by nicotine).
21. Oral contraceptives	:	Oestrogen containing pills may potentiate phenothiazine stimulated prolactin secretion resulting in mammary gland hypertrophy and galactorrhoea.
22. Phenytoin sodium	:	Rarely, phenothiazines may impair metabolism of phenytoin and increased phenytoin intoxication.
23. Plastic IV sets	:	Loss of drugs (because of adsorption)
24. Miscellaneous		
Quinidine	:	Increased myocardial depression. Increased quindine toxicity (so not use quinidine for ventricular tachycardia by phenothiazines).
Piperazine (antihelminthic)	:	Increased extrapyramidal syndrome and convulsions.
Procarbazine	:	Increased CNS depression (used in Hodgkin's disease)
Orphenadrine	:	Symptomatic hypoglycemia.

Effects on Laboratory Tests

A. Blood tests

i. Bilirubin	:	Increased levels (direct > indirect) (due to hypersensitivity).
ii. Cholesterol	:	Increased serum cholesterol by phenothiazines.

iii. Creatinine phosphokinase (CPK)	:	Increased serum levels by injectables (because local muscle injury or increased psychomotor activity).
iv. Glucose	:	Increased blood glucose (therefore activation of adrenergic mechanism) by large doses.
v. Thyroid function tests	:	Decreased protein bound iodine (by large doses). Increases I131 uptake
vi. Uric acid	:	Increased serum levels.

B. Urine tests

i. Colour	:	Pink to red or red-brown (with phenothiazines).
ii. Bilirubin	:	False positive results if using Bili-Lab-Stix test.
iii. Catecholeamines	:	Phenothiazines and their metabolites interfere with chromato or spectrophotometric (not fluorimetric) analysis of metanephrines.
iv. Glucose	:	Glycosuria
v. 5-HIAA (a metabolite of serotonin)	:	False decrease in urinary levels.
vi. Ketone	:	False positive
vii. Steroids	:	Increased absorbance and altered colour in urinary 17-ketosteroids (17-KS) and 17 OH KS estimation. (decreased ACTH secretion by phenothiazines)
viii. Urobilinogen	:	False increased values
ix. VMA	:	Decreased urinary VMA levels (by 20%).

Comments

i. All antipsychotics are equally efficacious, however, they differ in potency and side effects profile.
ii. Some conditions and the choice of antipsychotics are :

A. Disease/disorder		**Probable preference**
a. Schizophrenia		
Acute attack	:	Any antipsychotic (chlorpromazine has additional sedative effect).
Chronic	:	Any (longer acting, e.g. penfluridol, fluphenazine (oral and injectable, pimozide, etc. are preferred for maintenance).
Non-compliance	:	Depot preparation (fluphenazine decanoate injection)
Resistance/Negative	:	Clozapine, olanzapine, risperidone, quetiapine, flupenthixol, evenamide (under trial)

b. Mania		
Acute excitement	:	Chlorpromazine (has additional sedative effect) Haloperidol (reduces psychomotor activity without causing much sedation). Olanzapine (newer antipsychotic with mood stabilizing effect) ziprasidone
c. Schizoaffective		
Schizomania	:	Any (chlorpromazine, haloperidol, olanzapine)
Schizodepression	:	Flupenthixol, amoxapine, lurasidone
d. Autistic disorder	:	Risperidone, aripiprazole, haloperidol
e. Organic psychoses		
– Delirium, dementia	:	Haloperidol, pimozide, risperidone, olanzapine, lurasidone, etc. (therefore less sedative effect and less clouding)
– Postical or interictal	:	Haloperidol, trifluperidol, trifluoperazine, fluphenazine (minimal or no effect on seizure threshold)
– Drug induced or withdrawal	:	Haloperidol, trifluperidol, trifluoperazine (minimal or no effect on seizure threshold)
f. Anxiety disorders		
– Obsessive compulsive disorder	:	SSRIs, clomipramine
– Monosymptomatic hypochondriasis	:	Haloperidol (sometimes), olanzapine, pimozide
g. Gilles de la Tourette's syndrome	:	Tetrabenazine, haloperidol, pimozide, olanzapine
h. Huntington's Chorea	:	Haloperidol
i. To regain weight loss	:	Phenothiazine, risperidone, olanzapine
j. To avoid weight gain	:	Quetiapine, aripiprazole
k. Pruritus	:	Phenothiazine

Thioridazine has minimal extrapyramidal side effects (clozapine, olanzapine, quetiapine have none) while the so-called high potency drugs such as haloperidol and thiothixene have fewest sedative and postural hypotension effects; butyrophenones safe in hepatic impairments.

B. Symptoms condition	**Recommended drug**
Psychiatric	
Agitation and psychosis	Chlorpromazine, olanzapine, aripiprazole
Withdrawal and psychosis	Clozapine, olanzapine, risperidone, quetiapine
Tendency for severe Parkinsonism or acute dystonia	Thioridazine, clozapine, olanzapine, risperidone, quetiapine
Tendency of akathisia	Olanzapine, thioridazine, chlorpromazine
Negative features	Clozapine, olanzapine, risperidone, quetiapine

Ophthalmologic	
Accommodation difficulties	Fluphenazine, haloperidol, trifluoperazine, clozapine, olanzapine, risperidone, quetiapine
Allergies	
Pulmonary	
Chronic obstructive pulmonary disease	Haloperidol, prochlorperazine, trifluoperazine
Cardiovascular	
Coronary artery disease	Fluphenazine, haloperidol, atypical antipsychotics
Hypertension treated with prazosin	Fluphenazine, trifluoperazine, olanzapine
Arrhythmia	Avoid thioridazine
Gastrointestinal	
Nausea and vomiting	Any neuroleptic except thioridazine.
Diarrhoea	Chlorpromazine
Urologic	
Urinary retention	Fluphenazine, haloperidol, prochlorperazine, trifluoperazine
Endocrinologic	
Galactorrhea, menstrual irregularity caused by use of neuroleptic, breast cancer	Switch to quetiapine, thioridazine
Neurologic	
Parkinson's disease	Risperidone, olanzapine, clozapine, quetiapine
Dementia with behavioural disorganization	Risperidone, olanzapine, halopheridol, quetiapine

Anti-Parkinsonian Drugs (drugs used for treatment of extrapyramidal syndromes).

- Butyrophenones and piperazine derivatives are the most potent producers of extrapyramidal side effects.
- Levodopa is not effective in drug induced Parkinsonism and may induce psychiatric symptoms in about 15% of patients.

Classification, Indications and ***Dosages*** of various drugs are given in **Table 1.9**.

Side Effects

- Reduce serum levels of phenothiazines, possibly by enzyme induction. Therefore, preferably reduce levels by lowering dosage of phenothiazines.
- Acute organic syndromes (delirium like), especially in elderly and those with organic psychoses.

BOX 1.1: Guidelines for antipsychotic drug therapy

- Inform the patient and relatives of risks of drugs (especially tardive dyskinesia)
- Select drug on the basis of side effect profile, risk/benefit ratio and history of prior use and response by patient
- Initiate drug at low dose (e.g. chlorpromazine 50 mg tid)
- Gradually increase dose (50 to 100 mg chlorpromazine every other day) until improvement or usual maximum dose is reched
- Maintain maximum dose for 2 to 4 weeks
- If response is inadequate, obtain plasma level of drugs
- If level is low, increase dose to equivalent 1000 mg CPZ (chlorpromazine)
- Maintain dose for 2 to 4 weeks (maximum 6 weeks) (if improvement is inqdequate, gradually decrease drug and substitute with an antipsychotic from a different class)
- Use prophylactic anticholinergic (antiparkinson) medication with high potency neuroleptics or in patients younger than 40 years
- Use sedative drugs or beta-blockers for agitation
- Monitor patient closely for both therapeutic and side effects of treatment
- Thorough medical evaluation including evaluation for tardive dyskinesia
- Decrease dosage of antipsychotic medications as soon as possible after initial control of symptoms

TABLE 1.9: Drugs for treatment of extrapyramidal disorders

Generic name	*Trade name*	*Starting dose*	*Uses*
I. Anticholinergic drugs			
• Trihexyphenidyl	Pacitane, parkitane bexol, parkin	1 mg TID	Dyst, Akin, Park, Rabb, Proph
• Procyclidine	Kemadrin	2.5 mg TID	— do —
• Orphenadrine	Disipal	100 mg BID (60 mg IV)	— do — Dyst
• Biperiden	Dyskinon	2 mg TID 2 mg IM/IV	Dyst, Akin, Park, Rabb, Proph Dyst
• Benztropine	Congentin	0.5 mg TID 1 mg IM/IV	Dyst, Akin, Park, Rabb, Proph Dyst.
• Diphenhydramine	Benadryl Mucosal	25 mg QID 25 mg IM/IV	Dyst, Akin, Park, Rabb, Proph Dyst
• Ethopropazide	(Parsidol)	50 mg BID	Dyst, Akin, Park, Rabb, Proph
• Promethazone	Phenergan	25 mg TID	— do —
II. Dopamine agonists			
• Amantadine	Amantrel	100 mg BID	Akin, Park, Rabb, Proph
• Bromocriptine	Proctinal	1.25 mg	BID NMS
III. Beta-blockers			
Propranolol	Inderal Ciplar Migrabeta Betacap	20 mg TID	Akathisia

Contd...

Contd...

Generic name	*Trade name*	*Starting dose*	*Uses*
IV. Muscle relaxant			
Dantrolene	Dantrium Nandromate	4 mg/kg/d in 4 divided doses 1 mg/kg IV (max 10 mg/kg)	NMS
V. Antidopaminergic			
Reserpine	Serpasil	1 mg	TD

Name in the brackets indicates not available in India.
Abbreviations: Dyst: Dystonia; Akin: Akinesia; Park: Parkinsonism; Rabb: Rabbit syndrome; Proph: Prophylactic treatment; NMS: Neuroleptic malignant syndrome; TD: Tardive dyskinesia

- *Anticholinergic side effects* more when given with phenothiazines. They induce, e.g. dry mouth, constipation, sweating, blurred vision, tachycardia, warm dry skin, fever, reduced bowel sounds retention of urine (in prostatic hypertrophy) agitation, restlessness, confusion, memory disturbance, dysarthria, myoclonus, hallucinations, delirium, seizures and exacerbation of glaucoma.
- Excitement and euphoric effects in higher dose may lead to abuse among adolescents.
- May predispose to tardive dyskinesia or mask early symptoms.

Antidepressant drugs: These are group of drugs which are used for the treatment of depressive disorders. They are known as mood elevators or thymoleptics.

The first antidepressant drug to be discovered was iproniazid (a monoamine oxidase inhibitor) by Crane (1957) and Kline (1958) but due to severe hepatic necrosis caused by it, this was withdrawn. In 1958, imipramine (a tricyclic) was discovered by Kuhn. Since then, a number of antidepressants have been discovered.

Classification: Antidepressant drugs are classified on the basis of:

a. Structure
b. Biogenic amine reuptake blockade

A. On the basis of structure

i. Tricyclic antidepressants : Imipramine, amitriptyline, desipramine, triimipramine, nortriptyline, doxepin, clomipramine, dothiepin, etc.

ii. Second generation antidepressants
- Tetracyclics : Mianserin, maprotiline
- Bicyclics : Zimelidine, viloxazine
- Miscellaneous : Amoxapine, trazodone, nomifensine, bupropion, alprazolam

iii. Monoamine oxidase (MAO) inhibitors
- *Hydrazine derivatives* : Isocarboxazid, phenelzine, nilamide

– *Amines*	:	Tranylcypromine, pargyline
– *Natural alkaloids*	:	Harmine
iv. CNS sympathomimetic stimulants	:	Dextroamphetamine, methylphenidate
v. Miscellaneous	:	Carbamazepine, clorgyline, iprindole, opipramol, dibenzepin, lithium, flupenthixol, steroids, L-tryptophan, thyroxine, cannabis, atropine, etc.

Both tricyclics and tetracyclic drugs are included under 'heterocyclic' antidepressants.

B. Biogenic amine reuptake blockade

Both NE and 5-HT reuptake blockers (NSRI)	:	Imipramine, amitriptyline, venlafaxine
Selective NE reuptake blockers (SNRI)	:	Desipramine, maprotiline, reboxetine
Selective 5-HT reuptake inhibitors (SSRIs)	:	Clomipramine, trazodone, fluoxetine, paroxetine, sertraline, citalopram, escitalopram, fluvoxamine
NE and dopamine reuptake inhibitors (NDRI)	:	Nomifensine, bupropion
Weak or Non-reuptake inhibitors	:	Doxepine, mianserin, iprindole, alprozolam
Serotonin transport blockers and antogonist	:	Nefazodone
NE and specific serotonergic (NaSSA)	:	Mirtazapine

Therapeutic Uses

- Depression
  - Major depression [Manic-depressive psychosis (MDP) depression, Endogenous depression] [with electroconvulsive therapy (ECT)].
  - Major depression with psychotic features or melancholia (with ECT's or antipsychotics).
  - Neurotic depression (with psychotherapy).
  - Reactive depression (with psychotherapy).
  - Atypical depression and unclassified depression (MAO inhibitors)
  - Masked or latent depression.
  - Depression, in other psychiatric disorders (e.g. hysteria, schizophrenia, anxiety neurosis, hypochondriasis) and medical disorders (e.g. malignancy, Cushing's syndrome, etc.)
- **Panic disorder** (with anti anxiety drugs).
- **Agoraphobia, social phobia, school phobia** (MAO inhibitors).
- **Obsessive compulsive disorder with or without and other SSRI's depression** (clomipramine, fluoxetine are particularly helpful).
- **Enuresis** (with behaviour therapy).
- **Chronic pain**.
- **Attention deficit disorder** (in low doses, avoid in children below 6 years of age).

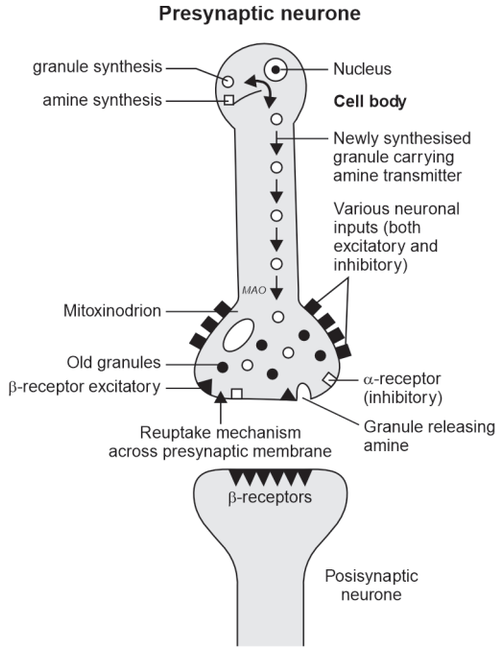


Fig. 1.2: A schematic representation of an aminergic neurone.

- **Bulimia nervosa**.
- **Migraine headaches**.
- **Peptic ulcer disease**.
- **Cataplexy** (associated with narcolepsy).
- **Miscellaneous**
  - Abnormal grief reaction.
  - Trichotillomania (especially clomipramine, fluoxetine).
  - Premenstrual and menopausal syndromes.
  - Night terrors or somnambulism.
  - Cardiac arrythmias.
  - Tic disorder.
  - Obesity (CNS stimulants).
  - Depersonalization (CNS stimulants).
  - Anorexia nervosa.
  - Post-traumatic stress disorder (PTSD).
  - Pseudobulbar affect (pathological laughing/uncoping).
  - Organic mood disorders.
  - Personality disorders.

Contraindications and precautions: They are given in **Table 1.8**.

Tricyclic Drugs

Pharmacological actions: Imipramine is different from phenothiazines in replacement of sulphur with an ethylene linkage. Tricyclics exhibit properties similar to phenothiazines, e.g. they cause:

- Ataxia;
- Prolongation of hexobarbitone sleeping time;
- Decrease in spontaneous motor activity;
- Decrease in body temperature;
- Suppression of conditioned avoidance response.

Other chlorpromazine like actions are:

- Anticholinergic effects
- Antihistaminic effects
- Antiserotonin action
- Potentiation of responses of catecholeamines.

PRECURSOR AMINO ACIDS IN THE BLOOD

For doses and main effects of these drugs, see **Table 1.10** and **1.11**.

Mechanism of action: The exact mode of these drugs is not known. There appears to be increase in brain catecholeamine levels by inhibiting their reuptake (monoamine reuptake inhibitors).

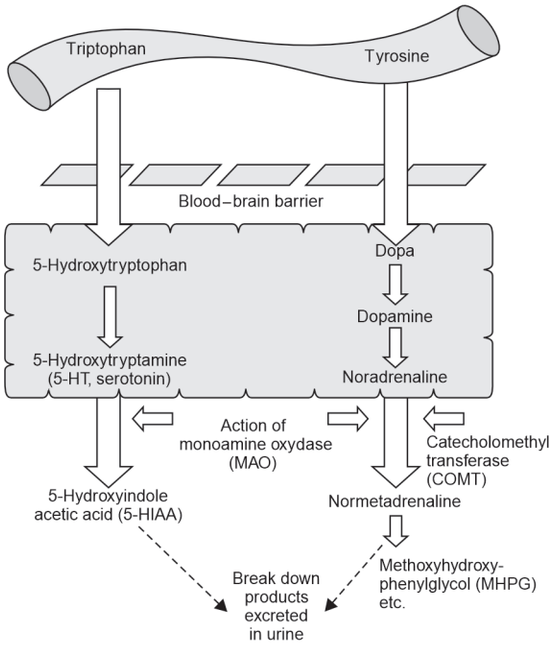


Fig. 1.3: An outline of synthetic and metabolic pathways in aminergic neurones.

TABLE 1.10: Classification, indications and properties of antidepressants

Class	Examples of trade names	Avg. daily dose (mg)	Side effects			CVS	Other side effects	Contra-indications	Interactions
			Equivalent dose (to 75 mg imipramine)	Sedation	Anti-cholinergic				
I. First generation									
Tricyclics									
Imipramine	Depsonil, depsol	75–300	75	++	+++	+++	Anticholinergic, cardiac arrhythmias, confusion, drowsiness, weight gain, loss of libido, epileptic seizures, blood dyscrasia	Mycardial infarction, severe liver damage, glaucoma, urinary obstruction, in pregnancy avoid clomipramine with MAOI	Potentiation of alcohol and barbiturates
Amitriptyline	Tryptomer, amitone	75–300	75	++++	++++	++++			
Triimipramine	Surmontil	75–300	75	++	+++	++			
Clomipramine	Anafranil, clofranil, clonil	75–300	75	++	+++	+++			
Doxepin	Spectra, doxetar	75–300	75–100	++++	++	+			
Dothiepin	Prothiaden, exodep, doreme	75–300	75	+++	+++	++			
Nortriptyline	Sensival	75–250	75	+	++	+			
Desipramine	(Norpramin)	75–300	75	+	+	+++			
Protriptyline	(Vivacil)	20–40	20	0	++	++			
II. Second generation									
a. Tricyclics									
Lofepramine	(Lofamin)	50–250	70	++	+	+	Mild anticholnergic	Pregnancy	
b. Tetracyclics									
Mianserin	Depnon	30–120	20	+++	0	+	Seizures, bone marrow depression	Myocardial infarction, pregnancy	
Maprotiline	(Ludiomil)	75–300	75	++	++	++			
c. Bicyclics									
Zimelidine	—	50–300	50	a	0	0	—	—	—
Viloxamine	(Vivalan)	100–300	100	+	+	+	Nausea	—	—
d. Others									
Trazodone	Trazonil, trazolon	75–400	150	+++	0	0	Priapism	Epilepsy, severe hepatic/renal disease	—
Nefazodone	(Serzone)	100–400	150	++	0	0	—	—do—	—
Flupenthixol	Fluanxol		0.75	++	+	±	Extrapyramidal (rare)	Parkinsonism, severe arteriosclerosis, delirium	—

Contd...

Contd...

Class	Examples of trade names	Avg. daily dose (mg)	Side effects			CVS	Other side effects	Contra-indications	Interactions
			Equivalent dose (to 75 mg imipramine)	Sedation	Anticholinergic				
III. Third Generation									
Fluoxetine	Flunil, prodep, trizac, loftil	20–60	20	a	0	0	Nausea, insomnia weight loss, nervousness, headache	Hepatic/ renal disease, pregnancy	MAOI Tryptophan
Paroxetine	Paxidep, xet	20–60	20	a	0	0	″	″	″
Sertraline	Serlift, zosert, sertima, serta, serenata	50–150	50	a	0	0	″	″	—
Fluvoxamine	Fluvoxin, uvox	75–300	150	a	0	0	″	″	—
Citalopram	Citopram citara cytop, C-talo, madam celepra	10–40	20	a	0	0	Nausea diarrhoea, insomnia dry mouth, ejaculatory problems allergy	″	—
Escitalopram	Nexito Feliz-S	5–20	10	a	0	0	″	″	—
Vilazodone	Vilano valz	20–40	10	a	0	0	″	Pregnancy, lactation	—
IV. Others									
Nomifensine	(Merital)	75–300	75	0	+	+	Hypersensitivity reaction, hemolytic anemia	Withdrawn due to side effects	—
Amoxapine	Demelox	150–300	150	++	+	+	Neuroleptic malignant syndrome seizures, tardive dyskinesia	Parkinsonism hepatic renal disease, pregnancy	—
Bupropion	Bupron, zyban	150–300	—	a	0	0	Agitation, headache, weight loss, seizures, psychosis GIT upset	Psychosis, seizures, prolonged use	—
Venlafaxine	Veniz, ventab, venlift, venlor	75–375	—	+	±	±	Nausea headache	HT CAD	MAOI

Contd...

Contd...

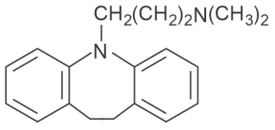
Class	Examples of trade names	Avg. daily dose (mg)	Side effects			CVS	Other side effects	Contra-indications	Interactions
			Equivalent dose (to 75 mg imipramine)	Sedation	Anticholinergic				
Venlafaxine	Vortidif, torvox vortisign, trintellix	5–20 mg	—	—	—	—	Nausea, dizziness, sedation, dizzness, agitation, dry mouth	SIADH, glaucoma, constipation, seizures, MAOI	MAOI
Duloxetine	Duzela, duvanta, duxet	40–120		+	±	±	As above	Hypersensitivity MAOI	MAOI
Amneptine	Survector	100–300	—	0	0	0	Nausea, nervousness, hepatic dysfunction	Huntington's chorea, glaucoma, pregnancy, CRF, MI	MAOI
Tianeptin	Stablon	25–375	—	a	0	0	Nausea, dry mouth, insomnia, nightmares	Children-below 15 years, pregnancy, lactation	MAOI
Reboxetin	Reboxxin	4–12	—	a	0	0	Insomnia, seating dizzness, tachycardia hypo/hypertension	Hypersensitivity pregnancy lactation	MAOI
Mirtazapine	Mirtaz, mimite	15–45	—	A++	+	+	Nausea, sedation dizziness	Seizures, MAOI	MAOI
Milracipon	Milname, milborn, milza	100–200	—	a	0	0	Somnolence, dizziness, fatigue	Hypersensitivity, MAOI	MAOI
Agomelatine	Agoprex, circaltin	25–50	—	+	0	0	Headache, nausea, diarrhea, liver enzymes, sedation, dizziness	Fluvoxamine tramadol	
V. MAO Inhibitors									
a. Irreversible, nonselective									
Isocarboxazid	(Marplan)	10–30	10	+++	+	+	Tremors, insomnia, dry mouth, constipation, Orthostatic hypotension, jaundice, weight gain, sexual disturbance, manic or	Hepatic disease, CHF phacochromocytoma, hypertension, unrelaible patients about dietary restrictions, patients on tricyclics, SSRI's	Hypertensive crisis with tyramine foods (cheese, beer, red wine, etc.) or ephedrine adrenaline, pethidine, Increased action of barbiturates alcohol, narcotic
Phenelzine	(Nardil)	45–90	45	+	+	+			
Tranylcypromine	(Parnate)	15–30	15	a	+	+			
Selective (MAO-AI)									
Clorgyline		5–30	5	a	0	0			

Contd...

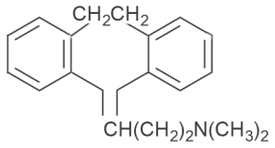
Contd...

Class	Examples of trade names	Avg. daily dose (mg)	Side effects			CVS	Other side effects	Contra-indications	Interactions
			Equivalent dose (to 75 mg imipramine)	Sedation	Anti-cholinergic				
							psychotic states (more with tranylcypromine)		analgestics anti-Parkinsonians
b. **Reversible (selective) (MAO-B)** Selegiline	Jumex, Selerin, Eldepryl, Selgin (MAO-B inhibitor)	5–30	5	a	0	0	Insominia	—	Same as above
Moclobemide	Rimarex	5–30	—	a	0	0	—	—	—
Broforamine	(Consonar)	—	—	a	0	0	—		
VI. CNS stimulants									
Dextroamphetamine	(Dexedrine)	10–40	—	a	0	0	Anorexia, weight loss, insomnia dependence, psychosis, hypertension	Hypersensitivity Heart disease, psychoses, tics	
Methylphenidate	Addwize	5–20	—	a	0	0			
VII. Other									
Carbamazepine	Tegretol, Mazetol, Zeptol, Carbatol, Zen	600–1600	—	+++	0	+	Nausea, vomiting, diplopia vertigo, tics, nystagmus, thyroid dysfunction	Hepatic insufficiency Bone marrow depression. Pregnancy and lactation	Potentiates sedative effects of alcohol and other drugs
Lithium	Licab, Lithosun, Intalith	600–1800	—	+	0	++	Hypothyroidism, diabetes insipidus, cardiac, GIT upset, myopathy	Renal disease, Addison's disease CHF	Diuretics (thiazides) Increases levels
Divalproex	Dicorate Divaa Desval Valance	1000–2000	—	+	0	+	Dizziness, vomitting sedation weight gain, alopecia	Liver toxicity pregnancy	Clonazepam, warfarin, alcohol
Lamotrigine	Lamitor, lamez, lamiz								Liver enzyme inducers

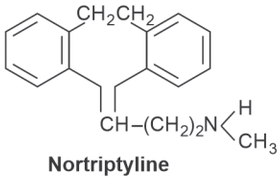
Trade name in brackets indicate the drugs are not available in india.
a = activating; 0 = Absent; — = Probable; + = mild; ++ = moderate; +++ = Severe; ++++ = Very strong.



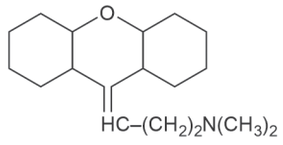
Imipramine



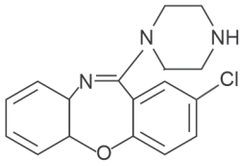
Amitriptyline



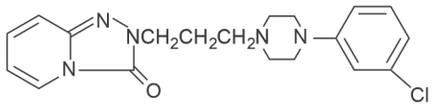
Nortriptyline



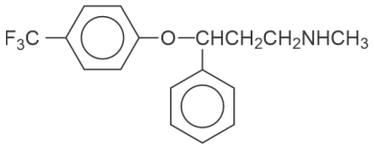
Doxepin



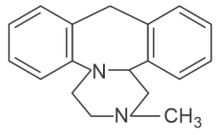
Amoxapine



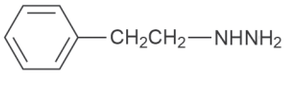
Trazadone



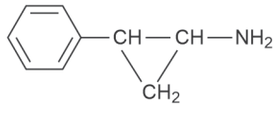
Fuoxetine



Mianserin



Phenelzine



Tranylcypromine

Fig. 1.4. Structures of some important antidepressant drugs

TABLE 1.11: Biochemical activity of selected antidepressant drugs

Drug	Reuptake inhibition			Receptor affinity			Muscarinic	D_2
	NA	ST	DA	α_1	α_2	H_1		
Both NA and ST reuptake inhibitors								
Amitriptyline	+	++	0	+++	+	+++	++++	+
Nortriptyline	++	+	0	+	0	+	++	+
Imipramine	+	+	0	+	0	+	++	0
Desimipramine	+++	0	0	+	0	0	+	0
NA reuptake inhibitors								
Maprotiline	++	0	0	+	0	++	+	+
Amoxapine	++	0	0	++	0	+	+	++
ST reuptake inhibitors								
Fluoxetine	0	+++	0	0	0	0	0	0
Trazodone	0	+	0	++	+	0	0	0
DA reuptake inhibitors								
Bupropion	0	0	++	0	0	0	0	0
Nomifensine	++	0	+++	0	0	0	0	0
Non-reuptake inhibitors								
Iprindole	0	+	0	0	0	0	0	0
Mianserin	0	0	0	++	+++	+++	+	0
Alprazolam	0	0	0	0	0	0	0	0

0 = lacking, + = weakly active, + to ++++ = active to strongly active.

The main modes of action of these drugs are:

- Blocking the reuptake of norepinephrine and/or serotonin (5-HT) at nerve terminals, thus increasing their concentration at receptor site.
- Downregulation of β-adrenergic receptors.

Unlike phenothiazines, they have got no effect on dopamine receptors (except amoxapine).

MONOAMINE OXIDASE INHIBITORS (MAOI)

Pharmacological Actions

- They produce elevation of mood and CNS stimulation both in depressed and normal persons (cf tricyclic drugs). Their onset of action is delayed and the effect is noticed after a week.
- They lower the blood pressure and one of them (pargyline) has been used in the treatment of hypertension.
- They have got anti-Parkinsonian which may be due to increase in the dopamine contents of the midbrain caused by them.
- They suppress REM sleep and have been tried in the treatment of narcolepsy.

Mode of action: The clinically used MAO inhibitors (MAOI) are irreversible inhibitors of MAO which metabolises catecholamines and 5-HT. Harmine which is an investigative drug inhibits MAO reversibly. Catecholamines are destroyed by two enzymes MAO and catechol-O-methyl transferase (COMT).

- MAO is an intracellular enzyme and metabolises intracellular catecholeamines present in the non-granular cytoplasmic pool. MAO also causes oxidative deamination of 5-HT. Inhibition of intracellular MAO by MAO inhibitors results in increase in the catecholamine content of various organs including the CNS. (They also increase 5-HT contents of the various organs.) Their antidepressant action seems to be related to increase in the brain catecholamine contents.
- COMT metabolises extracellular catecholeamines liberated by the nerve impulse or administered exogenously.

As circulating catecholamines are not acted upon by MAO, thus MAO inhibitors fail to potentiate the action of injected adrenaline and noradrenaline. However, they potentiate the action of tyramine and other indirectly acting amines because

- Tyramine is destroyed by MAO.
- MAOI increase the catecholeamine contents of various organs and thus, more catecholeamines are available to be released by indirectly acting sympathomimetic amines.

Adverse effects of tricyclic antidepressants and MAO inhibitors are given in **Table 1.12**.

Choosing an Antidepressant

Factors that matter in choosing an antidepressant are: Age-associated pharmacokinetics (less important for newer ones), depression type (psychotic/nonpsychotic) and risks (if suicide potential, choose the drug safe in overdose toxicity), prior response to a drug, safety, potential side effects, tolerability, likely compliance, drug interactions/and comorbidity (physical disorder, dementia, drug dependence).

Interactions

A. Tricyclic Antidepressants (TCAs)

Drug group		Effects
a. Those enhancing one or more effects of tricyclics		
i. Anti-Parkinsonian drugs, glutethimide, meperidine phenothiazines	:	Increased anticholinergic effects (dry mouth, constipation, paralytic ileus, urinary retention, acute glaucoma, blurred vision)
	:	Increased levels of TCAs by phenothiazines (because inhibit microsomal enzymes and compete for same)
ii. Anticonvulsants	:	TCA produce epileptic seizures in susceptibles (higher dose produce seizures even in nonepileptics)
iii. Acetazolamide, sodium bicarbonate, thiazide	:	Alkalinization of urine—more unionized drug in kidney—increased reabsorption
iv. Methylphenidate	:	Inhibit TCA metabolism—increased blood levels

v. Thyroid hormones	:	Increased sensitivity of adrenergic neurones receptors while TCAs block reuptake of catecholeamines—potentiation

b. Drugs decreasing one or more effects of TCA

i. Barbiturates (and smoking)	:	Increased metabolism of TCAs (decreased blood levels)
	:	Respiratory depression
ii. Alcohol	:	Increased sedation
	:	Decreased intestinal movements
	:	Fatty change in liver
	:	May show unusual and unexpected behavioural disorders
iii. Chlordiazepoxide, diazepam, oxazepam	:	Increased sedation. Increased atropine like effects (especially chlordiazepoxide)
iv. MAOI	:	Blockade of TCA, metabolising enzymes by MAOI (excitation, hyperpyrexia, convulsions)
v. Antihypertensives reserpine contra-indicated guanethidine	:	Antagonism of its effect by TCA (contraindicated)
	:	TCA inhibit reuptake of guanethidine into adrenergic neurosis (Doxepin has less antagonism)
Clonidine	:	Decrease its effect
vi. NH_4Cl, ascorbic acid	:	Acidification of urine—increased ionized drug in urine—decreased reabsorption by kidney (less important if kidney normal)
vii. Sympathomimetics	:	TCA inhibit uptake of norepinephrine by adrenergic neurones
viii. Vasodilators	:	Increased hypotensive action
ix. Meperidine, narcotic analgesics	:	Increased risk of respiratory depression
x. Ethchlorvynol	:	Transient delirium
xi. Disulfiram	:	Amitriptyline increases alcohol reaction in patients with disulfiram
xii. Analgesics (baclofen)	:	Decreased enzymatic metabolism of phenazone
	:	Prolongation of plasma half-life
	:	Increased bone marrow depression
	:	Decreased phenylbutazone absorption due to decreased absorption
xiii. Anticoagulants	:	Increased effect of coumarin drugs (therefore, decreased metabolism—haemorrhage)
xiv. Levodopa	:	Levodopa is enhanced in its actions by TCAs but TCAs may induce Parkinsonism
xv. Pethidine	:	Increased respiratory depression

Effects on Tests

xv. Pethidine

a. Blood tests

Bilirubin	Increases (with amitriptyline, desipramine)
Glucose	Increases (GTT is impaired)
Sulfobromphthalein (BSP)	Increases retention if cholestatic jaundice with TCAs
Alkaline PO_4	Increases with Amitriptyline

b. Urine tests

Colour	Blue green (with Amitriptyline)
Catecholeamines	False increase. Metanephrines
VMA	Decreases excretion (upto 30%)
5 HIAA	Decreases excretion (upto 50%)

B. MAO Inhibitors (MAOI)

(Irreversible type, which binds MAO irreversibly; synthesis of new enzyme takes 2–3 weeks).

• Tricyclic antidepressants	Severe reactions (due to blockade of TCA metabolising enzymes) Have a gap of 2 weeks before starting other therapy
• Anticholinergic agents	Effect potentiated (because of inhibition of hepatic microsomal enzymes)
• Phenothiazines	Inhibition of metabolism of phenothiazines. (increased side effects and toxicity).
• Anticonvulsants carbamazepine	Because of structural similarity with TCA, it may be dangerous.
Barbiturates	Decrease their metabolism.
• Levodopa	Levodopa is converted to dopamine (metabolised by MAO), which then changes to norepinephrine. Levodopa → Dopamine → Norepinephrine (NE). So, MAOI lead to decreased degradation of dopamine and increased NE. Adverse cardiovasular effects may result (hypertension, flushing of face, palpitations, light headedness).
• Antihypertensives— Propranolol	Blockade of β-adrenergic receptors resulting in hypertensive crisis. (i.e. unopposed by α-adrenergic receptors)
Reserpine	Increases NE in storage sites and receptors resulting in excitation and hypertension
Methyldopa Guanethidine	Decreases hypotensive effect
• Antidiabetics (oral and insulin)	Increased or prolonged hypoglycemic response.

• CNS stimulants—Amphetamine	Increased catecholeamine at adrenergic neurones—hypertensive crisis (more with tranylcypromine)
Methylphenidate	
• Succinylcholine	Phenelzine prolongs effect of scoline.
• Sympathomimetics—Epinephrine	Enhancement of action (therefore denervation supersensitivity by MAOI).
Norepinephrine	Metabolised by COMT—slight increased action
Phenylephrine, ephedrine Metarminol, phenylpropranolamine	Increased hypertensive reponse
• Alcoholic beverages (beer, red wine, liver, yeast or banana)	Hypertensive crisis
• Narcotic analgesics—mepiridine, morphine, dextromethorphan (in cough expectorants)	Hypertensive crisis
• Anaesthetic agents	Anaethesia potentiated vasopressor drugs in local anaesthetic (adrenaline, NE) will interact in hypertensive crisis
• Anticoagulant	Inhibition of coumarin metabolism (haemorrhage, treatment is vitamin K)
• Antihistaminics—Promethazine Phenylpropanolamines	Increased cardiovascular toxicity (hence increased catecholeamines)
• Caffeine or Xanthines	Hyperexcitability reactions including insomnia
• Thiazide diuretics	Increased hypotensive effects
• Tryptophan	Drowsiness, unsteadiness, hyperreflexia, ataxia

Effects on Tests (by MAOI)

a. Blood tests

Bilirubin	Increases if viral hepatitis like Jaundice in few patients
BSP	Increases retention (because increases hepatic injury)
Glucose	Decreases (because decreases compensatory adrenergic response)
Ammonia	Increases (except iproniazid decreases)
Pheochomocytoma	Increases response to tyramine test

b. Urine tests

5-HIAA	Decreases
VMA	Decreases formation and excretion

TABLE 1.12: Adverse effects of antidepressants

Type	*Side effects*	*Mechanism of origin*	*Management*
I. Autonomic			
a. Anticholinergic	Dry mouth, constipation, urinary retention, mydriasis, cycloplegia, precipitation of narrow angle, glaucoma, delirium	Blockade of muscarinic cholinergic receptors	*See* Table 1.6
b. Antiadrenergic	Increased sweating	Paradoxical effect	Don't use in elderly and patients with past history Stop or change drug
	Orthostatic hypotension Impaired ejaculation (impotence)	Alpha 1 Adrenergic blockage	*See* Table 1.2
c. Others	Priapism (with trazodone)	Not known	Stop drug, muscle relaxation or surgery
II. Cardiac	Quinidine like action. Increased AV conduction vent. Tachycardia and VF. Bundle branch block ECG changes (increased QT interval, flattening of T wave and ST segment) PAT, arrhythmias (PAT) (in high doses, pre-disposed individuals) Direct myocardial depressant S_1, S_2, S_3	Anticholinergic	Use minimum dose, use newer safer drugs in elderly and those with past history of cardiac problem
III. CNS	Sedation	α_1-adrenergic blockage	Start in low dose, decrease dose or change it, give at night
	Tremors and other extrapyramidal effects Seizures Precipitation of psychosis Precipitation of mania Jitteriness (early tricyclic syndrome) Withdrawal syndrome	Not known Decreases seizures threshold Sympathomimetic Sympathomimetic Adrenergic Neuroadaptation	Decrease or change drug Decrease or change drug Stop drug, start in low dose Stop drug, start in low dose Tolerance occurs in 1–2 weeks Slow withdrawal
IV. Metabolic	Weight gain	Water retention, decreased activity due to illness and sedation of drug, increased appetite	Exercise, diet control, change drug
	Oedema (Occasionally)	Water retention	

Contd...

Contd...

Type	*Side effects*	*Mechanism of origin*	*Management*
V. Allergic side effects	Skin rashes Urticaria Cholestatic, jaundice Agranulocytosis, pruritus Photosensitivity	Hypersensitivity -do- -do- -do- -do-	Stop drug, antihistaminics Change drug Benign course Stop drug, treat infection Supportive care Stop drug, antihistaminics Avoid sun exposure. Use barrier creams (PABA)
VI. Specific side effects MAO inhibitors	Hypertensive crises (throbbing headache, palpitations, hyperpyrexia, convulsions, coma, death)	Interaction with tyramine containing foods (cheese, beer, red wine, chocolates, etc.) or indirectly acting sympathomimetic amines (e.g. ephedrine, amphetamine, etc.)	Dietary restriction and avoid use of sympathomimetic agents Use alpha sympathetic blockers (e.g. phentolamine 5–10 mg IV) Use safer, new reversible MAOI (selegiline, Moclobemide, etc.)
	Severe hepatic necrosis (uncommon) (with hydrazine derivatives) Hyperpyrexia and convulsions	Toxic (Hypersensitive) Interaction with tricyclics	Stop drug, supportive care, high mortality Stop drug. Keep an interval of 10 days between 2 treatments. Supportive care
VII. Acute tricyclic over dose toxicity (lethal dose 1–2 g)	Hyperpyrexia, hypertension Convulsions Cardiac arrythmia Delirium, coma	Potentiation of catecholeamines. Anticholinergic	Gastric lavage, Cold sponges (for fever). Alpha-adrenergic blockers (for hypertension). Diazepam (for convulsions). Propranolol (for arrhythmias) Physostigmine (for anticholinergic side effects)
VIII. Acute withdrawal	Nausea, headache, restlessness, sweating, insomnia	Psychological dependence resulting in acute rebound phenomenon	Gradual withdrawal Avoid prolonged used

Guidelines for Use of Antidepressant Drugs

- Complete a thorough medical evaluation, especially with regard to cardiovascular and thyroid status.
- Select drug on the basis of side effect profile (sedating, stimulating, anticholinergic and cardiovascular effect), availability of relevant therapeutic levels and history of previous response.
- Inform the patient and family of risks and benefits. Explain the expected 'dalay' in therapeutic response, indicated side effect, etc.
- Initiate and increase dose of heterocyclic antidepressant slowly (e.g. for imipramine, start at 25 mg TID and increase by 25 mg every day).
- Increase dosage until dose equivalent of 200 mg imipramine is reached. Stabilize at that dose for one week.
- If there is no significant therapeutic effect after one week, increase dosage to maximum recommended dose (e.g. imipramine 300 mg).
- If there is no significant improvement after one week, obtain plasma level (if appropriate), ECG and adjust dose (e.g. 50 mg per week). Obtain level and ECG before each dose increase.
- A therepeutic trial is defined as a six-week treatment with antidepressant, with at least three week on the highest tolerated, safe dose.

Indications for Use of Antidepressant Levels

- Patient has not responded to an adequate trial of nortriptyline, imipramine or desipramine.
- Patient requires rapid increases in dose because of extraordinary suicidal risk.
- Patient is at high risk because of age or medical illness and requires treatment with the lowest possible effective dose.
- Concern about patient compliance with medication regimen.
- Documentation of plasma level to which the patient responded for use in future treatment.
- Potential for drug interactions that may lead to an increase or decrease in plasma levels.

Prediction to tricyclic antidepressant response	
Predictors of positive response	**Predictors of negative response**
• Insidious onset • Anorexia • Weight loss • Middle and late insomnia • Psychomotor disturbance • Upper Socio-economic class	• Neurotic, hypochondriacal or hysterical traits • Multiple prior episodes • Delusions

Pretreatment

Urinary MHPG (low for imipramine; high for amitriptyline).

Guidelines for Patients Taking MAO Inhibitors

A. Avoid:

a. Foods	:	All cheese or cheese-containing food, chocolates. Bean pods. Liver (chicken, beef or pork), liver crust. Meat extract or yeast extract. All fermented or aged foods (fish, meat, etc.).
b. Drinks	:	Red wine, sheery, beer, cognac, ale.
c. Drugs	:	Cold medication, e.g. dristan, contac. Nasal decongestants, asthma inhalants, allergy of hay fever medication, demerol, cocaine, amphetamine, antiappetite (diet) medicines, sympathomimetics (e.g. epinephrine, methulphenidate, ephedrine, pseudo-ephedrine, metarminol, phenylephrine), local anesthetics with epinephrine, levodopa and dopamine
d. Misellaneous	:	Mushroom, chocolates, coffee, colas, beet root, licorice, snails, curry powder, rhubarb, figs, raisins, dates, etc.

B. Safe:

a. Foods	:	Fresh cottage cheese, cream cheese, yoghurt Baked foods, yeast, fresh fruits
b. Drinks	:	Gin, vodka, whiskey
c. Drugs	:	Pure steroid inhalants, pure antihistaminics (e.g. chlorpheniramine, brompheniramine), other narcotics e.g codeine (low dose), local anesthetics without epinephrine, all laxatives, aspirin, antibiotics (penicillin, tetracycline, eryhromycin)

Choice of antidepressants

A. Tricyclics and Others

Disorders	*Drug preferred*
i. Agitated depression	Amitriptyline, dothiepin, doxepin, trimipramine, maprotiline, mianserin, trazodone, milnacipran
ii. Retarded depression	Fluoxetine, nortriptyline, fluovoxamine, sertraline
iii. With cardiac, gut or	Fluoxetine, trazodone, mianserian, doxepin, vortioxetine
Glaucoma problems	Dothiepin, maprotiline, nomifensine

iv.	Obsessive compulsive disorder	Clomipramine, fluoxetine, sertraline, fluvoxamine, paroxetine
v.	Compulsive hair plucking or naibiting	Clomipramine Fluoxetine
vi.	With Parkinson's disease	Nomifensine
vii.	Schizodepression	Flupenthixol, amoxapine
viii.	Epilepsy	SSRIs, MAOI, doxepin
ix.	Diabetes	Tricyclics, SSRIs (may mimic symptoms of hypoglycemia)
x.	Pregnancy	Avoid all
xi.	Lactation	Avoid all. If must, then give SSRIs (fluoxetine) or TCAs
xii.	Renal disease	TCAs mianserin, moclobemide
xiii.	Liver disease	Paroxetine, mianserin
xiv.	Elderly	SSRIs trazodone, mirtazapine, venlafaxine, tryptophan, moclobemide, desipramine
xv.	Sexual dysfunction	Bupropion, moclobemide, nefazodone

B. ***MAO inhibitors (MAOI)***
(preferred in depressives with phobias, anxiety, atypical features, etc.)

Phenelzine	Most widely used
Isocarboxazid	Sedative
Tranylcypromine	Stimulant
Newer selective MAOI	(reversible inhibition)
Selegiline, moclobemide	No drug or food interactions. No hyprtensive crisis.

ANTIAGGRESSIVE DRUGS

A. Anticonvulsants
Carbamazepine
Diphenylhydantoin
Primidone
B. Lithium carbonate
C. Antipsychotics (neuroleptics)
D. Sedative and hypnotics (especially with antipsychotics)
Barbiturates, benzodiazepines and related drugs.
E. Beta-blockers
Propranolol, nadolol, pindolol, metoprolol.

DISULFIRAM

It is used in the treatment of alcoholism. If taken with alcohol, the patient experiences severe headache, nausea, facial flushing and general malaise.

Mode of Action: Unpleasant reaction is produced if alcohol is taken after ingestion of disulfiram and fear of reaction deters the patient from taking alcohol. It retards the oxidation of acetaldehyde produced by oxidation of alcohol because it inhibits the enzyme aldehyde dehydrogenase. Thus, the blood level of acetaldehyde rises which is responsible for the unpleasant reaction.

Pharmacokinetics: It is well-absorbed from GIT. Full effect develops after 12 hours because initially it is accumulated in the fat. Termination of action is slow (20% remains in the body even one week after the cessation of therepy).

Dose: 0.5 g orally (in morning) first day. 0.25 g/day subsequently.

After a few days, a test dose of beverage is given and unpleasant reaction occurs within 20 minutes after the test dose and lasts for 30–120 minutes.

Reaction

Mild reaction—vasodilation, flushing, warmth, throbbing headache, fall in blood pressure, sweating, nausea and vomiting.

Severe reaction—convulsions, circulatory collapse.

Side Effects

- Nausea, constipation, fatigue
- Breath odour, metallic staste in mouth
- Psychotic and confusional states
- Reduction in libido
- Interferes with metabolism of other drugs, especially barbiturates, phenytoin, warfarin, paraldehyde
- Hypothyroidism
- Acneform rash
- Muscular fatigue and cramps.

Contraindications

- Cardiac failure or ischaemic heart disease
- Pregnancy
- Psychosis (may exacerbrate schizophrenic psychosis)
- Epilepsy
- Patient taking paraldehyde.

Treatment of Severe Antabuse/Alcohol Reaction

- Oxygen

- Dextrose drip
- Parenteral antihistamine
- Horizontal position—raise legs.

Other disulfiram like drugs: Calcium carbimide, animal charcoal, metronidazole, chloral hydrate and oral hypoglycemics.

LITHIUM

It is the lightest of the alkali metals and was discovered by *Arfuedson* in 1817. Since *JFJ Cade* first reported the use of lithium as an antimanic drug in 1949, in Australia, it has become one of the most valuable drugs in the treatment of mood (affective) disorders. Lithium was previously used as a substitute for table salt in cardiac patients (but due to risk of cardiac toxicity, it was discarded) and those suffering from gout (abandoned because of toxicity). In Denmark, Schou et al (1954) populatized its use in mania.

- **Mood (Affective) Disorders**
  - **Mania:** *Cade* (1949) first demonstrated the antimanic effect of lithium. By the end of three weeks, lithium and chlorpromazine are equally effective. Lithium is equally effective in acute phase of mania and its prophylaxis, though in acute mania, some psychiatrists prefer to use lithium in combination with neuroleptics.
  - **Major depression:** *Goodwin* et al (1969) first demonstrated the antidepressant effects of lithium in bipolar depressed patients (with history of mania or hypomania). It is now believed that lithium has antidepressant effects in some patients with major depression (without history of mania or hypomania; unipolar illness).
    Lithium has the advantages over antidepressants that the antidepressants (tricylics as well as MAO inhibitors) may precipitate hypomania or mania and secondly, the tricyclics might accelerate the cycles of mania and depression (in patients with a cyclical history of affective disorders).
  - **Rapid cyclers:** There are reports that lithium is not effective in all patients with recurrent affective disorders. It is not only ineffective in these cases but may also induce this condition.
- **Schizoaffective disorder:** Lithium has been tried in the prophylaxis of recurrent schizoaffective disorders.
- **Alcoholism:** Lithium is probably effective but only in those alcoholics where there is affective symptomatology.
- **Periodic catatonia:** A condition described by *Gjessing* (1967) characterized by periodic episodes of catatonia, probably due to retention of nitrogenous products by the body and the patient is completely normal in between episodes. Lithium has a beneficial effect.
- **Uncontrolled aggressive (impulsive) behaviour:** There is significant reduction in aggressive behaviour among prisoners on lithium, over against placebo.
- **Abnormal mood swings** in children and adolescents, lithium has been effectively used.
- **Other uses:** Lithium has been tried in the treatment of migraine, premenstrual tension, tardive dyskinesia, thyroid disease (hyper-thyroidism), neutropenia, Felty's syndrome

and in conjunction with cytotoxic drugs, Kleine Levin syndrome (rarely) and Huntington's chorea.

Mechanism of action: The exact mode of action of lithium in preventing affective disorders is unknown but it has the following physiological properties.

- Neurotransmitters
  - ***Synapses:*** Lithium is thought to increase presynaptic destruction of catecholeamines, inhibits release of neurotransmitter, decrease sensitivity of post synaptic receptor.
  - ***Ions:*** Lithium influences sodium and calcium ion transfer across cell membranes. These ions affect neurotransmitter release and receptor activity.
  - ***Cyclic AMP:*** Lithium inhibits prostaglandin E—stimulated cyclic AMP.
  - ***Pineal.*** Lithium-mediated pineal stimulation results in increased serotonergic fluorescence and melatonin content (*Tilak effect*) and response to altered electrolyte balance.
- **Cations and water:** Lithium stimulates exit of sodium from cells, probably by stimulating pump mechanism, where intracellular sodium is elevated (as in depression). It stipulates t he entry of sodium into cells where intracellular sodium is low (as may be the case in mania).
- **Cell membranes:** Lithium may interact with both calcium and magnesium and increase cell membrane permeability.
- **Other actions:**
  - It restores diurnal rhythm of corticosteroids to normal in mania (but may simply reflect changes in behaviour as mania ameliorates).
  - In depressed patients, restoration of normal slow wave EEG rhythms during sleep and decrease in stage 1 and REM sleep correlates with serum lithium levels.
  - *Carbohydrate metabolism.* The changes in magnesium and calcium may be the secondary effects of altered carbohydrate metabolism. Lithium influences this by releasing insulin and increasing transport of glucose of muscle glycogen formation. It may be the cause of weight gain.

Pharmacokinetics: Lithium is an element with atomic weight 6.94 and atomic number 3. Lithium is available in the form of tablets and capsules of strengths of 250 mg, 300 mg, 400 mg and 400 or 450 mg slow release.

Dosage: Therepeutic levels of lithium are likely to be achieved by a daily dosage of *800–1600 mg* (i.e. 0.5 mEq/kg body weight). In the early stages of treatment, frequent dosage allows more ready access of lithium to the intracellular compartment. In the manic phase, a greater proportion of lithium is held intracellularly and with recovery, the daily dose may have to be reduced to avoid excessively higher serum lithium. It is advisable to give smaller doses of lithium more frequently than the larger dose infrequently. The current view is that the longer the renal tubule is in contact with low urinary concentrations of lithium, the less likely are the side effects such as polyuria. Slow release preparations of lithium also smoothen the peaks. the parameters for control of total dosage are—serum levels, side effects and clinical improvement.

Serum levels*:* The serum levels are measured by any time between 12 and 24 hours after the last dose, as long as the interval is constant. Usually, morning fasting level is taken.

Therapeutic levels—0.6–1.4 mEq/L (mOsm/L).
Prophylaxis—0.5–1.0 mEq/L
Children and elderly—0.4–0.8 mEq/L.

Absorption and excretion: Lithium is administered as carbonate (most often), citrate or acetate salt.

- Absorption is rapid and is complete within 6–8 hours. Serum levels peak at 3–4 hours.
- Lithium is distributed in total body water—shifting slowly to cells (in plasma as free ion and in CSF at about half the serum concentration). It replaces up to 10% of sodium in bone and is concentrated in muscle and thyroid (2–5 times). In milk, the levels are about one-third to equal that of serum levels.
- There is no protein binding and no metabolism. It is excreted unchanged by kidney. About 1/2–2/3rds oral dose appears in urine after 8–12 hours, rest excreted over days. Lithium clerance is about 20% of the glomerular filtration rate, is independent of the plasma level, and diminishes with age. Lithium clearance depends on renal function, the amount of fluid passing through kidney and its sodium content. Lithium is excreted in saliva (the levels are about twice of those of serum levels). Salivary concentration remains constant and it is potential for monitoring lithium levels as ratio of plasma concentration.
- Lithium tends to follow sodium in reabsorption at proximal levels, hence:
  - Increased sodium intake produces decreased reabsorption of lithium.
  - Sodium restricted diet produces increased reabsorption and lithium levels may become toxic.
  - Thiazide diuretics decrease lithium clearance by about 25% due to compensatory reabsorption of sodium in proximal tubules.
- *Monitoring plasma levels.* The fasting blood sample is taken 12 hours after the last dose because of '*peaking*' of levels. Therepeutic and toxic ranges refer to this 'basic' level.

Preliminaries to lithium treatment: The baseline renal, cardiac and thyroid function, and body weight are taken before starting lithium. For this purpose:

- A full blood count, plasma electrolytes and urea, creatinine clearance, and ECG and serum T_4 and TSH levels are required.
- The lithium treatment is monitored initially by weekly serum levels (an estimation is done 5–7 days after any dosage change), followed by monthly (after stable levels are achieved) and then every 2–3 months.
- Thyroid function should be checked every 6 months.
- A raised TSH levels on two occasions suggest hypothyroidism. (There is no need to stop lithium but thyroxine should be added gradually until the TSH falls to within normal limits).
- 24 hours urine volume should be done every 6 months and an ECG should be performced every year.

Side effects: The side effects of lithium are given in **Table 1.13**. Toxicity occurs if blood levels reach about 2.0 mEq/L and it is fatal at levels of about 3.5 mEq/L and it is fatal at levels of about 3.5 mEq/L (these levels of toxicity may be lower in children and elderly).

TABLE 1.13: Side effects of ithium carbonate

	Common	*Less common*
1. GIT	Transient nausea, gastric discomfort, loose stools and and dry mouth	Vomiting and diarrhoea (with an excessive dose). Constipation. Metallic taste. Poor appetite
2. Neuropsychiatric	Fine tremors (in hands, also in jaw and lower limbs) Fasciculation Mild cognitive or volitional impairment Drowsiness	Dysphoria, significant cognitive impairment headache Parkinsonian symptoms (cogwheel rigidity) Fits, blurred vision, restlessness, coarse tremors, dysphagia. Others tinnitus hyper-reflexia, clonus, nystagmus, facial spasms and transient facial paralysis
3. Genitourinary	Reversible polyuria	Proteinuria, impaired erection, structural renal changes (nephritis), impaired water reabsorption, nephrotic syndrome
4. Cardiovascular	Ankle oedema Reversible ECG changes (T-wave depression, inversion or amplification)	Extrasystoles Tachy-bradycardia syndrome Sinus node dysfunction
5. Haematological	Leucocytosis (neutrophilia)	
6. Endocrinal	Increased thirst, weakness and fatigue weight gain (15–20%). Hypothyroidism (more in women)	Goitre (with or without hypothyroidism) Abnormal thyroid dysfunction (30–60%)
7. Pregnancy and lactation	Fetal cardiac malformations (Ebstein's anomaly)	Neonatal goitre Absent Moro's reflex Poor sucking, hypotonia, increased heart rate and respiration
8. Dermatological	Acneiform eruptions Folliculitis	Exacerbation of psoriasis Alopecia Maculopapular lesions Hypotonia (Myopathy)
9. Others		Exacerbation of myasthenia gravis, precipitation of thyrotoxicosis reversible exophthalmos, pretibial oedema hyperparathyroidism, stuffy nose

In acute administration, the gastrointestinal side effects are the commonest, though neurological side effects (especially tremors) are not uncommon. During long term maintenance therapy, renal side effects are the commonest.

Some common side effects and their management are:

- ***Tremors:*** Usually there are fine tremors, made worse by voluntary movements and resistent to anti-Parkinsonian or benzodiazepine medication. It occurs in about 30–50% patients and responds to either decrease in dosage or to beta sympthetic blockers (e.g. propranolol).
- ***Hypothyroidism:*** It is more common in women and occurs in about 3% per annum of chronic lithium takers. It is reversible but recurs on restarting lithium. It does not require stoppage of lithium. Thyroxine may be added slowly until TSH levels come to normal.

(If hypothyroidism is not noticed and controlled then neurospsychiatric and depressive features may become prominent, which are resistant to antidepressants and other drugs).

- ***Nephrogenic diabetes insipidus:*** Polyuria and polydipsia may occur at therepeutic plasma concentration. Distal tubules become resistant to the influence of antidiuretic hormones due to blockage of ADH—sensitive adenyl cyclase. It is reversible but may take weeks, months or years after discontinuation of lithium. Thiazide duretics may be used (they have 'paradoxical' effect on kidney tubules but require constant monitoring, as they may precipitate toxicity). Fluid should not be restricted, but rather the reverse.
- ***Gastrointestinal side effects:*** These side effects especially gastric discomfort and diarrhoea may be controlled by taking lithium salt after meals, by taking small frequent doses or enteric coated tablets or capsules or by decreasing the dosage.
- ***Toxicity:*** It usually appears when the serum lithium are above 2.0 mEq/L. The common signs are coarse tremors, ataxia, apraxia, aphasia, incoordination, slurring of speech, permanent cerebelar defect, confusion, disorientation, convulsions, coma and death. EEG shows generalized slow waves and reduced alpha activity and increased theta and delta waves. Toxicity is treated by stopping lithium and increasing its excretion. Give high fluid intake and NaCl (oral/IV).
  - Forced diuresis with urea (20 g, IV, 2–5 times/d), mannitol (50–100 g, IV, per day).
  - Aminophylline 0.5 g by slow IV increases excretion.
  - Use PCT blocker diuretic, e.g. accetazolamide (DCT blockers, e.g. thiazide or spironolactone increase toxicity).
  - If levels are above 3 mEq/L, forced alkaline diuretic; peritoneal or haemodialysis.
- ***Others:*** For example, 'cogwheel' rigidity (which does not respond to anti-Parkinsonian drugs but may require decrease in dosage or benzodiazepines).

Predictors of Good Response to Mood Stabilizers

Lithium	Valproate/Carbamazepine
• Clear cut onset, recovery from episodes	• Rapid cycling
• Absence of comorbid complications	• Mixed or dysphoric mania
• Good adherence to treatment	• No family history
• Endogenomorphic unipolar illness	• Longer delay until onset
• Family history of bipolar illness	• EEG abnormalities
• Mania followed by depression	• Substance abuse not associated with mood disorder
• Previous good reponse to treatment	• Progression in symptoms
• Poor response if rapid cycling	
• No paranoid features, substance abuse	
• Good psychosocial support	
• Absence of depression followed by mania	

Drugs Interactions and Cautions

- ***Avoid*** the lithium use with
  - Diuretics
  - Low salt diet
  - Diarrhoea/vomiting
  - Obesity
  - Pregnancy (second and third trimesters)
  - Dehydration
  - High grade fever
  - Parkinsonism
- ***Use cautiously*** in association with
  - Major tranquillizers (especially haloperidol)
  - Thyroid disease
  - Renal insufficiency
  - Patients on electroconvulsive therapy
  - Cardiac patients
- Contrandications
  - Marked renal failure
  - Psoriasis
  - Myaesthenia gravis or myopathies
  - Addison's disease
  - Pregnancy (first trimester)/lactation
  - Impaired bone development
  - Acute myocardinal infarclion

Drug Interactions of Lithium with

- Thiazide diuretics and acetazolamide (precipitate lithium toxicity as well as cardiac toxicity due to hypokalemia).
- Indomethacine, phenylbutazone, antihypertensives (e.g. methyldopa), tetracyclines, etc., increase lithium retention.
- Digoxin—may cause severe bradycardia in the presence of atrial fibrillation.
- Neuroleptics—precipitate tremors, Parkinsonism and cerebellar defect (which may be permanent).
- Carbamazepine and phenytoin—increased lithium toxicity.

Effects on Laboratory Tests

Blood tests	**Urinary tests**
Increased blood glucose	Increased excretion of
Increased serum magnesium	• glucose
Decreased serum levels (minimal)	• protein
Decreased thyroid function (decreased PBI, increased I^{131} uptake, decreased free T_4)	• Vinyl-mandellic acid (VMA)
Decreased uric acid	

HYPNOSEDATIVE DRUGS

A hypnotic drug is one which produces sleep resembling natural sleep.

A sedative is a drug that reduces excitement.

Both groups, hypnotics and sedatives, induce depression of the cental nervous system, the difference being mainly quantiative.

Anodyne hypnotic drugs like morphine and pethidine, besides acting as analgesics, also possess hypnotic property.

Classification

- **Urea derivatives**
  - Diureides—barbiturates
  - Related diuredies—glutethimide, methyprylon.
- **Alcohols**—chloral hydrate, ethanol.
- **Aldehydes**—paraldehyde.
- **Acetylated carbinols**—ethychlorvynol.
- **Benzodiazepines** and other tranquillizers.
- **Miscellaneous**—methaqualone, antihistaminics, scopolamine.
- **Inorganic Ions**—bromide.

The commonly used hypnosedative drugs are:

- **Barbiturates:** The derivatives of barbituric acid were in the past the most commonly employed hypnotics, had been replaced by benzodiazepines.
  Classification. On the basis duration of action, they are grouped as:
  On the basis of duration of action—
  - ***Long-acting*** (more than 8 hours)—phenobarbital, barbital.
  - ***Medium-acting*** (5 to 8 hours)—pentobarbital, amobarbital, butabarbital.
  - ***Short-acting*** (1 to 5 hours)—secobarbital.
  - ***Very-short acting*** (less than 1 hour)—thiopental, methohexitone.

Pharmacological Actions

- **CNS:** Barbiturates produce irregular descending paralysis of CNS. They act at all levels of CNS. The inhibition of arousal mechanisms in the brainstem reticular formation is considered to be responsible for the hypnotic action of barbiturates.
  - **Sedative action:** In small doses, they allay anxiety.
  - **Hypnotic action:** Barbiturates produce sleep resembling normal physiological sleep but they reduce the period of rapid eye movement (REM) sleep (i.e. REM rebound after abrupt withdrawal). There is minimal hangover which may persist for even a day.
  - **Analgesic and hyperalgesia:** Barbiturates reduce the postoperative pain by reducing reaction to pain or may produce excitement, restelessness and delirium in those having severe pain. So, if sleep is to be induced they are given along with analgesics. They may even produce hyperalgesic (e.g. thiopental).

- **Anaesthesia:** Ultra-short-acting ones, when given IV produce general anaesthesia of short duration, electric shock induced convulsions. The anticonvulsive effect is independent of sedative action. (Amphetamines may antagonise their sedative effect but not the anticonvulsant action.) Barbiturates enhance the postsynaptic effects of GABA (an inhibitory neurotransmitter).
- **Effect on EEG:** Small doses produce disinhibition and increase in the fast activity (called *'barbiturate activation'*). With larger doses producing sleep large amplitude slow waves (spindles) are superimposed over the high frequency waves. With still larger doses producing general anaesthesia, there is progressive decrease in amptitude and finally all activity disappears.
- **Spinal cord:** Barbiturates depress mono-synaptic and polysynaptic reflexes.
- **Medulla**
  - ***Respiration:*** They may abolish neurogenic drive to respiration (By reticulation formation) but the chemical drive to CO_2 remains. In larger doses, respiratory centre becomes less responsive or even insensitive to CO_2 and respiration is driven by hypoxia (Pure oxygen is contraindicated).
  - ***Blood pressure:*** Barbiturates cause a fall in BP due to depression to vasomotor centre and ganglion blocking.

- **Action on peripheral nerves:** Conduction is slowed.
- **CVS:** Hypnotic doses produce minimal effect while high doses reduce the cardiac contractility which is associated with alterations in distributions of intracellular calcium. High doses of thiobarbiturates causes vasoconstriction due to release of catecholeamines whereas oxybarbiturates cause vasodilation.
- **GIT:** Oxybarbiturates depress tone and motility while thiobarbiturates stimulate.
- **Kidney:** Barbiturates depress directly the tubular reabsorption of sodium. Indirectly, they reduce the urine flow (due to release of ADH and hypotention).
- **Liver:** They induce microsomal drug metabolising enzymes thus increasing metabolism of a large number of drugs.

Barbiturates may show pseudotolerance (due to induction of their own metabolism), true tolerance (e.g. tolerance to hypnotic effect), acute tolerance (tolerance after administration of a single high dose), cross tolerance (with alcohol and volatile anaesthetics and dependence (physical as well as psychic).

Pharmacokinetics

Routes of administration: Oral route is the route of choice, though they can be given by rectal, intramuscular and intravenous routes.

Absorption, metabolism and excretion: They are well-absorbed from GIT, cross blood—brain barrier quickly and reabsorbed from the tubules. Ultra- short-acting barbiturates are very highly lipid soluble and used as IV anaesthetics. Redistribution to various tissues terminate their action. The long acting barbiturates are partly metabolised and partly excerted unchanged in the urine (about 90% of barbitone and 50% of phenobarbitone). Their excertion can be enhanced by making the urine alkaline. The short and intermediate barbiturates are completely metabolised by liver.

The various metabolic pathways are oxidation, dealkylation, desulfuration of thiobarbiturates and hydrolytic cleavage of ring.

The dosage of barbiturates are

Drugs	Half-life	Adult dose (mg)
Hexobarbital	2.7–7	250–500 HS
Amobarbital	8–42	22–50 bid or tid
Butabarbital	34–42	7.5–60 tid or qid
Pentabarbital	15–48	20 tid or qid
Secobarbital	19–34	30–50 tid or qid
Phenobarbital	24–140	15–30 bid or tid

Therapeutic Uses

- ***To produce hypnosis,*** i.e. induction of sleep. Intermediate-acting ones (e.g. amylobarbitone) are suitable for those who have no difficulty in going to bed but complain of early morning wakefulness or of interrupted sleep. Those who have initial insomnia may be given short acting barbiturates (e.g. secobarbital).
- ***To produce sedation:*** Long-acting barbiturates are used for day time sedation, sedative dose is 1/4th – 1/3rd of the hypnotic dose. Now, they have been replaced by benzodiazepines.
- ***Anticonvulsants:*** Phenobarbitone and methylbarbitone are used as anticonvulsants. For emergency treatment of convulsions (e.g. due to eclampsia, tetanus and poisoning by convulsants), various barbiturates can be given by IV route.
- ***Preanaesthetic medication:*** Short-acting barbiturates are used. Very-short acting ones (e.g. Thiopentone are used as premedication for electroconvulsive therapy (ECT).
- ***For basal anaethesia and general anaesthesia:*** Ultra-short acting barbiturates are used.
- ***Obstetric analgesia:*** Short-acting and ultra-short-acting barbiturates are used as adjuants.
- ***Congenital hyperbilirubinemia:*** Phenobarbital is used as it causes liver enzyme induction and thus decrease in bilirubin level.
- ***Other uses***
  - to decrease restlessness in certain childhood illness such as pertusis.
  - to reduce cerebral edema after head trauma.
  - to determine cerebral dominance (by injecting into carotid artery).
  - in abreaction, thiopentone, amylobarbitone or pentobarbitone are used for narcoanalysis.

Adverse effects

- ***Hangover***—especially with long-acting barbiturates.
- ***Excitement pain***—occurs in neurotic patients after prolonged use.
- ***Neuralgic pain***—occurs in neurotic patients after prolonged use.
- ***Allergic reactions***—localized swelling and erythematous dermatitis.
- ***Porphyria***—they can precipitate acute-intermittent porphyria.
- ***Anaemia***—prolonged phenobarbitone therapy may produce megaloblastic anaemia which responds to folic acid.

Barbiturate poisoning: Signs and symptoms of barbiturate poisoning are depressed respiration (slow or rapid and shallow or Cheyne Stokes type), circulatory shock (rapid weak pulse, cold clammy skin, rise in haematocrit, low blood pressure), pupils (are initially constricted and then get dilated due to asphyxia), hypothermia, pulmonary complications (pneumonia, acute pulmonary oedema and atelectesis), renal failure and coma.

Treatment

- ***Removal of unabsorbed drug:*** Inducing emesis by apomorphine, slowing absorption by giving activated charcol and gastric aspiration (soon after ingestion). Gastric lavage is avoided in unconscious patient due to risk of aspiration pneumonia.
- ***Maintenance of respiration:*** Keeping the airway patent (endotracheal intubation or tracheostomy), oxygen (not 100%), aspirating secretions and mechanical ventilation.
- ***Treatment of shock*** by intravenous fluids, blood and sympathomimetic amines.
- ***Prevent renal failure*** by treating shock and hypoxia and haemodialysis (if renal failure occurs).
- ***Excretion enhanced:*** Osmotic and alkaline diuresis if renal function is satisfactory. Frusemide may be effective. This method is effective if poisoning is due to long-acting barbiturates.
- ***Prophylactic*** antibiotics to prevent pneumonia.
- ***After care:*** Psychiatric care for persons who attempt suicide.

- **Non-barbiturate, non-benzodiazepine hypnotics**
  - ***Inorganic salts***—chloral hydrate, paraldehyde.
  - ***Alcohols*** (unsaturated, tertiary)—ethchlorvynol methylpentynol.
  - ***Aldehyde derivatives***—chloral hydrate, paraldehyde.
  - ***Heterocyclic compounds***—methaqualone, glutethimide methyprylon.
  - ***Monoureides***—carbronal, bromizovalium.
  - ***Carbomates of monohydric alcohols***—ethinamate.
  - ***Miscellaneous***—chlorbutanol, thalidomide, antihistaminics.

  Some popular hypnotic agents are:
  - ***Bromides*** of sodium, potassium are used as hypnotics but they are not used in therapeutics because (a) their action starts after administering them for days and (b) their prolonged use leads to chronic bromide intoxication.

  Bromide poisoning

  - Acute bromide poisoning does not occur because they are irritant and the poisoning dose if taken would be vomited out.
  - ***Chronic poisoning*** is characterized by disturbances in *CNS*—drowsiness, irritability, impaired memory, in severe cases delusions, delirium and hallucinations.

  Skin—acneform, nodose bromoderma, pemphigus like vesicles.

  GIT—anorexia, gastric distress, foul breath, furred tongue, constipation.

  Treatment—heavy doses of sodium chloride (6 g/day in divided doses).
  - Chloral hydrate

Actions

CNS sedative, hypnotic (onset of action within half an hour, duration of action 6 to 8 hours, no nangover, not suppresses REM sleep, specially indicated for elderly and children) and anticonvulsant in tetanus cases.

CVS—In large doses, it depress contractility and shortness refractory period of the heart.

Pharmacokinetics: It is hygroscopic, so cannot be dispensed as tablets.

Dose: Oral—sedative 250 mg, hypnotic 0.5–1.0 g, rectal 0.5–1.0 g.

Absorption: Well-absorbed from GIT but a stomach irritant.

Metablism: Trichlorethanol is an active metabolite.

Adverse effects: Gastric irritation; tolerance and habituation, allergic reactions (urticaria, erythematous rash), overdose toxicity (vomiting, pin-point pupil, coma and jaundice and albuminuria if the patient survives.

Contraindications: Gastritis, severe liver, kidney or cardiac damage.

Drug interactions: Accelerates the inactivation of coumarin derivatives.

- Potentiates alcohol and combination of alcohol and chloral hydrate is known as 'Mickey Finn or knockout drops.'
- **Methaqualone**

Actions. Hypnotic (onset—15 minutes, duration 6 to 8 hours, no REM sleep alteration, no hangover, doses not depress reticular formation), potentiates narcotic analgesics, anti-inflammatory action, anticonvulsant, antipyretic, centrally-acting muscle relaxant and has antitussive action.

Pharmacokinetics

Dose: Sedative—75 mg, hypnotic 150 to 300 mg.

Absorption and metabolism. Well-absorbed from GIT and action is terminated by partioning into the fat depots and metabolism by hydroxylation, subsequent conjugation and excretion.

Adverse effects: Transient paresthesia (preceeding onset of sleep), epistaxis, menstrual disturbances, GIT upset.

Contraindications: Liver disease, pregnancy.

Drug interaction: Potentiates alcohol.

Advantages: Not a liver enzyme inducer; no effect on REM sleep (in low doses), and no hangover.

Comment: But it has become a street drug and a drug of abuse, it is discarded as a hypnotic and antianxiety drug.

- **Glutethimide**

Actions—hypnotic (onset and duration like secobarbital, minimal hangover, suppresses REM sleep), anticonvulsant, anticholingeric and antimotion sickness.

Pharmacokinetics

Dose: Sedative—250 mg, hypnotic—500 mg.

Absorption and excretion: Absorption from gut is irregular, 50% bound to plasma proteins, metabolised in liver by hydroxylation and subsequent conjugation (85% of the drug as metabolites is excreted in the bile and undergoes enterohepatic circulation).

Adverse effects: Gastric irritation, dryness of mouth, blurring of vision, dizziness, confusion, ataxia, megaloblastic anaemia and skin rash. Tolerance, dependence (psychic and physical) and addiction liability is equal to barbiturates and so this is not commonly used.

Drug interactions: Stimulates hepatic enzymes and increases ALA-synthetase activity precipitating porphyria.

- **Methyprylon**

Actions: As a hypnotic (300 mg) and suppresses REM sleep.

Pharmacokinetics: Absorbed better from GIT, metabolised by the dehydrogenation and subsequent conjugation.

Adverse effects: Nausea, vomiting, diarrhoea and constipation, drowsiness, vertigo, headache, pruritus, skin rash and habituation, tolerance and dependence.

- **Paraldehyde**
  It is used as a hypnotic (onset—quick in 10 to 15 minutes, no hangover), anticonvulsant (in tetanus, eclampsia, status epilepticus and convulsant drug poisoning), obstetrical analgesia, basal anaesthetic and to sedate patients in delirium tremens.

Pharmacokinetics: Well-absorbed from gut, a significant fraction is excreted unchanged through the lungs giving bad smell. In liver, it is depolymerised to acetaldehyde which is oxidised to acetic acid and then to CO_2 and water.

Dosage: 5 to 10 ml.

Addiction: Tolerance and physical dependence occurs.

Routes of Administration

Oral—1 to 20 parts of water (it is a gastric irritant).
Rectal—Retention enema in 2 volumes of saline or olive oil.
Deep IM injection may damage sciatic nerve.
Comment: It is not a safe hypnotic and therapeutic index is low.

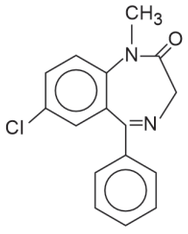
- **Benzodiazepines (BZs)**
  Sternbach discovered chlordiazepoxide in 1957. Benzodiazepines are the most prescribed medications and are the drugs of choice as anxiolytic and hypnotic.
  Classification: The classification and properties of benzodiazepines are given in **Table 1.14**.
  Therapeutic uses and specificity of benzodiazepines: Although all benzodiazepines have more or less common pharmacological actions and can be interchanged therapeutically for

TABLE 1.14: Classification and properties of benzodiazepines

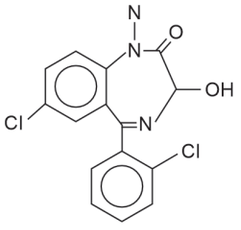
Type	*Example*	*Half-life (hours)*	*Peak time of effect (hours)*	*Protein binding (%)*	*Oral dose (mg/d)*	*Hypnotic dose (mg HS)*	*Active meta-bolities*	*Trade name*
Long-acting	Chlordiaze-poxide	5–30	2.4	96.5	10–100	10–30	Desmethyl diazepam	Equibrum Librium
				(+1.8)			Nordia-zepam	
	Diazepam	20–200	1.5–2	98.7	5–80	5–10		Calmpose Valium
	Nitrazepan	20–60	2	(+0.2)	5–20	5–20		Nitrosun
				87			Nordia-zepam	Nitravet
	Flurazepam	40–250	1		15–60	15–60	Desalkyl flurazepam	Nindral
				96.6				
	Chlorzepate	30–200	1.2	X	7.5–60	15–30	Nordia-zepam	Tranxene
Inter-mediate-acting	Oxazepam	5–15	1.4		15–120	15–30	None	Serepax
	Temazepam	10–20	0.8–14.4	97.8 (+2.2)	15–30	15–30	Oxazepam	Restoril
	Lorazepam	10–20	1.4	97.6	2–10	1–2	None	Trapex
				97.6				Ativan
								Larpose
	Alprazolam	6–20	1.2		0.5–6	0.5–1.0	α-hydroxy alprazolam	Trika Zolax
				71 (+3)				Alzolam
	Etizolam	3–6	3.5	93	1–2	1–2	α-hydroxy etizolam	Etilaam Etizola
Short-acting	Triazolam	1.5–5	2	90.1	0.25–1.0	2.5–0.5	α-hydroxy triazolam	

use in different situations but the ones given below are preferred to others in the specific situations;

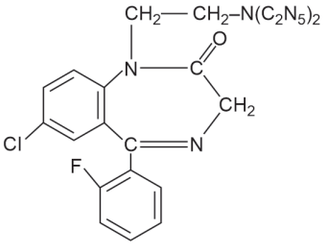
- Acute and chronic anxiety—chlordiazepoxide, clobazam, alprazolam
- Mixed anxiety– depression states—alprazolam
- Status epilepticus—diazepam
- Myoclonic and petitmal seizures—clonazepam, clobazam
- Neuromuscular disorders, e.g. cerebral palsy and Stiffman syndrome—diazepam
- Insommia—zopiclone, zolpidem, nitrazepam, temazepam, triazolam, clobazam
- Alcohol withdrawal syndrome—chlorazepate, chlordiazepoxide, diazepam, clobazam, clonazepam



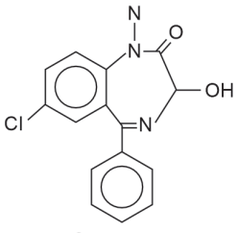
Diazepam



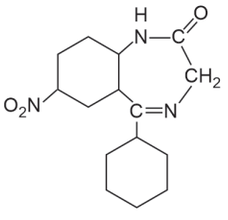
Lorazepam



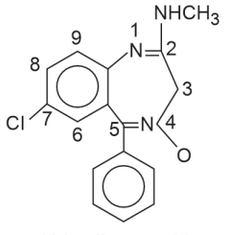
Flurazepam



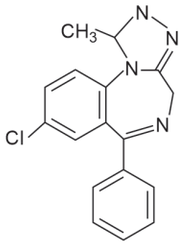
Oxazepam



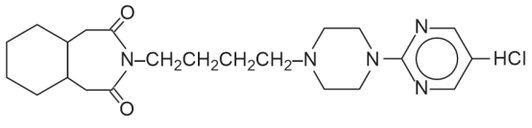
Nitrazepam



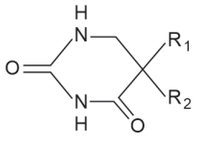
Chlordiazepoxide



Alprazolam



Buspirone



Barbiturate nucleus

$CCl_3–CH(OH)_2$

Chlora hydrate

Fig. 1.5. Structures of some important hypnosedative drugs

- Absence seizures and other type of childhood seizures—clonazepam
- Sedation—anaesthesia—midazolam.
- Panic disorder with phobias—alprazolam, oxazepam, lorazepam, clonazepam.
- Anxiety in patients with hepatic impairment—oxazepam, lorazepam.

Newer Benzodiazepines

- ***Bromazepam (lexotan):*** Second generation bebzodiazepine is a sound choice for short term treatment of anxious patients because it reduces tension without lowering vitality. It is more effective and less sedative than diazepam.
- ***Lorazepam:*** Unlike diazepam and chlordiazepoxide, lorazepam does not have any pharmacokinetic interaction with cimetidine and oral contraceptives.
- ***Laprozolam:*** It does not deteriorate psychomoter performance, does not cause attention disorders and antegrade amnesia.
- ***Loflazepate:*** New anxiolytic compound synthesized in France in 1975, it has anxiolytic and strong anticonvulsant activity in animals.
- ***Clobazam:*** Anxiolytic, hypnotic and with anticonvulsant properties. Used in dose of 20–80 mg/d.
- ***Elizolam:*** Anxiolytic hypnotic, muscle relaxant. Causes less is sedation, psychomotor retardation as compared to alprazolam. Dose 0.5–2.0 mg.
- ***Tofisopam:*** Unlike other benzodiazepines, it does not cause motor-skill deficits, sedation or dependence. Dose is 50–100 mg 1–3 times daily.

Pharmacokinetics

Absorption: They are completely absorbed from gut except chlorazepate which gets decarboxylated very rapidly in the gastric juice to N-desmethyldiazepam (nordiazepam) and then absorbed. Flunitrazepam can be given sublingually.

Metabolism: With the probable exception of oxazepam and lorazepam (which are primarily metabolised to inactive, glucuronides), the other benzodiazepines used for anxiety, are typically biotransformed to active metabolites through biotransformation in liver leading to N-alkylated or orixised products. A rapid biotransformation of flurazepam in small intestine has been reported.

Chlordiazepoxide, diazepam and flurazepam induce their own metabolism, biotransformation hence called *'self inducers'*.

The protein binding of active metabolites ranges from about 70% for alprazolam to nearly 99% for diazepam.

Diazepam has a biphasic half-life—initial rapid distributive (alpha) with half-life of about 2 to 2.5 hours, followed by a prolonged terminal elimination half-life (beta) of 1 to 2 days, due to its active metabolite nordiazepam.

Mechanism of action: The exact mode of action of benzodiazepines is not known.

Benzodiazepine receptors

Benzodiazepine receptor was discovered in the nervous system in 1977 (Mohler and Okada, 1977; Squires and Braestrup, 1977). These receptors are centrally as well as peripherally located.

- Central receptors
  - ***BZ1 type:*** These are predominant in cerebellum and responsible for anxiolytic action.
  - ***BZ2 type:*** They are mainly responsible for anticonvulsant and hypnotic effects, predominant in cerebral cortex.
- **Peripheral receptors (acceptors),** are found in mast cells, liver, heart, platelets, lymphocytes, etc.

Mode of action: Benzodiazepines are believed to potentiate GABA (an inhibitory neurotransmitter) activity by increasing the *frequency* of chloride channel opening (whereas barbiturates potentiate GABA activity by simply increasing the time that the chloride channel remain open).

- These drugs may stimulate the GABA receptors selectively, i.e. benzodiazepines bind with benzodiazepine receptors (A type rather than B type) to form a complex with GABA receptors to release GABA which exerts anxiolytic, anticonvulsant and muscle relaxant action.
  (GABA-A receptors are biculline sensitive while GABA-B receptors are beclofen sensitive).
- Recently, a group of drugs known to be BZA receptor ligands have been found to exert proconvulsant, convulsant and anxiogenic actions (called 'inverse agonists or contragonists') e.g. triazolam which acts as an inverse agonist at BZ receptors expressed in spinal cord cells in culture, exerting its anxiolytic effect mediated by BZ receptors.

Contraindications

- ***Respiratory insufficiency:*** Administer benzodiazepines with care in elderly and in patients with limited pulmonary reserve. The depression of ventillatory response is maximum after 15 to 30 minutes and may return to normal after 60 minutes (due to acute tolerance).
- ***Hepatic failure:*** Oxazepam and lorazepam are safer as the formation of glucuronides is not restricted to hepatic microsomes. The dose of diazepam has to be reduced to one-third.
- ***Obstetrics:*** Benzodiazepines are not recommended as they produce *'Floppy infant'* syndrome manifested by hypotonia, lethargy and sucking difficulties in newborns.
- ***Pregnancy and lactation:*** Benzodizepines cross placental barrier and may increase the risk of cleft palate and lip in babies). Chronic administration of diazepam in nursing mothers may cause lethargy and loss of weight in infants.
- ***Renal insufficiency***
- ***Acute intrermittent porphyria,*** e.g. chloridiazepoxide.
- ***Tartrazine insensitivity:*** Some of the BZs have tartrazine which may cause allergic reactions including bronchial asthma
- ***Paradoxical reactions:*** In hyperactive, aggressive children, excitment, stimulation or acute rage have been reported.
- ***Analgesics:*** With benzodiazepines, the dose of narcotic analgesics should be reduced to one-third.

- ***Shock, coma and acute alcohol intoxication:*** With BZs, there is risk of depression of vital signs.
- ***Acute narrow angle glaucoma:*** Alprazolam and chlordiazepoxide are avoided.

Drug Interactions

- ***Alcohol:*** Action is potentiated.
- ***Antacids:*** Rate of absorption (not extent) is reduced, especially of diazepam and chlordiazepoxide.
- ***Anticoagulants:*** For example, heparin reduces the plasma protein binding of diazepam.
- ***Atropine and other cholinergic:*** Atropine injection reduces the diazepam absorption.
- ***Cimetidine:*** Plasma concentration and half-life of diazepam is increased.
- ***Disulfiram:*** Inhibits the biotransformation of chlordiazepoxide.
- ***Oral contraceptives:*** They impair metabolism of chlordiazepoxide, diazepam, desmethyldiazepam and alprazolam.
- ***Erythromycin:*** Significantly inhibits the metabolism of triazolam.
- ***Levodopa:*** BZs decrease its effectiveness as an anti-Parkinsonian drug.
- ***Morphine:*** Oxazepam inhibits glucuronidation of morphine.
- ***Phenytoin:*** Phenytoin intoxication may be precipitated with BZs.
- ***Valproic acid:*** It increases the plasma levels and half-life of diazepam.
- ***Scopolamine:*** With lorazepam, it increases incidence of sedation, hallucinations and irrational behaviour.
- ***Lithium:*** With diazepam, hypothermia may develop (not seen when either drug is given alone).
- ***ECT:*** BZs increase the seizure threshold.
- ***Phenothiazines:*** Antihistaminics, barbiturates, psychotropic medication, tricyclic antidepressants and MAO inhibitors—potentiate BZs.
- ***Smoking:*** Sedative effect of BZs is less in smokers (due to liver enzyme induction by nicotine).
- ***Isoniazid (INH) and rifampicin:*** INH prolongs the half-life of diazepam by impairing its clearance while rifampicin increase clearance of diazepam.

Adverse effects: The side effects of BZs include drowsiness, lethargy, impaired psychomotor performance, gastric upset (nausea, vomiting, diarrhoea, epigastric pain), blurring of vision, bodyaches, impotence, urinary incontinence, ataxia (in high doses), retrograde and antegrade amnesia, disinhibited behaviour, dependence and withdrawal syndrome, cross tolerance with barbiturates and alcohol, and coma. Benzodiazepines may produce nightmares, paradoxical delirium, confusion, depression, aggression, hostile behaviour, metallic taste and headaches. There is also impaired psychomotor performance (be careful in drivers or those working with machines), retrograde amnesia (be careful in students), respiratory or cardiac arrest or both, hypotension and phlebitis at the site of injection.

Benzodiazepine withdrawal

It is characterized by anxiety type symptoms (anxiety, dysphoria, tremor, myalgia, fatigue, sleep disturbance, headache, nausea, anorexia, sweating), disturbance of perception (hypersensitivity to stimuli, abnormal body sensation, sense of body sway, depersonalization visual disturbances) and severe but rare symptoms, e.g. paranoid psychosis, depression or seizures.

Non-benzodiazepine anxiolytics: There are many non-benzodiazepine anxiolytics, whose anticonvulsant and sedative effects are low.

- **Pyrazolopyridines:** Etazolate and cartazolate increase the binding ability of BZ receptors.
- **Zopiclone:** A pyrollopyrazine, has very high affinity for central BZ receptors. Shorter-acting, no withdrawal, hangover or dependence (7.5–15 mg/d).
- **Zolpidem:** Imidazopyridine. Higher affinity for BZ1 than BZ2 receptors (10–20 mg/d). Shorter acting, no withdrawal, hangover or dependence.

Atypical Compounds

- ***Buspirone:*** An azaspirodecanedione, is anxiolytic which acts without interacting with BZ receptors. It is a potent dopamine stimulant which indicates the role of dopamine in the etiology of anxiety. Buspirone is a selective dopamine auto-receptor antagonist. It lacks hypnotic, anticonvulsant and muscle relaxing properties, hence anxioselective, causes less sedation, no dependence and no withdrawal syndrome. It does not potentiate the effects of alcohol. It is given in the dose of 10–30 mg/day (in divided doses). It is completely absorbed orally and undergoes extensive first-pass metabolism. It is 95% protein bound and does not displace tightly bound drugs, e.g. phenytoin, propranolol or warfarin. It is completely metabolised and its half-life is 2 to 3 hours (*see* **Table 1.15)**.

Buspirone interacts with serotonin (5-HT) receptors in the hippocampus, inhibits spontaneous firing of serotonin dorsal raphe neurons and decreases striatal levels of serotonin

TABLE 1.15: Buspirone versus benzodiazepine

Effect	*Buspirone*	*Benzodiazepine*
• Onset	Delayed onset	Rapid
• Effectiveness	GAD only	Many anxiety disorders
• Specific effectiveness	For psychic symptoms	For somatic symptoms
• Sedation	No	May cause
• Performance	No effect	May impair
• Alcohol	No additive effect	Additive effect
• Dependence/withdrawal	Absent	May cause
• Abuse potential	No	Low
• Oldage	No change in plasma levels	Higher plasma levels and
	No effect on falls	May increase falls

and 5-HIAA; the chronic administration decreases the number of 5-HT binding sites in the frontal cortex. It may block presynaptic dopamine receptors and increase striatal homovanillic acid (HVA). Its dopaminergic effects are opposite of the effects of antipsychotics.

Side effects include dizziness, headache, light headedness and diarrhoea.

- **Beta-sympathetic blockers** (e.g. propranolol). There are particularly useful in the treatment of anticipatory or situational anxiety (in students appearing in exams, especially when sedative effect of benzodiazepines is to be avoided). It is effective is controlling somatic symptoms of anxiety (e.g. palpitations, sweating, tremors, urinary frequency, diarrhoea, etc.). These are used alone or in combination with benzodiazepines.

  The dosage of propranolol are 20–120 mg (may be up to 280 mg) in divided doses.

  Propranolol is well-absorbed after oral administration, 90% protein bound, half-life is 3.5 hours, 95% metabolised in liver. One major metabolite is 4-hydroxypropranolol.

Side Effects

- GIT—nausea, vomiting, diarrhoea, constipation.
- CNS—dizziness, fatigue, insomnia, nightmares, depression.
- Respiratory system—asthmatic wheezing.
- Allergic reactions—skin rashes, thrombo-cytopenic purpura.
- Others—impotence.
- Overdose toxicity—precipitation of CHF, hypotension, AV block, bronchoconstriction, etc.
- Withdrawal toxicity—acute anxiety attack, restlessness, tremors, palpitations, etc., are common.

The pulse rate of a patient on propranolol below 60/minute needs careful ECG monitoring and decrease in dosage.

Contraindications

- Impending heart failure, hypotension, complete heart block, bronchial asthma, patients receiving insulin or other sympathoplegic drugs.

Uses

- ***Cardiac arrythmias*** (digitalis induced ventricular tachycardia, atrial fibrillation).
- ***Phaeochromocytoma*** in association with alpha-blockers.
- ***Hypertrophic subaortic stenosis***
- ***Angina pectoris***
- ***Hypertension***
- ***Thyrotoxicosis***
- ***Anxiolytic*** (generalized anxiety state, social phobia, agoraphobia with panic attacks, etc.).

Oxprenolol hydrochloride (slow transicor) its slow release preparation and atenolol (cardioselective betablocker) have also been used as anxiolytics.

- **Antidepressants and antipsychotic** (in low dose), e.g. doxepin, mianserin, amoxapine, chlorpromazine) may be used as hypnotics.

MISCELLNEOUS DRUGS

Melatonin—basic biology: Chronobiotics are substances which can therapeutically adjust the timing of circadian rhythms; in other words, they can 'reset' the biological clock. Melatonin is a hormone produced by the pineal gland at night in the dark. When administered exogenously, its actions are prototypic of a new class of drugs termed chronobiotics. The prime targets for chronobiotic treatment are the circadian rhythm sleep disorders, which include sleep disorders, jet lag and shift work maladaptation. Certain mood disorders, including winter depression may also involve circadian rhythm disturbances. All of these disorders have a common underlying pathophysiology; that is, a desynchrony between the timing of endogenous circadian rhythms and the timing of the environmental day–night cycle and/or the timing of the desired sleep–wake schedule (in some cases sleep is desired at an atypical time; for example, during the day in night workers).

Chronobiotic activity should be distinguished from hypnotic activity. Hypnotic drugs directly induce drowsiness or sleep but do not necessarily shift circadian rhythms. Chronobiotics are not necessarily hypnotic; intead, they improve sleep by optimizing the alignment between endogenous circadian sleep drive and the desired sleep time.

Melatonin may have both chronobiotic and hypnotic actions, especially in higher doses, but it may be possible to tease apart the two actions at lower doses.

The phase resetting action of exogenous melatonin administration was discovered quite recently.

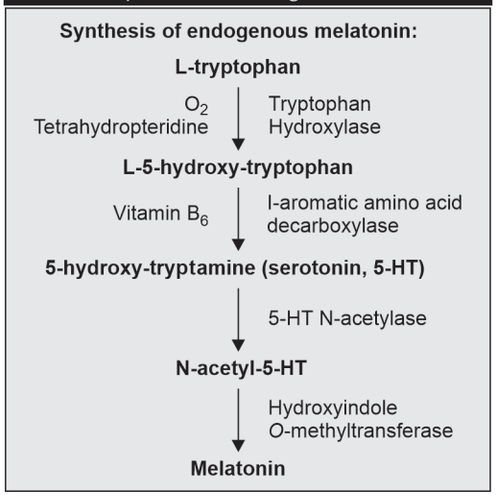
It is synthesized in the pineal gland from tryptophan via serotonin as an intermediate precursor. Pyridoxine (vit. B_6) acts as a co-enzyme in the conversion of tryptophan to serotonin. Melatonin is always produced at night, regardless or whether an animal is day-active or night-active. In nature, melatonin secretion is suppressed by light at dusk and dawn; consequently, the duration of secretion varies with the seasonal changes in the day length. It is useful to think of melatonin as a hormonal signal for nocturnal darkness, and that the message may be used by different species in different ways.

Exogenous melatonin administration is interpreted by melatonin receptive areas in the hypothalamus as 'early' dusk or a 'late' dawn, depending on the time it is given, and the circadian pacemaker responds by adjusting its phase accordingly.

The endocrine cells of the pineal gland (the pinealocytes) receive sympathetic nerve endings which release the neurotransmitter noradrenaline during the darkness; by acting on beta-adrenergic receptors, this neurotransmitter determines the uptake of tryptophan and the synthesis of melatonin from the precursor serotonin, after different enzymes have been activated (*see* **Box 1.2**).

Pharmacodynamics and drug action: Low oral dose of melatonin given at noon, increases blood melatonin concentrations to those normally occurring nocturnally and facilitates sleep onset as assessed using an involuntary muscle relaxation test.

BOX 1.2: Synthesis of endogenous melatonin



Nocturnal melatonin secretion may be involved in physiologic sleep onset and that exogenous melatonin may be useful in treating insomnia.

Pharmacokinetics: Exogenous melatonin is absorbed rapidly, yielding peak serum levels within 60 to 150 minutes. Melatonin is also rapidly degraded with an elimination half-life of 45–60 minutes. Melatonin is metabolized by the liver into 6-hydroxymelatonin, a biologically inactive metabolite. Because of the robust metabolism of circulating melatonin, oral administration of melatonin incurs significant first pass hepatic metabolism.

Safety concerns: Judging from animal studies, melatonin is non-toxic.

Indications: Melatonin is indicated in:
- Sleep disorders
- Regulation of circadian rhythm disorders
- Jet lag

Contraindications: In people on steroids like cortisone and dexamethasone, pregnancy or women wanting to conceive, nursing mothers, severe mental illness, severe allergies, autoimmune diseases, lymphomas and leukaemias and in children, melatonin should not be administered.

Adverse effects: No adverse effects of melatonin have been reported so far.

Dosage: One oral tablet to be swallowed with plain water half an hour to two hours before bedtime.

Overdose: Overdose or poisoning of melatonin is not heard of.

Warning: Pregnant or nursing women should consult the physician before taking melatonin. Melatonin tablets are not to be consumed by children. See contraindications.

Precautions: Some persons may experience drowsiness after taking melatonin and it is advisable not to drive after taking melatonin.

Conclusions: Melatonin administration several hours prior to its endogenous rise will induce phase advances (set the circadian clock earlier), while administration around the time of the endogenous decline will induce phase delays (set the circadian clock later).

Presentation: Each tablet contains melatonin 1, 3, 5 and 10 mg.

OREXIN-RECEPTOR ANTAGONISTS

Newer hypnotic drugs—suvorexant (10–40 mg), lemborexant (2.5–10 mg) and daridorexant (25–50 mg) once at night.

CNS STIMULANTS

Three commonly used stimulants are dextroamphetamine (D), methylphenidate (MP) and pemoline (P). Dosage is given below.

		Dosage		
Compound	***Tablets***	***Starting dose (mg/d)***	***Average dose (mg/d)***	***Max. dose (mg/d)***
D	5,10 5 mg/5 ml	2.5–10	10–20	40
MP	5, 10, 20	5–10	20–30	60–80
P	18.75, 37.5, 75	18.75–37.5	56.25–75	112.5

Indications

1. Attention deficit/Hyperactivity disorder
2. Narcolepsy
3. Depression
4. Obesity (rarely)

Adverse effects: Common ones are insomnia, anorexia, dependence, nausea, growth impairment, irritability, dizziness, nightmares, dysphoria, agitation

Anticonvulsant (Appendix at end)

HOW TO IMPROVE COMPLIANCE WITH TREATMENT

- Give verbal instructions
- Give written instructions
- Assess financial status of patient
- Modify or negotiate regimens
- Simplyfy regime (write minimum medicines and preferably with less frequency)
- Use depot but do not overdose
- Therapeutic alliance
- Explain disease, duration of treatment and pattern
- Educate about side effects
- Adequate treatment

- Manage side effects and drug or dietary interactions
- Promote regular pattern of response (i.e. improvement in symptoms)
- Treat comorbid condition
- Anticipate destabilising events
- Respect patient's or family's expectations
- Identify early relapse
- Encourage support and supervision
- Emphasize patient self-management of disease or illness
- Involve relatives or attendants
- Regularly check compliance and improvement
- Prefer scientific knowledge over your beliefs
- Improve communication between therapist, patient and family
- Ask about the amount of medication left
- Do not hesitate to use depot injectables in treatment
- Use technology and devices

Rational drugs irrational prescriptions—how to correct them?

- Work with a few established drugs and know them well
- Avoid prescribing more than one drug of the same chemical class at the same time
- If a drug fails, change to one of a different chemical group
- Understand the pharmacokinetics of psychotropic drug
- Do not deny a patient appropriate medication
- Choose the drug with the best risk/benefit ratio
- Prescribing 'as required' can be risky
- Do not prescribe more than three psychtropic drugs at a time
- Hypnotics may not be necessary to control insomnia
- Do not reject drugs too soon as ineffective
- Time the medication intake to suit the patient's lifestyle
- Learn the differences between preperations
- Avoid polypharmacy whenever possible
- Prescribe the simplest drug regimen to increase compliance
- Provide the most cost effective treatment
- Use non biological treatments when they are as effective as pharmacotherapy
- Exercise special care with medically ill patients
- Establish on going therapeutic relationship
- Complete each drug trial
- Special care for risk prone groups, i.e. pregnant women, infants, elderly
- Avoid rapid rise to high dose/rapid withdrawal
- Anticipate drug interactions
- Avoid biases—
  - More attached to particular drug/brand/company
  - Patient/relative biases, i.e. writing to suit relatives
  - More oriented to a particular class of drugs (e.g. tricyclics)
  - More oriented to a particular group of psychiatric disorders, e.g. personality disorders
  - Avoid irrational combinations, e.g. antidepressant with depressant drugs (e.g. benzodiazepines)

Contd...

Contd...

- Avoid 2 or more of the same class of drugs with similar effects
- Avoid subtherapeutic doses of one or more preparations
- Periodically assess response or iatrogenic effects
- Avoiding drugs due to fear of side effects
- Care for interaction of food, smoking, caffeine and alcohol with medication
- Avoid overuse/underuse/inappropriate use
- Write name (brand) of the drug correctly and clearly

The most typical manifestations of attributes of patients

- Overuse or inappropriate use because of:
  - Impulsiveness
  - Misunderstanding of the risks of the drug, its mechanism of action, or the regimen prescribed
  - Inadvertent polypharmacy (e.g. taking a substance such as alcohol without realizing that it may potentiate the effects of other agents)
- Underuse (which is most common in clinical practice) because of:
  - Fear of adverse reactions
  - Concern about dependence and addiction
  - Inconvenience of the medication regimen
  - Misunderstanding the prescribed regimen
- Inappropriate use because of:
  - Struggles with the clinician for control
  - Tendency toward self-regulation of feeling states

Note: For detailed pharmacology of Individual drugs, read next section.

LIST OF INDIVIDUAL DRUGS

A

AGOMELATIN
ALPRAZOLAM
AMANTADINE
AMINEPTINE
AMISULPRIDE
AMITRIPTYLINE
AMOBARBITAL
AMOXAPINE
ARIPIPRAZOLE
ARMODAFINIL
ASENAPINE
ATENOLOL
ATOMOXETINE
ATROPINE

B

BACLOFEN
BENPERIDOL
BENZHEXOL
BENZTROPINE
BIPERIDEN
BREXPIPRAZOLE
BROMOCRIPTINE
BUPRENORPHINE
BUPROPION
BUSPIRONE

C

CANNABIDIOL
CARBAMAZEPINE
CARBIDOPA
CARIPRAZINE
CHLORDIAZEPOXIDE
CHLORPROMAZINE
CHLORPROTHIXENE
CINNARIZINE
CLOBAZAM
CLOMIPROMINE
CLONAZEPAM
CLONIDINE
CLORAZEPATE
CLOZAPINE
COCAINE
CODEINE
CYPROHEPTADINE

D

DANTROLENE
DARIDOREXANT
DESIPRAMINE
DEXTROAMPHETAMINE
DIAZEPAM
DILTIAZEM
DISULFIRAM
DONEPEZIL
DOXEPIN

DROPERIDOL
DULOXETINE

E

ENDOXIFEN
ESCITALOPRAM
ESTAZOLAM
ETIZOLAM
ETHOSUXIMIDE

F

FENFLURAMINE
FLUMAZENIL
FLUNARIZINE
FLUOXETINE
FLUPENTHIXOL
FLUPHENAZINE
FLURAZEPAM
FLUVOXAMINE

G

GEPIRONE
GABAPENTIN

H

HALAZEPAM
HALOPERIDOL
HYDROXYZINE

I

ILOPERIDONE
IMIPRAMINE

K

KETAMINE

L

L-TRYPTOPHAN
LEMBOREXANT
LEVODOPA
LEVOSULPIRIDE
LITHIUM
LORAZEPAM
LOXAPINE
LUMATEPERONE
LURASIDONE

M

MAPROTILINE
MELATONIN
MEMANTINE
MESORIDAZINE
METHADONE
METHYLPHENIDATE
MIANSERIN
MIDAZOLAM
MILNACIPRAN
MIRTAZAPINE
MODAFINIL
MOLINDONE
MORPHINE

N

NAFAZODONE
NALOXONE
NALTREXONE
NICOTINE
NITROXAZEPINE
NORTRIPTYLINE

O

OLANZAPINE
OXAZEPAM
OXCARBAZEPINE

P

PALIPERIDONE
PAROXETINE
PENFLURIDOL
PHENOBARBITONE
PHENYTOIN
PIMAVANSERIN
PIMOZIDE
PIRIBEDIL
PITOLISANT
POMAGLUMETAD METHIONIL
PROMETHAZINE
PROTRIPTYLINE

Q

QUETIAPINE

R

REMIMAZOLAM
RISPERIDONE
RIVASTIGMINE

S

SALBUTAMINE
SCOLINE
SELEGILINE
SERTRALINE
SILDENAFIL (VIAGRA)
SODIUM VALPROATE
SULRIAMFETOL
SULPIRIDE
SULTOPRIDE
SUMATRIPTAN
SUVOREXANT

T

TACRINE
TAPENTADOL
TEMAZEPAM
TESTOSTERONE
THIOPENTAL (Thiopentone Sodium)
THIORIDAZINE
THIOTHIXENE
THYROXINE
TIANEPTINE
TIAPRIDE
TRAMADOL
TRAZODONE
TRIAZOLAM
TRIFLUOPERAZINE
TRIHEXYPHENIDYL

V

VENLAFAXINE
VIGABATRIN
VILAZODONE
VORTIOXETINE

Y

YOHIMBINE

Z

ZIPRASIDONE
ZOLPIDEM
ZOPICLONE