SECTION 7

Drugs Acting on Central Nervous System

Chapter 27 General Anaesthetics

General anaesthetics (GAs) are drugs which produce reversible loss of all sensation and consciousness. The cardinal features of general anaesthesia are:

- Loss of all sensation, especially pain
- Sleep (unconsciousness) and amnesia
- Immobility and muscle relaxation
- Abolition of somatic and autonomic reflexes.

In the modern practice of balanced anaesthesia, these modalities are achieved by using combination of inhaled and i.v. drugs, each drug for a specific purpose. Anaesthesia has developed as a highly specialized science in itself.

History Before the middle of 19th century a number of agents like alcohol, opium, cannabis, or even concussion and asphyxia were used to obtund surgical pain, but operations were horrible ordeals. Horace Wells, a dentist, picked up the idea of using *nitrous oxide* (N_2O) from a demonstration of laughing gas in 1844. However, he often failed to relieve dental pain completely and the use of N_2O had to wait till other advances were made. Morton, a dentist and medical student at Boston, after experimenting on animals, gave a demonstration of *ether* anaesthesia in 1846, and it soon became very popular. *Chloroform* was used by Simpson in Britain for obstetrical purpose in 1847, and despite its toxic potential, it became a very popular surgical anaesthetic. *Cyclopropane* was introduced in 1929, but the new generation of anaesthetics was heralded by *halothane* in 1956. The first i.v. anaesthetic *thiopentone* was introduced in 1935.

MECHANISM OF GENERAL ANAESTHESIA

The mechanism of action of GAs is not precisely known. A wide variety of chemical agents produce general anaesthesia. Therefore, GA action had been related to some common physicochemical property of the drugs. Mayer and Overton (1901) pointed out a direct parallelism between lipid/water partition coefficient of the GAs and their anaesthetic potency.

Minimal alveolar concentration (MAC) is the lowest concentration of the anaesthetic in pulmonary alveoli needed to produce immobility in response to a painful stimulus (surgical incision) in 50% individuals. It is accepted as a valid measure of potency of inhalational GAs, because it remains fairly constant for most young adults. The MAC of all inhalational anaesthetics declines progressively as age advances beyond 50 years.

The MAC of a number of GAs shows excellent correlation with their oil/gas partition coefficient. However, this only reflects capacity of the anaesthetic to enter into CNS and attain sufficient concentration in the neuronal membrane, but not the mechanism by which

anaesthesia is produced. The *'unitary hypothesis'* that some single common molecular mechanism (like membrane expansion/perturbation/fluidization) is responsible for the action of all inhalational anaesthetics has now been replaced by the *'agent specific theory'* according to which different GAs produce anaesthesia by different mechanisms.

Recent evidence favours a direct interaction of the GA molecules with hydrophobic domains of membrane proteins or the lipid-protein interface.

Not only different anaesthetics appear to act by different molecular mechanisms, they also may exhibit stereospecific effects, and that various components of the anaesthetic state may involve action at discrete loci in the cerebrospinal axis. The principal locus of causation of unconsciousness appears to be in the thalamus or reticular activating system, amnesia may result from action in cerebral cortex and hippocampus, while spinal cord is the likely seat of immobility on surgical stimulation.

Recent findings show that ligand gated ion channels (but not voltage sensitive ion channels) are the major targets of anaesthetic action. The $GABA_A$ receptor gated Cl^- channel is the most important of these. Many inhalational anaesthetics, barbiturates, benzodiazepines and propofol potentiate the action of inhibitory transmitter GABA to open Cl^- channels. Each of the above anaesthetics appears to interact with its own specific binding site on the $GABA_A$ receptor-Cl^- channel complex, but none binds to the GABA binding site as such; though some inhaled anaesthetics and barbiturates (but not benzodiazepines) can directly activate Cl^- channels. Action of glycine (another inhibitory transmitter which also activates Cl^- channels) in the spinal cord and medulla is augmented by barbiturates, propofol and many inhalational anaesthetics. This action may block responsiveness to painful stimuli resulting in immobility of the anaesthetic state. Certain fluorinated anaesthetics and barbiturates, in addition, inhibit the neuronal cation channel gated by nicotinic cholinergic receptor which may mediate analgesia and amnesia.

On the other hand, N_2O and ketamine do not affect GABA or glycine gated Cl^- channels. Rather they selectively inhibit the excitatory NMDA type of glutamate receptor. This receptor gates mainly Ca^{2+} selective cation channels in the neurones, inhibition of which appears to be the primary mechanism of anaesthetic action of ketamine as well as N_2O. The volatile anaesthetics have little action on this receptor.

Neuronal hyperpolarization caused by GAs has been ascribed to activation of a specific type of K^+ channels called 'two-pore domain' channels. This may cause inhibition of presynaptic transmitter release as well as postsynaptic activation. Inhibition of transmitter release from presynaptic neurones has also been related to interaction with certain critical synaptic proteins. Thus, different facets of anaesthetic action may have distinct neuronal basis, as opposed to the earlier belief of a global neuronal depression.

Unlike local anaesthetics which act primarily by blocking axonal conduction, the GAs appear to act by depressing synaptic transmission.

STAGES OF ANAESTHESIA

GAs cause an irregularly descending depression of the CNS, i.e. the higher functions are lost first and progressively lower areas of the brain are involved, but in the spinal cord lower segments are affected somewhat earlier than the higher segments. The vital centres located in the medulla are paralysed the last as the depth of anaesthesia increases. Guedel (1920) described four stages with *ether* anaesthesia, dividing the III stage into 4 planes. These clear-cut stages are not seen now-a-days with the use of faster acting GAs, premedication and employment of many drugs together. The precise sequence of events differs somewhat with anaesthetics other than ether. However, ether continues to be used in resource poor remote areas, and description of these stages still serves to define the effects of light and deep anaesthesia. Important features of different stages are depicted in Fig. 27.1.

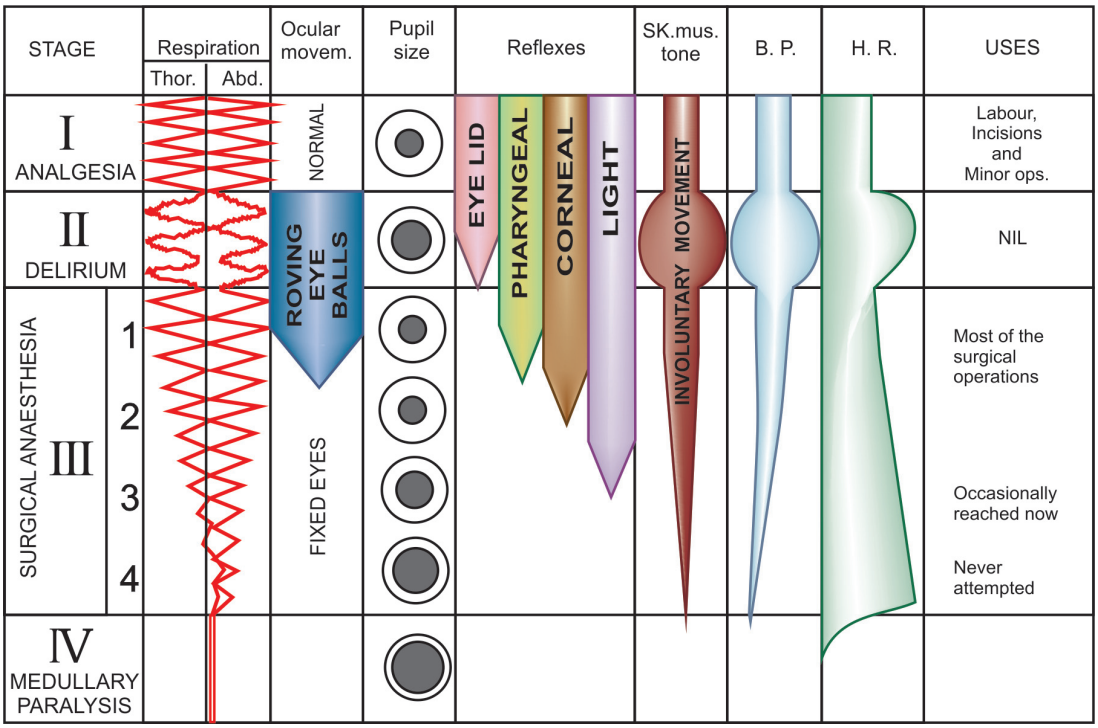


Fig. 27.1: Physiological changes during stages of general anaesthesia (with ether)

I. Stage of analgesia Starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness. Pain is progressively abolished. Patient remains conscious, can hear and see, and feels a dream like state; amnesia develops by the end of this stage. Reflexes and respiration remain normal.

Though some minor operations can be carried out during this stage, it is rather difficult to maintain—use is limited to short procedures.

II. Stage of delirium From loss of consciousness to beginning of regular respiration. Apparent excitement is seen—patient may shout, struggle and hold his breath; muscle tone increases, jaws are tightly closed, breathing is jerky; vomiting, involuntary micturition or defecation may occur. Heart rate and BP may rise and pupils dilate due to sympathetic stimulation.

No stimulus should be applied or operative procedure carried out during this stage. This stage is inconspicuous in modern anaesthesia.

III. Surgical anaesthesia Extends from onset of regular respiration to cessation of spontaneous breathing. This has been divided into 4 planes which may be distinguished as:

Plane 1 Roving eyeballs. This plane ends when eyes become fixed.

Plane 2 Loss of corneal and laryngeal reflexes.

Plane 3 Pupil starts dilating and light reflex is lost.

Plane 4 Intercostal paralysis, shallow abdominal respiration, dilated pupil.

As anaesthesia passes to deeper planes, progressively—muscle tone decreases, BP falls, HR increases with weak pulse, respiration decreases in depth and later in frequency also. Thoracic respiration lags behind abdominal respiration.

IV. Medullary paralysis Cessation of breathing to failure of circulation and death. Pupil is widely dilated, muscles are totally flabby, pulse is thready or imperceptible and BP is very low.

Many of the above indices of anaesthesia have been robbed by the use of atropine (pupillary, heart rate), morphine (respiration, pupillary), muscle relaxants (muscle tone, respiration, eye movements, reflexes), etc. and the modern anaesthetist has to depend on several other observations to gauge the depth of anaesthesia.

- If eyelash reflex is present and patient is making swallowing movements—stage II has not been reached.
- Loss of response to painful stimulus (e.g. pressure on the upper nasal border of orbit) — stage III has been reached.

- Incision of the skin causes reflex increase in respiration, BP rise or other effects; insertion of endotracheal tube is resisted and induces coughing, vomiting, laryngospasm; tears appear in eye; passive inflation of lungs is resisted—anaesthesia is light.
- Fall in BP, cardiac and respiratory depression are signs of deep anaesthesia.

In the present day practice, anaesthesia is generally kept light; adequate analgesia, amnesia and muscle relaxation are produced by the use of intravenous drugs. Premedication with CNS depressants and opioids or their concurrent use lowers MAC of the inhaled anaesthetic. When a combination of two inhalational anaesthetics (e.g. N_2O + isoflurane) is used, their MACs are additive: lower concentration of each is required, e.g. 0.5 MAC of N_2O (53%) and 0.5 MAC of isoflurane (0.6%) produce CNS depression equivalent to 1 MAC of isoflurane alone. The dose-response relationship of inhaled anaesthetics is very steep; just 30% higher concentration (1.3 MAC) immobilizes 95% subjects. Concentrations of inhalational anaesthetics exceeding 1.5 MAC are rarely used, and 2–3 MAC is often lethal. Anaesthetized subjects generally wake up when anaesthetic concentration falls to 0.4 MAC.

PHARMACOKINETICS OF INHALATIONAL ANAESTHETICS

Inhalational anaesthetics are gases or vapours that diffuse rapidly across pulmonary alveoli and tissue barriers. The depth of anaesthesia depends on the potency of the agent (MAC is an index of potency) and its partial pressure (PP) in the brain, while induction and recovery depend on the rate of change of PP in the brain. Transfer of the anaesthetic between lung and brain depends on a series of tension gradients which may be summarized as—

$$\text{Alveoli} \rightleftharpoons \text{Blood} \rightleftharpoons \text{Brain}$$

Factors affecting the PP of anaesthetic attained in the brain are—

1. *PP of anaesthetic in the inspired gas* This is proportional to its concentration in the inspired gas mixture. Higher the inspired tension more anaesthetic will be transferred to the blood. Thus, induction can be hastened by administering the GA at high concentration in the beginning.

2. *Pulmonary ventilation* It governs delivery of the GA to the alveoli. Hyperventilation will bring in more anaesthetic per minute and respiratory depression will have the opposite effect. Influence of minute volume on the rate of induction is greatest in the case of agents which have high blood solubility because their PP in blood takes a long time to approach the PP in alveoli. However, it does not affect the terminal depth of anaesthesia attained at any given concentration of a GA.

3. *Alveolar exchange* The GAs diffuse freely across alveoli, but if alveolar ventilation and perfusion are mismatched (as occurs in emphysema and other lung diseases) the attainment of equilibrium between alveoli and blood is delayed: well perfused alveoli may not be well ventilated—blood draining these alveoli carries less anaesthetic and dilutes the blood coming from well ventilated alveoli. Induction and recovery both are slowed.

4. *Solubility of anaesthetic in blood* This is the most important property determining induction and recovery. Large amount of an anaesthetic that is highly soluble in blood (ether) must dissolve before its PP is raised. The rise as well as fall of PP in blood and consequently induction as well as recovery are slow. Drugs with low blood solubility, e.g. N_2O, sevoflurane, desflurane induce quickly.

Blood: gas partition coefficient (λ) given by the ratio of the concentration of the anaesthetic in blood to that in the gas phase at equilibrium is the index of solubility of the GA in blood.

5. *Solubility of anaesthetic in tissues* Relative solubility of the anaesthetic in blood and tissue determines its concentration in that tissue at equilibrium. Most of the GAs are

equally soluble in lean tissues as in blood, but more soluble in fatty tissue. Anaesthetics with higher lipid solubility (halothane) continue to enter adipose tissue for hours and also leave it slowly. The concentration of these agents is much higher in white matter than in grey matter.

6. *Cerebral blood flow* Brain is a highly perfused organ; as such GAs are quickly delivered to it. This can be hastened by CO_2 inhalation which causes cerebral vasodilatation—induction and recovery are accelerated. Carbon dioxide stimulates respiration and this also speeds up the transport.

Elimination When anaesthetic inhalation is discontinued, gradients are reversed and the channel of absorption (pulmonary epithelium) becomes the channel of elimination. All inhaled anaesthetics are eliminated mainly through lungs. The same factors which govern induction also govern recovery. Anaesthetics, in general, continue to enter and persist for long periods in adipose tissue because of their high lipid solubility and low blood flow to fatty tissues. Muscles occupy an intermediate position between brain and adipose tissue. Most GAs are eliminated unchanged. Metabolism is significant only for halothane which is >20% metabolized in liver. Others are practically not metabolized. Recovery may be delayed after prolonged anaesthesia, especially in case of more lipid-soluble anaesthetics (halothane, isoflurane), because large quantities of the anaesthetic have entered the muscle and fat, from which it is released slowly into blood.

Second gas effect and diffusion hypoxia

In the initial part of induction, diffusion gradient from alveoli to blood is high and larger quantity of anaesthetic is entering blood. If the inhaled concentration of anaesthetic is high, substantial loss of alveolar gas volume will occur and the gas mixture will be sucked in, independent of ventilatory exchange—gas flow will be higher than tidal volume. This is significant only with N_2O, since it is given at 70–80% concentration; though it has low solubility in blood, about 1 litre/min of N_2O enters blood in the first few minutes. As such, gas flow is 1 litre/min higher than minute volume. If another potent anaesthetic, e.g. halothane (1–2%) is being given at the same time, it also will be delivered to blood at a rate 1 litre/min higher than minute volume and induction will be faster. This is called *'second gas effect'*.

The reverse occurs when N_2O is discontinued after prolonged anaesthesia; N_2O having low blood solubility rapidly diffuses into alveoli and dilutes the alveolar air, and PP of oxygen in alveoli is reduced. The resulting hypoxia, called *diffusion hypoxia*, is not of much consequence if cardiopulmonary reserve is normal, but may be dangerous if it is low. Diffusion hypoxia can be prevented by continuing 100% O_2 inhalation for a few minutes after discontinuing N_2O, instead of straight away switching over to air. Diffusion hypoxia is not significant with other anaesthetics, because they are administered at low concentrations (0.2–4%) and cannot dilute alveolar air by more than 1–2% in any case.

TECHNIQUES OF INHALATION OF ANAESTHETICS

Different techniques are used according to facility available, agent used, condition of the patient, type and duration of operation.

1. Open drop method Liquid anaesthetic is poured over a mask with gauze and its vapour is inhaled with air. A lot of anaesthetic vapour escapes in the surroundings and the concentration of anaesthetic breathed by the patient cannot be determined. It is wasteful—can be used only for a cheap anaesthetic. However, it is simple and requires no special apparatus. Use now is limited to peripheral areas. Either is the only agent administered by this method, especially in children.

2. Through anaesthetic machines Use is made of gas cylinders, specialized graduated vaporisers, flow meters, unidirectional valves, corrugated rubber tubing and reservoir bag.

The gases are delivered to the patient through a tightly fitting face mask or endotracheal tube. Administration of the anaesthetic can be more precisely controlled and in many situations its concentration estimated. Respiration can be controlled and assisted by the anaesthetist.

(a) *Open system* The exhaled gases are allowed to escape through a valve and fresh anaesthetic mixture is drawn in each time. No rebreathing is allowed—flow rates are high—more drug is consumed. However, predetermined O_2 and anaesthetic concentration can be accurately delivered.

(b) *Closed system* The patient rebreaths the exhaled gas mixture after it has circulated through sodalime which absorbs CO_2. Only as much O_2 and anaesthetic as have been taken up by the patient are added to the circuit. Flow rates are low. This is especially useful for expensive and explosive agents (little anaesthetic escapes in the surrounding air). Halothane, isoflurane, desflurane can be used through closed system. However, control of inhaled anaesthetic concentration is imprecise.

(c) *Semiclosed system* Partial rebreathing is allowed through a partially closed valve. Conditions are intermediate with moderate flow rates.

Properties of an ideal anaesthetic

A. *For the patient* It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

B. *For the surgeon* It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and nonexplosive so that cautery may be used.

C. *For the anaesthetist* Its administration should be easy, controllable and versatile.

- Margin of safety should be wide—no fall in BP.
- Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anaesthesia should be possible.
- It should be cheap, stable and easily stored.
- It should not react with rubber tubing or soda lime.

The important physical and anaesthetic properties of inhalational anaesthetics are presented in Table 27.1.

CLASSIFICATION

Inhalational

Gas	*Volatile liquids*
Nitrous oxide	Ether
	Halothane
	Isoflurane
	Desflurane
	Sevoflurane

TABLE 27.1 Physical and anaesthetic properties of inhalational anaesthetics

Anaesthetic	*Boiling point (°C)*	*Inflammability*	*Irritancy (odour)*	*Oil: Gas partition coefficient**	*Blood: Gas partition coefficient**	*MAC (%)*	*Induction*	*Muscle relaxation*
1. Ether	35	Infl. + Explo.	+++ (Pungent)	65	12.1	1.9	Slow	V. good
2. Halothane	50	Noninfl.	– (Pleasant)	224	2.3	0.75	Interm.	Fair
3. Isoflurane	48	Noninfl.	± (Unpleasant)	99	1.4	1.2	Interm.	Good
4. Desflurane	24	Noninfl.	+ (Unpleasant)	19	0.42	6.0	Fast	Good
5. Sevoflurane	59	Noninfl.	– (Pleasant)	50	0.68	2.0	Fast	Good
6. Nitrous oxide	Gas	Noninfl.	–	1.4	0.47	105	Fast	Poor

*At 37°C; Oil: gas and blood: gas partition coefficients are measures of solubility of the anaesthetic in lipid and blood respectively.
MAC—Minimal alveolar concentration; Infl.—Inflammable; Explo.—Explosive; Interm.—Intermediate

Intravenous

Fast acting drugs	*Slower acting drugs*
Thiopentone sod.	*Benzodiazepines*
Methohexitone sod.	Diazepam
Propofol	Lorazepam
Etomidate	Midazolam
	Dissociative anaesthesia
	Ketamine
	Opioid analgesia
	Fentanyl

Cyclopropane, trichloroethylene, methoxyflurane and enflurane are no longer used.

INHALATIONAL ANAESTHETICS

1. Nitrous oxide (N_2O) It is a colourless, odourless, heavier than air, noninflammable gas supplied under pressure in steel cylinders. It is nonirritating, but low potency anaesthetic; unconsciousness cannot be produced in all individuals without concomitant hypoxia; MAC is 105% implying that even pure N_2O cannot produce adequate anaesthesia at 1 atmosphere pressure. Patients maintained on 70% N_2O + 30% O_2 along with muscle relaxants often recall the events during anaesthesia, but some lose awareness completely.

Nitrous oxide is a good analgesic; even 20% produces analgesia equivalent to that produced by conventional doses of morphine. Muscle relaxation is minimal. Neuromuscular blockers are mostly required. Onset of N_2O action is quick and smooth (but thiopentone is often used for induction), recovery is rapid, because of its low blood solubility. Second gas effect and diffusion hypoxia occur with N_2O only. Post-anaesthetic nausea is not marked. It tends to increase sympathetic tone which counteracts weak direct depressant action on heart and circulation.

Nitrous oxide is generally used as a carrier and adjuvant to other anaesthetics. A mixture of 70% N_2O + 25–30% O_2 + 0.2–2% another potent anaesthetic is employed for most surgical procedures. In this way concentration of the other anaesthetic can be reduced to 1/3 for the same level of anaesthesia. Because N_2O has little effect on respiration, heart and BP: breathing and circulation are better maintained with the mixture than with the potent anaesthetic given alone in full doses. However, N_2O can expand pneumothorax and other abnormal air pockets in the body. It increases cerebral blood flow and tends to elevate intracranial pressure.

As the sole agent, N_2O (50%) has been used with O_2 for dental and obstetric analgesia. It is nontoxic to liver, kidney and brain. However, prolonged N_2O anaesthesia has the potential to depress bone marrow and cause peripheral neuropathy. Metabolism of N_2O does not occur; it is quickly removed from the body by lungs. It is cheap and commonly used.

2. Ether (Diethyl ether) It is a highly volatile liquid, produces irritating vapours which are inflammable and explosive.

$$(C_2H_5 — O — C_2H_5)$$

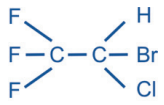
Ether is a potent anaesthetic, produces good analgesia and marked muscle relaxation by reducing ACh output from motor nerve endings. The dose of competitive neuromuscular blockers should be reduced to about 1/3.

It is highly soluble in blood. Induction is prolonged and unpleasant with struggling, breath-holding, salivation and marked respiratory secretions (atropine must be given as premedication to prevent the patient from drowning in his own secretions). Recovery is slow; post-anaesthetic nausea, vomiting and retching are marked.

Respiration and BP are generally well maintained because of reflex stimulation and high sympathetic tone. It does not sensitize the heart to Adr, and is not hepatotoxic.

Ether is not used now in developed countries because of its unpleasant and inflammable properties. However, it is still used in developing countries, particularly in peripheral areas because it is—cheap, can be given by open drop method (though congestion of eye, soreness of trachea and ether burns on face can occur) without the need for any equipment, and is relatively safe even in inexperienced hands.

3. Halothane (FLUOTHANE) It is a volatile liquid with sweet odour, nonirritant and noninflammable. Solubility in blood is intermediate—induction is reasonably quick and pleasant.



HALOTHANE

It is a potent anaesthetic—precise control of administered concentration is essential. For induction 2–4% and for maintenance 0.5–1% is delivered by the use of a special vaporizer. It is not a good analgesic or muscle relaxant, but it potentiates competitive neuromuscular blockers.

Halothane causes direct depression of myocardial contractility by reducing intracellular Ca^{2+} concentration. Moreover, sympathetic activity fails to increase reflexly. Cardiac output is reduced with deepening anaesthesia. BP starts falling early and parallels the depth. A 20–30 mm Hg drop in BP is common. Many vascular beds dilate but total peripheral resistance is not significantly reduced. Heart rate is reduced by vagal stimulation, direct depression of SA nodal automaticity and absence of baroreceptor activation even when BP falls. It tends to sensitize the heart to the arrhythmogenic action of Adr. The electrophysiological effects are conducive to reentry—tachyarrhythmias occur occasionally.

Halothane causes relatively greater depression of respiration; breathing is shallow and rapid—PP of CO_2 in blood rises if respiration is not assisted. Cerebral blood flow increases. Ventilatory support with added oxygen is frequently required. It tends to accentuate perfusion-ventilation mismatch in the lungs by causing vasodilatation in hypoxic alveoli.

Pharyngeal and laryngeal reflexes are abolished early and coughing is suppressed while bronchi dilate. As such, halothane is preferred for asthmatics. It inhibits intestinal and uterine contractions. This property is utilized for facilitating external or internal version during late pregnancy. However, its use during labour can prolong delivery and increase postpartal blood loss.

Urine formation is decreased during halothane anaesthesia—primarily due to low g.f.r. as a result of fall in BP.

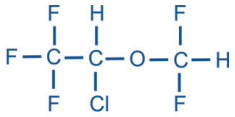
Hepatitis occurs in rare susceptible individuals (1 in 35000 to 1 in 10,000) especially after repeated use and in those with familial predisposition. A metabolite of halothane is probably involved—causes chemical or immunological injury.

A genetically determined reaction *malignant hyperthermia* occurs rarely. Many susceptible subjects have an abnormal RyR1 (Ryanodine receptor) calcium channel at the sarcoplasmic reticulum of skeletal muscles. This channel is triggered by halothane to release massive amounts of Ca^{2+} intracellularly causing persistent muscle contraction and increased heat production. Succinylcholine accentuates the condition (*see* Ch. 25). Rapid external cooling, bicarbonate infusion, 100% O_2 inhalation and i.v. dantrolene (*see* p. 356) are used to treat malignant hyperthermia.

About 20% of halothane that enters blood is metabolized in the liver, the rest is exhaled out. Elimination may continue for 24–48 hours after prolonged administration due to accumulation in fatty and other tissues. Recovery from halothane anaesthesia is smooth and reasonably quick; shivering may occur but nausea and vomiting are rare. Psychomotor performance and mental ability remain depressed for several hours after regaining consciousness.

Halothane is a popular anaesthetic in developing countries, because it is relatively cheap and nonirritant, noninflammable, pleasant with relatively rapid action. It is particularly suitable for use in children, both for induction as well as maintenance. In adults, it is mainly used as a maintenance anaesthetic after i.v. induction. Halothane toxicity is less frequent in children. However, in affluent countries it has been largely replaced by the newer agents which are costlier. Its deficiencies in terms of poor analgesia and muscle relaxation are compensated by concomitant use of N_2O or opioids and neuromuscular blockers.

4. Isoflurane (SOFANE, FORANE, ISORANE) This fluorinated anaesthetic introduced in 1981 is currently the routinely used anaesthetic all over. It has totally replaced its earlier introduced isomer enflurane. Isoflurane is somewhat less potent and less soluble in blood as well as in fat than halothane, but equally volatile. Compared to halothane, it produces relatively rapid induction and recovery, and is administered through a special vaporizer; 1.5–3% induces anaesthesia in 7–10 min, and 1–2% is used for maintenance.



ISOFLURANE

Magnitude of fall in BP is similar to halothane, but unlike halothane, this is primarily due to vasodilatation, while cardiac output is well maintained. Heart rate is increased. These cardiovascular effects probably result from stimulation of β adrenergic receptors, but it does not sensitize the heart to adrenergic arrhythmias. Isoflurane dilates coronaries. Though not encountered clinically, possibility of 'coronary steal' has been apprehended in coronary artery disease patients on theoretical grounds. Respiratory depression is prominent and assistance is usually needed to avoid hypercarbia. Secretions are slightly increased.

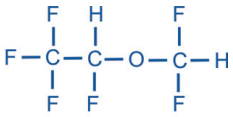
Uterine and skeletal muscle relaxation is similar to halothane. Potentiation of neuromuscular blockers is greater than that with halothane.

Metabolism of isoflurane is negligible. Renal and hepatic toxicity has not been encountered. Postanaesthetic nausea and vomiting is low.

Pupils do not dilate and light reflex is not lost even at deeper levels.

Though mildly pungent, isoflurane has many advantages, i.e. better adjustment of depth of anaesthesia and low toxicity. It is a good maintenance anaesthetic, but not preferred for induction because of ether like odour which is not liked by conscious patients, especially children. In contrast to enflurane, it does not provoke seizures and is particularly suitable for neurosurgery.

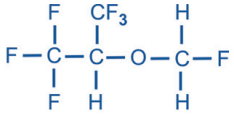
5. Desflurane It is a newer all fluorinated congener of isoflurane which has gained popularity as an anaesthetic for out patient surgery. Though it is highly volatile, a thermostatically heated special vapourizer is used to deliver a precise concentration of pure desflurane vapour in the carrier gas ($N_2O + O_2$) mixture. Its distinctive properties are lower lipid solubility as well as very low solubility in blood and tissues, because of which induction and recovery are very fast. Depth of anaesthesia changes rapidly with change in inhaled concentration giving the anaesthetist better control. Postanaesthetic cognitive and motor impairment is shortlived, so that patient can be discharged a few hours after surgery.



DESFLURANE

Desflurane is 5 times less potent than isoflurane; higher concentration has to be used for induction which irritates air passage and may induce coughing, breath-holding and laryngospasm. A somewhat pungent odour makes it unsuitable for induction. Rapid induction sometimes causes brief sympathetic stimulation and tachycardia which may be risky in those with cardiovascular disease. Degree of respiratory depression, muscle relaxation, vasodilatation and fall in BP are similar to isoflurane. Cardiac contractility and coronary blood flow are maintained. Lack of seizure provoking potential arrhythmogenicity and absence of liver as well as kidney toxicity are also similar to isoflurane. It is rapidly exhaled unchanged. As such, desflurane can serve as a good alternative to isoflurane for routine surgery as well, especially prolonged operations. If closed circuit is used, soda lime should be fresh and well hydrated.

6. Sevoflurane (SEVORANE) This new polyfluorinated anaesthetic has properties intermediate between isoflurane and desflurane. Solubility in blood and tissues as well as potency are less than isoflurane but more than desflurane.



SEVOFLURANE

Induction and emergence from anaesthesia are fast so that rapid changes in depth can be achieved. Absence of pungency makes it pleasant and administrable through a face mask. Unlike desflurane, it poses no problem in induction and is frequently selected for this purpose. Acceptability is good even by pediatric patients. Recovery is smooth; orientation, cognitive and motor functions are regained almost as quickly as with desflurane. Sevoflurane is suitable both for outpatient as well as inpatient surgery, induction as well as maintenance, but its high cost and need for high-flow open or semiclosed system makes it very expensive to use. In India, only high-end hospitals are using it.

Sevoflurane does not cause sympathetic stimulation and airway irritation even during rapid induction. Fall in BP is due to vasodilatation as well as modest cardiac depression. Respiratory depression, and absence of seizure or arrhythmia precipitating propensity are similar to isoflurane. About 3% of absorbed sevoflurane is metabolized, but the amount of fluoride liberated is safe for kidney and liver. However, it reacts with sodalime—not recommended for use in fully closed circuit.

INTRAVENOUS ANAESTHETICS

FAST ACTING DRUGS

These are drugs which on i.v. injection produce loss of consciousness in one arm-brain circulation time (~11 sec). They are generally used for induction because of rapidity of onset of action. Anaesthesia is then usually maintained by an inhalational agent. They also serve to reduce the amount of maintenance anaesthetic. Supplemented with analgesics and muscle relaxants, they can also be used as the sole anaesthetic.

1. Thiopentone sod. It is an ultrashort acting thiobarbiturate, highly soluble in water yielding a very alkaline solution, which must be prepared freshly before injection. Extravasation of the solution or inadvertent intraarterial injection produces intense pain; necrosis and gangrene can occur.

Injected i.v. (3–5 mg/kg) as a 2.5% solution, it produces unconsciousness in 15–20 sec. Its undissociated form has high lipid solubility—enters brain almost instantaneously. Initial distribution depends on organ blood flow—brain gets large amounts. However, as other less vascular tissues (muscle, fat) gradually take up the drug, blood concentration falls and it back diffuses from the brain: consciousness is regained in 6–10 min (t½ of distribution phase is 3 min).

On repeated injection, the extracerebral sites are gradually filled up—lower doses produce anaesthesia which lasts longer. Its ultimate disposal occurs mainly by hepatic metabolism (elimination t½ is 8–12 hr), but this is irrelevant for termination of action of a single dose. Residual CNS depression may persist for > 12 hr. The patient should not be allowed to leave the hospital without an attendant before this time.

Thiopentone is a poor analgesic. Painful procedures should not be carried out under its influence unless an opioid or N_2O has been given; otherwise, the patient may struggle, shout and show reflex changes in BP and respiration.

It is a weak muscle relaxant; does not irritate air passages. Respiratory depression with inducing doses of thiopentone is generally marked but transient. With large doses it can be severe. BP falls immediately after injection mainly due to vasodilatation, but recovers rapidly. Cardiovascular collapse may occur if hypovolemia, shock or sepsis are present. Reflex tachycardia occurs, but thiopentone does not sensitize the heart to Adr, arrhythmias are rare.

TABLE 27.2 Effects of intravenous anaesthetics on vital functions

Anaesthetic drug	*HR*	*BP*	*Resp.*	*CBF*
1. Thiopentone	↑↑	↓↓	↓↓	↓↓↓
2. Propofol	–, ↓	↓↓↓	↓↓↓	↓↓↓
3. Etomidate	–	↓	↓	↓↓↓
4. Diazepan	–, ↑	↓	↓↓	↓↓
5. Ketamine	↑↑	↑↑	↓, –	↑↑↑
6. Fentanyl	↓	↓	↓↓↓	↓

HR—Heart rate; BP—Systemic arterial blood pressure; Resp.—Respiratory drive; CBF—Cerebral blood flow. (Changes in intracranial pressure parallel CBF).

Cerebral blood flow is reduced, both due to fall in BP as well as constriction of cerebral vessels. However, cerebral oxygenation does not suffer, because there is greater decrease in cerebral O_2 consumption and cerebral perfusion is maintained. A comparative summary of effects of i.v. anaesthetics is presented in Table 27.2.

Thiopentone is a commonly used inducing agent. It can be employed as the sole anaesthetic for short operations that are not painful.

Adverse effects Laryngospasm occurs generally when respiratory secretions or other irritants are present, or when intubation is attempted while anaesthesia is light. This can be prevented by atropine premedication and administration of succinylcholine immediately after thiopentone. Succinylcholine and thiopentone react chemically—should not be mixed in the same syringe.

Shivering and delirium may occur during recovery. Pain in the postoperative period is likely to induce restlessness; adequate analgesia should be provided. Postanaesthetic nausea and vomiting are uncommon.

It can precipitate acute intermittent porphyria in susceptible individuals, therefore contraindicated.

Other uses Occasionally used for rapid control of convulsions.

Gradual i.v. infusion of subanaesthetic doses can be used to facilitate verbal communication with psychiatric patients and for 'narcoanalysis' of criminals; acts by knocking off guarding.

PENTOTHAL, INTRAVAL SODIUM 0.5, 1 g powder for making fresh injectable solution.

2. Methohexitone sod. It is similar to thiopentone, 3 times more potent, has a quicker and briefer (5–8 min) action. Excitement during induction and recovery is more common. It is more rapidly metabolized (t½ 4 hr) than thiopentone: patient may be roadworthy more quickly.

3. Propofol Currently, propofol has superseded thiopentone as an i.v. anaesthetic, both for induction as well as maintenance. It is an oily liquid employed as a 1% emulsion. Unconsciousness after propofol injection occurs in 15–45 sec and lasts 5–10 min. Propofol distributes rapidly (distribution t½ 2–4 min). Elimination t½ (100 min) is much shorter than that of thiopentone due to rapid metabolism.

Intermittent injection or continuous infusion of propofol is frequently used for total i.v. anaesthesia when supplemented by fentanyl. It lacks airway irritancy and is not likely to induce bronchospasm: preferred in asthmatics. It is particularly suited for outpatient surgery, because residual impairment is less marked and shorter-lasting. Incidence of postoperative nausea and vomiting is low; patient acceptability is very good. Excitatory effects and involuntary movements are noted in few patients. Induction apnoea lasting ~1 min is common. Fall in BP due primarily to vasodilatation with less marked cardiac depression occurs consistently, and is occasionally severe, but short lasting. Baroreflex is suppressed; heart rate remains unchanged or may decrease. Maintenance anaesthesia with

propofol produces dose-dependent respiratory depression which is more marked than with thiopentone. Effect of cerebral blood flow and O_2 consumption is similar to thiopentone. Pain during injection is frequent; can be minimized by combining with lidocaine.

Dose: 2 mg/kg bolus i.v. for induction; 100–200 µg/kg/min for maintenance.

PROPOVAN 10 mg/ml and 20 mg/ml in 10, 20 ml vials.

In subanaesthetic doses (25–50 µg/kg/min) it is the drug of choice for sedating intubated patients in intensive care units. However, it is not approved for such use in children; prolonged sedation with higher doses has caused severe metabolic acidosis, lipaemia and heart failure even in adults.

4. Etomidate It is another induction anaesthetic (0.2–0.5 mg/kg) which has a briefer duration of action (4–8 min) than thiopentone; produces little cardiovascular and respiratory depression, but motor restlessness and rigidity is more prominent as are pain on injection or nausea and vomiting on recovery. It is a poor analgesic and has not found much favour.

SLOWER ACTING DRUGS

1. Benzodiazepines (BZDs) In addition to preanaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'. Relatively large doses (diazepam 0.2–0.3 mg/kg or equivalent) injected i.v. produce sedation, amnesia and then unconsciousness in 5–10 min. If no other anaesthetic or opioid is given, the patient becomes responsive in 1 hr or so due to redistribution of the drug (distribution t½ of diazepam is 15 min), but amnesia persists for 2–3 hr and sedation for 6 hr or more. Recovery is further delayed if larger doses are given. BZDs are poor analgesics : an opioid or N_2O is usually added if the procedure is painful.

By themselves, BZDs donot markedly depress respiration, cardiac contractility or BP, but when opioids are also given these functions are considerably compromised. BZDs decrease muscle tone by central action, but require neuromuscular blocking drugs for muscle relaxation of surgical grade. They do not provoke postoperative nausea or vomiting. Involuntary movements are not stimulated.

BZDs are now the preferred drugs for endoscopies, cardiac catheterization, angiographies, conscious sedation during local/regional anaesthesia, fracture setting, ECT, etc. They are a frequent component of balanced anaesthesia employing several drugs. The anaesthetic action of BZDs can be rapidly reversed by flumazenil 0.5–2 mg i.v.

Diazepam 0.2–0.5 mg/kg by slow undiluted injection in a running i.v. drip: this technique reduces the burning sensation in the vein and incidence of thrombophlebitis.

VALIUM, CALMPOSE 10 mg/2 ml inj.

Lorazepam Three times more potent, slower acting and less irritating than diazepam. It distributes more gradually—awakening may be delayed. Amnesia is more profound.

Dose: 2–4 mg (0.04 mg/kg) i.v. CALMESE 4 mg/2 ml inj.

Midazolam This BZD is water soluble, non-irritating to veins, faster and shorter acting (t½ 2 hours) and 3 times more potent than diazepam. Fall in BP is somewhat greater than with diazepam. It is being preferred over diazepam for anaesthetic use: 1–2.5 mg i.v. followed by 1/4th supplemental doses. Also used for sedation of intubated and mechanically ventilated patients and in other critical care anaesthesia as 0.02–0.1 mg/kg/hr continuous i.v. infusion.

FULSED, MEZOLAM, SHORTAL 1 mg/ml, 5 mg/ml inj.

2. Ketamine This unique anaesthetic is pharmacologically related to the hallucinogen phencyclidine. It induces a so called '*dissociative anaesthesia*' characterized by profound analgesia, immobility, amnesia with light sleep. The patient appears to be conscious, i.e. opens his eyes, makes swallowing movements and his muscles are stift, but he is unable to process sensory stimuli and does not reeact to them. Thus, the patient appears to be dissociated from his body and surroundings. The primary site of action is in the cortex and

subcortical areas; not in the reticular activating system, which is the site of action of barbiturates.

Respiration is not depressed, bronchi dilate, airway reflexes are maintained, muscle tone increases. Non-purposive limb movements occur. Heart rate, cardiac output and BP are elevated due to sympathetic stimulation. A dose of 1–2 (average 1.5) mg/kg i.v. or 3–5 mg/kg i.m. produces the above effects within a minute, and recovery starts after 10–15 min, but patient remains amnesic for 1–2 hr. Emergence delirium, hallucinations and involuntary movements occur in upto 50% patients during recovery; but the injection is not painful. Children tolerate the drug better. Ketamine is rapidly metabolized in the liver and has an elimination t½ of 2–4 hr.

Ketamine has been used for operations on the head and neck, in patients who have bled, in asthmatics (relieves bronchospasm), in those who do not want to lose consciousness and for short operations. It is good for repeated use; particularly suitable for burn dressing. Combined with diazepam, it has found use in angiographies, cardiac catheterization and trauma surgery. It may be dangerous for hypertensives, in ischaemic heart disease (increases cardiac work), in congestive heart failure and in those with raised intracranial pressure (ketamine increases cerebral blood flow and O_2 consumption), but is good for hypovolemic patients.

KETMIN, KETAMAX, ANEKET 50 mg/ml in 2 ml amp, 10 ml vial.

Clandestinely mixed in drinks, ketamine has been misused as rape drug.

3. Fentanyl This highly lipophilic, short acting (30–50 min) potent opioid analgesic related to pethidine (*see* Ch. 34) is generally given i.v. at the beginning of painful surgical procedures. Reflex effects of painful stimuli are abolished. It is frequently used to supplement anaesthetics in balanced anaesthesia. This permits use of lower anaesthetic concentrations with better haemodynamic stability. Combined with BZDs, it can obviate the need for inhaled anaesthetics for diagnostic, endoscopic, angiographic and other minor procedures in poor risk patients, as well as for burn dressing. Anaesthetic awareness with dreadful recall is a risk.

After i.v. fentanyl (2–4 µg/kg) the patient remains drowsy but conscious and his co-operation can be commanded. Respiratory depression is marked, but predictable; the patient may be encouraged to breathe and assistance may be provided. Tone of chest muscles and masseters may increase with rapid fentanyl injection: a muscle relaxant is then required to facilitate mechanical ventilation. Heart rate decreases, because fentanyl stimulates vagus. Fall in BP is slight and heart is not sensitized to Adr. Cerebral blood flow and O_2 consumption are slightly decreased. Supplemental doses of fentanyl are needed every 30 min or so, but recovery is prolonged after repeated doses.

Nausea, vomiting and itching often occurs during recovery. The opioid antagonist naloxone can be used to counteract persisting respiratory depression and mental clouding. Fentanyl is also employed as adjunct to spinal and nerve block anaesthesia, and to relieve postoperative pain.

TROFENTYL, FENDOP, FENT 50 µg/ml in 2 ml amp, 10 ml vial.

Alfentanil, *Sufentanil* and *remifentanil* are still shorter acting analogues which can be used in place of fentanyl.

4. Dexmedetomidine Activation of central α_2 adrenergic receptors has been known to cause sedation and analgesia. Clonidine (a selective α_2 agonist antihypertensive) given before surgery reduces anaesthetic requirement. Dexmedetomidine is a centrally active selective α_{2A} agonist that has been introduced for sedating critically ill/ventilated patients in intensive care units. It is also being used as an adjunct to anaesthesia.Analgesia and sedation are produced with little respiratory depression, amnesia or anaesthesia. Sympathetic response to stress and noxious stimulus is blunted. It is administered by i.v. infusion. Side effects are similar to those with clonidine, *viz.* hypotension, bradycardia and dry mouth. It has been recently approved for use in India as well.

CONSCIOUS SEDATION

'Conscious sedation' is a monitored state of altered consciousness that can be employed (supplemented with local/regional anaesthesia), to carryout diagnostic/short therapeutic/dental procedures in apprehensive subjects or medically compromised patients, in place of general anaesthesia. It allows the operative procedure to be performed with minimal physiologic and psychologic stress. In conscious

sedation, drugs are used to produce a state of CNS depression (but not unconsciousness), sufficient to withstand the trespass of the procedure, while maintaining communication with the patient, who at the same time responds to commands and is able to maintain a patent airway. The difference between conscious sedation and anaesthesia is one of degree. The protective airway and other reflexes are not lost, making it safer. Drugs used for conscious sedation are:

1. *Diazepam* It is injected i.v. in small (1–2 mg) repeated doses or by slow infusion until the desired level of sedation is produced indicated by relaxation, indifference, slurring of speech, ptosis, etc. Further injection is stopped, after which this state lasts for about 1 hour and psychomotor impairment persists for 6–24 hours; an escort is needed to take the patient back to home. Flumazenil can be used to reverse the sedation, but repeated doses are needed.

   Midazolam (i.v.) is a shorter acting alternative to diazepam. Oral diazepam administered 1 hr before is also used with the limitation that level of sedation cannot be titrated. The patient remains sedated (not roadworthy) for several hours.

2. *Propofol* Because of brief action, it has to be administered as continuous i.v. infusion throughout the procedure by using a regulated infusion pump. Advantage is that level of sedation can be altered during the procedure and recovery is relatively quick, permitting early discharge of the patient.

3. *Nitrous oxide* The patient is made to breathe 100% oxygen through a nose piece or hood and N_2O is added in 10% increments (to a maximum of 50%, rarely 70%) till the desired level of sedation assessed by constant verbal contact is obtained. This is maintained till the procedure is performed. Thereafter, N_2O is switched off, but 100% O_2 is continued for next 5 min. The patient is generally roadworthy in 30–60 min.

4. *Fentanyl* Injected i.v. (1–2 µg/kg every 15–30 min), it can be used alone or in combination with midazolam/propofol.

COMPLICATIONS OF GENERAL ANAESTHESIA

A. *During anaesthesia*

1. Respiratory depression and hypercarbia.
2. Salivation, respiratory secretions. This is less problematic now as nonirritant anaesthetics are mostly used.
3. Cardiac arrhythmias, asystole.
4. Fall in BP.
5. Aspiration of gastric contents: acid pneumonitis.
6. Laryngospasm and asphyxia.
7. Awareness: dreadful perception and recall of events during surgery. This may occur due to use of light anaesthesia + analgesics and muscle relaxants.
8. Delirium, convulsions and other excitatory effects are generally seen with i.v. anaesthetics; especially if phenothiazines or hyoscine have been given in premedication. These are suppressed by opioids.
9. Fire and explosion. This is rare now due to use of non-inflammable anaesthetics.

B. *After anaesthesia*

1. Nausea and vomiting.
2. Persisting sedation: impaired psychomotor function.
3. Pneumonia, atelectasis.
4. Organ toxicities: liver, kidney damage.
5. Nerve palsies—due to faulty positioning.
6. Emergence delirium.
7. Cognitive defects: prolonged excess cognitive decline has been observed in some patients, especially the elderly, who have undergone general anaesthesia, particularly of long duration.

DRUG INTERACTIONS

1. Patients on antihypertensives given general anaesthetics—BP may fall markedly.
2. Neuroleptics, opioids, clonidine and monoamine oxidase inhibitors potentiate anaesthetics.
3. Halothane sensitizes the heart to Adr.
4. If a patient on corticosteroids is to be anaesthetized, give 100 mg hydrocortisone intraoperatively because anaesthesia is a stressful state—can precipitate adrenal insufficiency and cardiovascular collapse.
5. Insulin need of a diabetic is increased during GA: switch over to plain insulin even if the patient is on oral hypoglycaemics.

PREANAESTHETIC MEDICATION

Preanaesthetic medication refers to the use of drugs before anaesthesia to make it more pleasant and safe. The aims are:

1. Relief of anxiety and apprehension preoperatively and to facilitate smooth induction.
2. Amnesia for pre- and postoperative events.
3. Supplement analgesic action of anaesthetics and potentiate them so that less anaesthetic is needed.
4. Decrease secretions and vagal stimulation that may be caused by the anaesthetic.
5. Antiemetic effect extending to the postoperative period.
6. Decrease acidity and volume of gastric juice so that it is less damaging if aspirated.

Different drugs achieve different purposes. One or more drugs may be used in a patient depending on the needs.

1. Sedative-antianxiety drugs Benzodiazepines like diazepam (5–10 mg oral) or lorazepam (2 mg oral or 0.05 mg/kg i.m. 1 hour before) have become popular drugs for preanaesthetic medication because they produce tranquility and smoothen induction; there is loss of recall of perioperative events (especially with lorazepam) with little respiratory depression or accentuation of postoperative vomiting. They counteract CNS toxicity of local anaesthetics and are being used along with pethidine/fentanyl for a variety of minor surgical and endoscopic procedures.

Midazolam is a good amnesic with potent and shorter lasting action; it is also better suited for i.v. injection, due to water solubility.

Promethazine (50 mg i.m.) is an antihistaminic with sedative, antiemetic and anticholinergic properties. It causes little respiratory depression.

2. Opioids Morphine (10 mg) or pethidine (50–100 mg), i.m. allay anxiety and apprehension of the operation, produce pre- and postoperative analgesia, smoothen induction, reduce the dose of anaesthetic required and supplement poor analgesics (thiopentone, halothane) or weak anaesthetics (N_2O). Postoperative restlessness is also reduced.

Disadvantages They depress respiration, interfere with pupillary signs of anaesthesia, may cause fall in BP during anaesthesia, can precipitate asthma and tend to delay recovery. Other disadvantages are lack of amnesia, flushing, delayed gastric emptying and biliary spasm. Some patients experience dysphoria. Morphine particularly contributes to postoperative constipation, vomiting and urinary retention. Tachycardia sometimes occurs when pethidine has been used.

Use of opioids is now mostly restricted to those having preoperative pain. When indicated, fentanyl is mostly injected i.v. just before induction.

3. Anticholinergics (*see* Ch. 8) Atropine or hyoscine (0.6 mg or 10–20 µg/kg i.m./i.v.) or glycopyrrolate (0.2–0.3 mg or 5–10 µg/kg i.m./i.v.) have been used, primarily to reduce salivary and bronchial secretions. This need is infrequent now due to use of non-irritant anaesthetics. However, they must be given beforehand when ether is used. The main aim of their use now is to prevent vagal bradycardia and hypotension (which occur reflexly due to certain surgical procedures), and prophylaxis of laryngospasm which is precipitated by respiratory secretions.

Hyoscine, in addition, produces amnesia and antiemetic effect, but tends to delay recovery. Some patients get disoriented; emergence delirium is more common. Moreover, antibradycardiac effect of hyoscine is less marked. Therefore, it is infrequently selected for use during anaesthesia.

Glycopyrrolate is twice as potent and longer acting quaternary antimuscarinic which does not produce central effects. Antisecretory action is more marked than atropine, while tachycardia is less marked, especially after i.m. injection. It acts rapidly when given i.v. and is the preferred antimuscarinic in anaesthetic practice.

Action	*Atropine*	*Glycopyrrolate*
1. Antisecretory	++	+++
2. Tachycardia	+++	++
3. CNS effects	+	–
4. Bronchodilatation	++	++

Antimuscarinics facilitate assisted ventilation by reducing airway resistance, but tend to increase the anatomic dead space. They dilate pupils, abolish the pupillary signs and increase chances of gastric reflux by decreasing tone of lower esophageal sphincter (LES). They should not be used in febrile patients. Dryness of mouth

in the pre- and postoperative period may be distressing. As such, they are now mostly used i.v. intraoperatively when need arises.

4. Neuroleptics Chlorpromazine (25 mg), triflupromazine (10 mg) or haloperidol (2–4 mg) i.m. are infrequently used in premedication. They allay anxiety, smoothen induction and have antiemetic action. However, they potentiate respiratory depression and hypotension caused by the anaesthetics and delay recovery.

Involuntary movements and muscle dystonias can occur, especially in children.

5. H_2 blockers/proton pump inhibitors Patients undergoing prolonged operations, caesarian section and obese patients are at increased risk of gastric regurgitation and aspiration pneumonia. Ranitidine (150 mg)/famotidine (20 mg) or omeprazole (20 mg)/pantoprazole (40 mg) given night before and in the morning benefit by raising pH of gastric juice and may also reduce its volume and thus chances of regurgitation. The chances of reflux and damage to lungs on aspiration is minimal if volume of gastric juice is <25 ml and pH is >3.5. Prevention of stress ulcers is another advantage. They are now routinely used before prolonged surgery.

6. Antiemetics *Metoclopramide* 10–20 mg i.m. preoperatively is effective in reducing postoperative vomiting. By enhancing gastric emptying and tone of LES, it reduces the chances of reflux and its aspiration. Extrapyramidal effects and motor restlessness can occur. Combined use of metoclopramide and H_2 blockers is more effective.

Domperidone is nearly as effective and does not produce extrapyramidal side effects.

Ondansetron (4–8 mg i.v.) the selective 5-HT_3 blocker has been found highly effective in reducing the incidence of post-anaesthetic nausea and vomiting (*see* Ch. 47). It is practically devoid of side effects and has become the antiemetic of choice in anaesthetic practice.

Chapter 28 Ethyl and Methyl Alcohols

ETHYL ALCOHOL (Ethanol)

Alcohols are hydroxy derivatives of aliphatic hydrocarbons. When unqualified, 'alcohol' refers to *ethyl alcohol* or *ethanol*. Pharmacology of alcohol is important for its presence in beverages (which have been used since recorded history), alcoholism and for alcohol intoxication, rather than as a medicinal substance.

Alcohol is manufactured by fermentation of sugars:

$$C_6H_{12}O_6 \xrightarrow[(in\ yeast)]{Zymase} 2CO_2 + 2C_2H_5OH$$

Fermentation proceeds till alcohol content reaches ~ 15%. Then the reaction is inhibited by alcohol itself. Starchy cereals, e.g. barley, when soaked produce malt:

$$STARCH \xrightarrow{Convertase} MALTOSE$$

which can then be fermented by yeast to produce alcohol. The major source of commercial alcohol is *mollases*, a byproduct of sugar industry.

ALCOHOLIC BEVERAGES

There are a large variety of alcoholic beverages.

A. Malted liquors Obtained by fermentation of germinating cereals; are undistilled—alcohol content is low (3–6%) e.g. Beers, Stout. Now strong beers (upto 10%) are also available.

B. Wines Produced by fermentation of natural sugars as present in grapes and other fruits. These are also undistilled.

Light wines Claret, Cider; alcohol content 9–12%, cannot exceed 15%.

Fortified wines Port, Sherry (alcohol 16–22%): distilled beverages are added from outside.

Effervescent wines Champagne (12–16% alcohol): bottled before fermentation is complete.

Wines are called 'dry' when all sugar present has been fermented and 'sweet' when some is left.

C. Spirits These are distilled after fermentation; e.g. Rum, Gin, Whiskey, Brandy, Vodka, etc. Though the alcohol content of these can vary from 40–55%, in India (and almost internationally) for all licenced brands it is standardized to 42.8% v/v or 37% w/w.

The taste, flavour and value of alcoholic beverages depends not only on alcohol content but on the presence of higher ethers, higher alcohols, aldehydes, esters, polymers, and volatile oils; many of these are formed during 'maturation' of the beverage.

Other forms of alcohol

1. *Absolute alcohol* 99% w/w ethanol (dehydrated alcohol).
2. *Rectified spirit* 90% w/w ethyl alcohol produced from fermented mollases, by distillation.
3. *Proof spirit* It is an old term. If whiskey is poured on gun powder and ignited and it explodes, then it was labelled to be of 'proof strength'. If water is mixed to it, gun powder will not ignite. 100% proof spirit is 49.29% w/w or 57.1% v/v alcohol.
4. *Methylated spirit (industrial)* Also called 'denatured spirit' is produced by adding 5 parts of wood naphtha (methyl alcohol) to 95 parts of rectified spirit so as to render it unfit for drinking. It is tinted blue by methylene blue dye for distinction. It can be applied on the skin for antiseptic, cleaning and astringent purposes.

PHARMACOLOGICAL ACTIONS

1. Local actions Ethanol is a mild rubefacient and counterirritant when rubbed on the skin. By evaporation it produces cooling. Applied to delicate skin (scrotum) or mucous membranes it produces irritation and burning sensation. Concentrated alcohol (spirit) should not be applied in the mouth, nose, etc. Injected s.c. it causes intense pain, inflammation and necrosis followed by fibrosis. Injected around a nerve it produces permanent damage.

Applied to the surface, alcohol is an astringent—precipitates surface proteins and hardens the skin. By precipitating bacterial proteins it acts as an antiseptic. The antiseptic

action increases with concentration from 20 to 70%, remains constant from 70 to 90% and decreases above that. That 100% ethanol is more dehydrating but poorer antiseptic than 90% ethanol, shows that antibacterial action is not due to dehydration of bacterial protoplasm. Alcohol does not kill bacterial spores.

2. CNS Alcohol is a neuronal depressant. Since the highest areas are most easily deranged and these are primarily inhibitory—apparent excitation and euphoria are experienced at lower plasma concentrations (30–60 mg/dl). Hesitation, caution, self-criticism and restraint are lost first. Mood and feelings are altered; anxiety may be allayed. With increasing concentration (80–150 mg/dl) mental clouding, disorganization of thought, impairment of attention, memory and other faculties, alteration of gait and perception and drowsiness supervene. At 150–200 mg/dl the person is sloppy, ataxic and drunk, 'blackouts' occur; 200–300 mg/dl result in stupor and above this unconsciousness prevails, medullary centres are paralysed and death may occur. Though, alcohol can produce anaesthesia, margin of safety is narrow.

Any measurable concentration of alcohol produces a measurable slowing of reflexes: driving is dangerous. Performance is impaired, fine discrimination and precise movements are obliterated; errors increase, except if fear of punishment and anxiety of failure has already impaired it. Under such situation performance may be improved by allaying of anxiety and fear.

At any given blood alcohol level, central effects are more marked when the concentration is rising than when it is falling. This is considered to be a manifestation of acute tolerance.

Alcohol can induce sleep but is not a dependable hypnotic. Some individuals report poor quality of sleep and repeated or early morning awakening. Sleep architecture may be disorganized and sleep apnoea aggravated. 'Hangover' (headache, dry mouth, laziness, disturbed mood, impaired performance) may occur the next morning. Alcohol raises pain threshold and also alters reaction to it, but is not a dependable analgesic—severe pain can precipitate confusion and convulsions. During the time alcohol is acting on brain, it exerts anticonvulsant action, but this is followed by lowering of threshold: seizures may be precipitated in epileptics. Chronic alcohol abuse damages brain neurones, causes shrinkage of brain.

The cortex and the reticular activating system are most sensitive to alcohol; other areas get depressed as concentration rises.

Mechanism of action Alcohol was believed to produce CNS depression by a generalized membrane action altering the state of membrane lipids. However, lately specific effect on multiple receptor operated and voltage gated ion channels/other critical proteins has been demonstrated at concentrations attained during moderate drinking. Thus, several neurohumoral systems are concurrently affected producing a complex pattern of action quite different from that produced by other depressants like barbiturates and benzodiazepines, which predominantly facilitate $GABA_A$ receptor mediated Cl^- channel opening. Alcohol has been shown to enhance GABA release at $GABA_A$ sites in the brain. It also inhibits NMDA and kainate type of excitatory amino acid receptors (operating through cation channels). Action of 5-HT on $5\text{-}HT_3$ inhibitory autoreceptor (having an intrinsic ion channel) is augmented. Some studies suggest that cerebral nicotinic cholinergic receptor (operating through Na^+ channel) may also be one of the targets of alcohol action. Ethanol can indirectly reduce neurotransmitter release by inhibiting voltage sensitive neuronal Ca^{2+} channels. It also activates specific type of K^+ channels in certain brain areas. Release and turnover of DA in brain is enhanced through β endorphin release in nucleus accumbens and an opioid receptor dependent mechanism. This is probably important in the pleasurable reinforcing effects of alcohol and in the genesis of alcohol dependence. Activity of membrane bound enzymes like Na^+ K^+ ATPase and adenylyl cyclase is also altered. The activity and translocation of channel/enzyme proteins in the membrane could be affected by alcohol through protein kinase C (PKC) and protein kinase A (PKA) mediated alteration in the state of their phosphorylation.

Alcohol : conscious → anaesthesia → death.

Ether : conscious → anaesthesia → death.

3. CVS The effects are dependent on dose.

Small doses: produce only cutaneous (especially on the face) and gastric vasodilatation. Skin is warm and flushed and there may be conjunctival injection; BP is not affected.

Moderate doses: cause tachycardia and a mild rise in BP due to increased muscular activity and sympathetic stimulation.

Large doses: cause direct myocardial as well as vasomotor centre depression and there is fall in BP.

Epidemiological studies have confirmed that chronic alcoholism contributes to hypertension and can lead to cardiomyopathy. Atrial fibrillation and other cardiac arrhythmias may occur due to conduction defects and Q-T prolongation.

4. Blood Regular intake of small to moderate amounts of alcohol (1–2 drinks) has been found to raise HDL-cholesterol levels and decrease LDL oxidation. This may be responsible for the 15–35% lower incidence of coronary artery disease in such individuals. Risk reduction is greatest in high risk subjects and protection is lost if ≥ 3 drinks are consumed daily. However, it is considered inapproptiate to advise nondrinkers to start drinking on this account, since other adverse consequences may more than nullify this benefit. Mild anaemia is common in chronic alcoholics. Megaloblastic anaemia occurring in chronic alcoholism is due to interference with folate metabolism.

5. Body temperature Alcohol is reputed to combat cold. It does produce a sense of warmth due to cutaneous and gastric vasodilatation, but heat loss is actually increased in cold surroundings. High doses depress temperature regulating centre.

6. Respiration Brandy or whiskey are reputed as respiratory stimulants in collapse. They irritate buccal and pharyngeal mucosa which may transiently stimulate respiration reflexly. However, it is better not to depend on this, because the direct action of alcohol on respiratory centre is only a depressant one.

7. GIT Alcoholic beverages have variable effect on gastric secretion depending on the beverage itself and whether the individual likes it. However, dilute alcohol (optimum 10%) put in the stomach by Ryle's tube is a strong stimulant of gastric secretion (especially of acid). It acts directly as well as reflexly. Higher concentrations (above 20%) inhibit gastric secretion, cause vomiting, mucosal congestion and gastritis. Alcoholism is an important cause of chronic gastritis. Lower esophageal sphincter (LES) tone is reduced by alcohol. Drinking may accentuate gastric reflux. Bowel movements may be altered in either direction. Acute pancreatitis is a complication of heavy drinking.

8. Liver Neither brief alcohol intoxication nor chronic intake of small-to-moderate amounts cause significant liver damage, provided adequate nutrition is maintained. However, it does mobilize peripheral fat and increases fat synthesis in liver in a dose-dependent manner. Proteins may also accumulate in liver because their secretion is decreased. Chronic alcoholism exposes liver to oxidative stress and causes cellular necrosis followed by fibrosis. Acetaldehyde produced during metabolism of alcohol appears to damage the hepatocytes and induce inflammation, especially on chronic ingestion of large amounts. Increased lipid peroxidation and glutathione depletion occurs. These combined with vitamin and other nutritional deficiencies may be responsible for the so called *alcoholic cirrhosis*.

Regular alcohol intake induces microsomal enzymes.

9. Skeletal muscle Alcohol produces little direct effect. Fatigue is allayed by small doses, but muscle work is increased or decreased depending on the predominating central effect. Weakness and myopathy occurs in chronic alcoholism.

10. Kidney Diuresis is often noticed after alcohol intake. This is due to water ingested along with drinks as well as alcohol induced inhibition of ADH secretion. It does not impair renal function.

11. Sex Alcohol is reputed as an aphrodisiac. Aggressive sexual behaviour is due to loss of restraint and inhibition. However, performance of the sexual act is often impaired. Chronic alcoholism can produce impotence, testicular atrophy, gynaecomastia and infertility in both men and women.

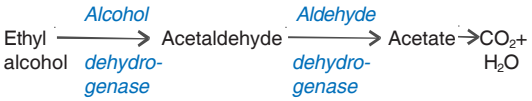
12. Endocrine effects Moderate amounts of alcohol increase Adr release which can cause hyperglycaemia and other sympathetic effects. However, acute intoxication is often associated with hypoglycaemia and depletion of hepatic glycogen, because gluconeogenesis is inhibited. Glucagon, thus fails to reverse it and glucose must be given to counteract hypoglycaemia.

13. Uterine contractions are suppressed at moderate blood levels.

PHARMACOKINETICS

Rate of alcohol absorption from the stomach is dependent on its concentration, presence of food, and other factors, but is generally quite slow. Absorption from intestines is very fast; peak levels are attained after ~30 min. Thus, gastric emptying determines rate of absorption. Limited first pass metabolism occurs in stomach and liver. Absorption of alcohol from skin of adults is minimal but may be significant in infants given alcohol sponges.

Alcohol gets distributed widely in the body (vol of distribution 0.7 L/kg), crosses blood brain barrier efficiently: concentration in brain is very near blood concentration. It also crosses placenta freely. Alcohol is oxidized in liver to the extent of 98%. Even with high doses, not more than 10% escapes metabolism.



In addition to alcohol dehydrogenase, small amounts of alcohol are oxidized by hepatic microsomal enzymes (mainly CYP2E1) as well. Metabolism of alcohol follows *zero order* kinetics, i.e. a constant amount (8–12 ml of absolute alcohol/ hour) is degraded in unit time, irrespective of blood concentration. Thus, rate of consuming drinks governs whether a person will get drunk.

Excretion of alcohol occurs through kidney and lungs, but neither is quantitatively significant. Concentration in exhaled air is about 0.05% of blood concentration: this is utilized for medico-legal determination of drunken state. The subject blows in a balloon and alcohol is measured by portable breath analyser.

INTERACTIONS

1. Alcohol synergises with anxiolytics, antidepressants, antihistaminics, hypnotics, opioids → marked CNS depression with motor impairment can occur: Chances of accidents increase.
2. Individuals taking a sulfonylurea, cefoperazone, or metronidazole have experienced bizarre, somewhat disulfiram-like reactions when they consume alcohol. This reaction occurs only in some individuals and its basis is unclear. It passes off with time as alcohol is metabolized. Only reassurance and supportive treatment is needed.
3. Acute alcohol ingestion inhibits, while chronic intake induces CYP enzymes (especially CYP2E1). Formation of toxic metabolite of paracetamol (NAPQI) is increased in chronic alcoholics (*see* p. 207). Safe dose limit of paracetamol is lower in them. Metabolism of tolbutamide, phenytoin and some other drugs is similarly affected by acute and chronic alcohol intake.
4. Hypoglycaemic action of insulin and sulfonylureas is enhanced by alcohol ingestion.
5. Aspirin and other NSAIDs cause more gastric bleeding when taken with alcohol.

Food value

Alcohol requires no digestion and is metabolized rapidly. It is an energy yielding substrate: 7 Cal/g, but these cannot be stored. However, it spares carbohydrates and fats as energy source, so that regular intake can contribute to obesity.

Alcohol does not supply body building and other essential constituents of food. Those who consume substantial part of their caloric intake as alcohol, often suffer from nutritional deficiencies. Thus, alcohol is an imperfect and expensive food.

CONTRAINDICATIONS

Alcohol is seldom prescribed medically. However, it is rampently consumed. Intake of alcohol should be avoided by—

1. Peptic ulcer, hyperacidity and gastroesophageal reflux patients (alcohol increases gastric secretion and relaxes LES).
2. Epileptics: seizures may be precipitated.
3. Severe liver disease patients.
4. Unstable personalities: they are likely to abuse it and become excessive drinkers.
5. Pregnant women: Even moderate drinking during pregnancy can produce *foetal alcohol syndrome* resulting in intrauterine and postnatal growth retardation, low IQ, microcephaly, cranio-facial and other abnormalities, and immunological impairment→increased susceptibility to infections. Heavy drinking during pregnancy, in addition, increases the incidence of miscarriage, stillbirths and low birth-weight babies.

Guidelines for safe drinking Physicians are often asked to advise on safe ways of drinking. Various official agencies, physician organizations and alcoholism experts have putforth guidelines in this regard, but they are not uniform. The following may be concluded:

- On an average 1–2 drinks per day is usually safe.
- Not more than 3 drinks on any one occasion.
- Consumption of >3 drinks per day is associated with documented adverse health effects.
- Do not drive or engage in hazardous activities after drinking.
- Do not drink if an interacting drug has been taken.
- Subjects with any contraindication should not drink.
- Safe limits are somewhat lower for women than for men, because metabolism of alcohol is slower and its bioavailability higher (due to less first pass metabolism in stomach) in women than in men.

[Note: 1 drink = 50 ml of spirits = 150 ml of wines = 400 ml of beer; all have roughly 16 g alcohol, which taken in empty stomach produces a peak alcohol blood level of ~ 30 mg/dl in an adult male of average built.]

TOXICITY

A. *Side effects of moderate drinking* Nausea, vomiting, flushing, hangover, traffic accidents.

B. *Acute alcoholic intoxication* Unawareness, unresponsiveness, stupor, hypotension, gastritis, hypoglycaemia, respiratory depression, collapse, coma and death.

Treatment: Gastric lavage is helpful only when the patient is brought soon after ingesting alcohol, which is rare. Since most patients are disoriented or comatose, the first priority is to maintain patent airway and prevent aspiration of vomitus. Tracheal intubation and positive pressure respiration may be needed if it is markedly depressed. Analeptics should not be given. They may precipitate convulsions. Most patients will recover with supportive treatment, maintenance of fluid and electrolyte balance and correction of hypoglycaemia by glucose infusion till alcohol is metabolized. Thiamine (100 mg in 500 ml glucose solution infused i.v.) should be added. Recovery can be hastened by haemodialysis. Insulin + fructose drip has been found to accelerate alcohol metabolism. However, its clinical impact is not remarkable.

C. *Chronic alcoholism* On chronic intake, tolerance develops to subjective and behavioral effects of alcohol, but is generally of a low degree. It is both pharmacokinetic (reduced rate of absorption due to gastritis and faster metabolism due to enzyme induction) and cellular tolerance. Psychic dependence often occurs even with moderate drinking; depends a lot on

individual's likings and attitudes. It is manifested in alcohol-seeking behaviour, and the priority that the subject accords to obtaining and consuming alcohol over other needs, or the extent to which he will go for maintaining alcohol intake.

Recent studies have confirmed that a genetic basis contributes to progression from social drinking to alcoholism in about 50% individuals. Alcoholism is often a familial trait. Some differences in sensitivity of various neuronal systems to alcohol among 'predisposed' and 'not predisposed' individuals have been demonstrated.

There is no single explanation for why people drink. Diverse feelings and behaviours are provoked by alcohol in different individuals and in the same individual on different occasions. Alcohol can make people happy as well as sad, curtious as well as mean, talkative as well as silent, friendly as well as hostile. All this cannot be explained on the basis of pharmacological actions of alcohol alone. Attitudes, beliefs, peer groups, social setting and learned experiences all have a bearing. Alcohol is said to produce good mood, sense of wellbeing, self confidence, sociability, etc. But these infact are learned behaviours. In some societies, alcoholic beverages have become an acceptable form of extending courtesy and of entertainment. Drinking is often related to 'celebration' and 'high living'. There is 'wine snobbery' in high social groups.

To some, excess drinking provides the excitement of risk taking. People often boast of their capacity to drink. To the young, drinking may be a symbol of rebellion against the oppressive older generation and rejection of the values of the establishment. 'Binge drinking' is a specific behavioural pattern of bouts of excessive drinking. Alcohol is often an excuse for bad behaviour. Society's view that intoxicated person is unaware of his actions (therefore not responsible) makes intoxication an attractive state, because there is increased freedom of what one can say or do after drinking. Thus, there are a variety of motivations for drinking.

Physical dependence occurs only on heavy and round-the-clock drinking (if alcohol is present in the body continuously). Heavy drinking is often associated with nutritional deficiencies, because food is neglected and malabsorption may occur. In addition to impaired mental and physical performance, neurological afflictions are common—polyneuritis, pellagra, tremors, seizures, loss of brain mass, Wernicke's encephalopathy, Korsakoff's psychosis and megaloblastic anaemia. Alcoholic cirrhosis of liver, hypertension, cardiomyopathy, CHF, arrhythmias, stroke, acute pancreatitis, impotence, gynaecomastia, infertility and skeletal myopathy are other complications. Incidence of oropharyngeal, esophageal and hepatic malignancy and respiratory infections is high; immune function is depressed.

Withdrawal syndrome When a physically dependent subject stops drinking, withdrawal syndrome appears within a day. Its severity depends on the duration and quantity of alcohol consumed by the subject. It consists of anxiety, sweating, techycardia, tremor, impairment of sleep, confusion, hallucinations, delirium tremens, convulsions and collapse.

Treatment Psychological and medical supportive measures are needed during withdrawal. Many CNS depressants like barbiturates, phenothiazines, chloral hydrate have been used as substitution therapy in the past (to suppress withdrawal syndrome) but benzodiazepines (chordiazepoxide, diazepam) are the preferred drugs now. These have a long duration of action and can be gradually withdrawn later.

Naltrexone: Several studies have demonstrated involvement of opioid system in the pleasurable reinforcing effects of alcohol through dopamine mediated reward function. The post-addict treated with the long-acting opioid antagonist naltrexone (*see* Ch. 34) does not experience the same pleasurable effect on taking alcohol; reinforcement is weakened. Trials have shown that it helps prevent relapse of alcoholism. It reduced alcohol craving, number of drinking days and chances of resumed heavy drinking. Naltrexone is approved for use as adjuvant in comprehensive treatment programmes for alcohol dependent subjects and is being used in India at most deaddiction centres, after the individual has undergone withdrawal and is motivated.

Acamprosate It is a weak NMDA-receptor antagonist with modest $GABA_A$ receptor agonistic activity that is being used in USA, UK and Europe for maintenance therapy of alcohol abstinence. In conjunction with social and motivational therapy, it has been found to reduce relapse of the drinking behaviour. The efficacy of acamprosate in this regard is rated comparable to naltrexone. It should be started soon after withdrawing alcohol and then given continuously at a dose

of 666 mg 2–3 times a day. Loose motion is a common side effect. Others are nausea, abdominal pain and itching.

The 5-HT_3 antagonist *ondansetron* and the antiepileptic *topiramate* have also shown some promise in treating alcoholism.

CLINICAL USES

Medicinal uses of ethanol are primarily restricted to external application and as a vehicle for liquid preparations used internally.

1. As antiseptic (*see* Ch. 65).
2. Rubefacient and counterirritant for sprains, joint pains, etc. Spirit is generally used as vehicle for other ingredients.
3. Rubbed into the skin to prevent bedsores. It should not be applied on already formed sores. Astringent action of alcohol is utilized in antiperspirant and aftershave lotions.
4. Alcoholic sponges to reduce body temperature in fever. However, cold water/ice may be better.
5. Intractable neuralgias (trigeminal and others), severe cancer pain. Injection of alcohol round the nerve causes permanent loss of transmission.
6. To ward off cold. Alcohol in the form of whiskey or brandy may benefit by causing vasodilatation of blanched mucosae; but further exposure after taking alcohol may be deleterious because alcohol increases heat loss due to cutaneous vasodilatation.
7. As appetite stimulant and carminative: 30–50 ml of 7–10% alcohol may be taken as beverages or tinctures (of ginger/cardemom, etc.) before meal.
8. Reflex stimulation in fainting/hysteria: 1 drop in nose.
9. To treat methanol poisoning (*see* below).

Aldehyde dehydrogenase inhibitor

Disulfiram It inhibits the enzyme aldehyde dehydrogenase (Fig. 28.1) probably after conversion into active metabolites. When alcohol is ingested after taking disulfiram, the concentration of acetaldehyde in tissues and blood rises and a number of highly distressing symptoms (aldehyde syndrome) are produced promptly. These are—flushing, burning sensation, throbbing headache, perspiration, uneasiness, tightness in chest, dizziness, vomiting, visual disturbances, mental confusion, postural fainting and circulatory collapse. Duration of the syndrome (1–4 hours) depends on the amount of alcohol consumed. Because of risk of severe reaction, disulfiram is to be used with great caution, only in well-motivated subjects.

Disulfiram aversion therapy is indicated in abstinent subjects who sincerely desire to leave the habit. After making sure that the subject has not taken alcohol in the past 12 hours, disufiram is given at a dose of 500 mg/day for one week followed by 250 mg daily. Sensitization to alcohol develops after 2–3 hours of first dose, reaches its peak at ~12 hours and lasts for 7–14 days after stopping it, because inhibition of aldehyde dehydrogenase with disulfiram is irreversible: synthesis of fresh enzyme is required for return of activity. The subject's resolve not to drink is reinforced by the distressing symptoms that occur if he drinks a little bit. The subject should be cautioned to avoid alcohol altogether. Disulfiram should not be used in patients who are physically dependent on alcohol.

Side effects of disulfiram (as such) are infrequent, include rashes, metallic taste, nervousness, malaise and abdominal upset. It inhibits a number of other enzymes as well including alcohol dehydrogenase, dopamine β hydroxylase and several cytochrome P450 isoenzymes. Thus, it prolongs t½ of many drugs.

ESPERAL, ANTADICT, DEADICT 250 mg tab. (internationally marketed as ANTABUSE)

METHYL ALCOHOL (Methanol, Wood alcohol)

Methyl alcohol is added to industrial rectified spirit to render it unfit for drinking. It is only of toxicological importance. Mixing of methylated spirit with alcoholic beverages by bootlegers or its inadvertent ingestion results in methanol poisoning.

Methanol is metabolized to formaldehyde and formic acid by alcohol and aldehyde dehydro-

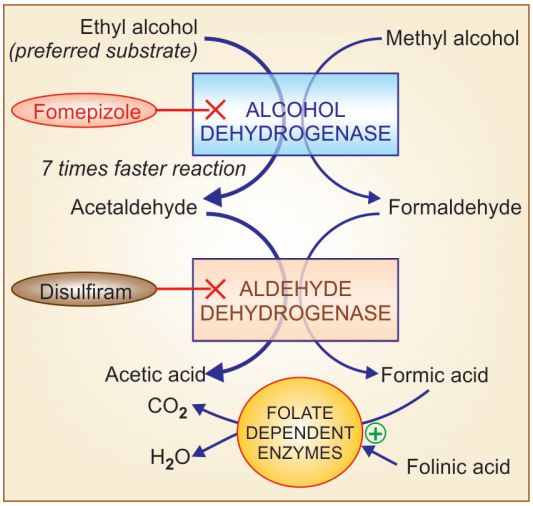


Fig. 28.1: Shared metabolic pathway of ethyl and methyl alcohols

genases respectively (Fig. 28.1), but the rate is 1/7th that of ethanol. Like ethanol, metabolism of methanol also follows *zero order* kinetics and t½ of 20–60 hours has been measured.

Methanol also is a CNS depressant, but less inebriating than ethanol. Toxic effects of methanol are largely due to formic acid, since its further metabolism is slow and folate dependent. A blood level of >50 mg/dl methanol is associated with severe poisoning. Even 15 ml of methanol has caused blindness and 30 ml has caused death; fatal dose is regarded to be 75–100 ml.

Manifestations of methanol poisoning are vomiting, headache, epigastric pain, uneasiness, drunkenness, disorientation, tachypnoea, dyspnoea, bradycardia and hypotension. Delirium and seizures may occur and the patient may suddenly pass into coma. *Acidosis* is prominent and entirely due to production of formic acid. The specific toxicity of formic acid is *retinal damage*. Blurring of vision, congestion of optic disc followed by blindness always precede death which is due to respiratory failure.

Treatment

1. Keep the patient in a quiet, dark room; protect the eyes from light.
2. Gastric lavage with sod. bicarbonate if the patient is brought within 2 hours of ingesting methanol. Supportive measures to maintain ventilation and BP should be instituted.
3. Combat acidosis by i.v. *Sod. bicarbonate* infusion. This is the most important measure; prevents retinal damage and other symptoms; large quantities may be needed.
4. Pot. chloride infusion is needed only when hypokalemia occurs due to alkali therapy.
5. *Ethanol* is preferentially metabolized by alcohol dehydrogenase over methanol. At a concentration of 100 mg/dl in blood it saturates alcohol dehydrogenase and retards methanol metabolism. This helps by reducing the rate of generation of formaldehyde and formic acid. Ethanol (10% in water) is administered through a nasogastric tube; loading dose of 0.7 ml/kg is followed by 0.15 ml/kg/hour. Because pharmacokinetics of alcohol changes over time and no i.v. formulation is available, maintenance of a fixed concentration is difficult. Alcohol blood level needs to be repeatedly measured. Moreover, the enzyme saturating concentration of ethanol itself produces intoxication and can cause hypoglycaemia. Use of ethanol for this purpose is tricky. Treatment has to be continued for several days because the sojourn of methanol in body is long.
6. Haemodialysis: clears methanol as well as formate and hastens recovery.
7. *Fomepizole* (4-methylpyrazole) is a specific inhibitor of alcohol dehydrogenase and the drug of choice for methanol poisoning by retarding its metabolism. A loading dose of 15 mg/kg i.v. followed by 10 mg/kg every 12 hours till serum methanol falls below 20 mg/dl, has been found effective and safe. It has several advantages over ethanol, *viz.* longer t½ and lack of inebriating action, but is not available commercially in India.
8. Folate therapy: Calcium leucovorin 50 mg injected 6 hourly has been shown to reduce blood formate levels by enhancing its oxidation. This is a promising adjuvant approach.

Ethylene glycol poisoning Ethylene glycol poisoning has occurred sporadically, especially among children. It is an industrial solvent, coolant and antifreeze. Ethylene glycol is oxidized in the body by alcohol dehydrogenase to glycoaldehyde and then to glycolic acid—glyoxylic acid—oxalic acid in steps. Ethylene glycol itself can cause intoxication similar to ethanol, but generation of metabolites results in acidosis, cardiopulmonary complications and renal tubular necrosis.

Fomepizole used in the same manner as for methanol poisoning is the drug of choice. It is approved by US-FDA for this indication and has 'orphan drug status'. Ethanol is employed as an alternative.

☞ PROBLEM DIRECTED STUDY

28.1 A school boy aged 16 years developed tonic-clonic epilepsy and was maintained on carbamazepine 200 mg 3 times a day. He was seizure free for the last one year, but reported back one afternoon with the complaint of recurrence of two seizure episodes since morning. On questioning, he revealed that last evening he attended a party with his friends and consumed 4 drinks of whiskey, and was awake till late night. This was the first time that he had taken an alcoholic drink.

(a) Could the recurrence of seizures be related to the intake of alcohol previous night? If so, what could be the mechanism?

(b) Does his antiepileptic therapy need any change or adjustment of doses due to this recurrence of seizures. What further advise will you give to this patient?

(see Appendix-1 for solution)

Chapter 29 Sedative-Hypnotics

Sedative A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced. Sedation refers to decreased responsiveness to any level of stimulation; is associated with some decrease in motor activity and ideation.

Hypnotic A drug that induces and/or maintains sleep, similar to normal arousable sleep. This is not to be confused with 'hypnosis' meaning a trans-like state in which the subject becomes passive and highly suggestible.

The sedatives and hypnotics are more or less global CNS depressants with somewhat differing time-action and dose-action relationships. Those with quicker onset, shorter duration and steeper dose-response curves are preferred as *hypnotics* while more slowly acting drugs with flatter dose-response curves are employed as *sedatives*. However, there is considerable overlap; a hypnotic at lower dose may act as sedative. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression. Hypnotics given in high doses can produce general anaesthesia. However, benzodiazepines (BZDs) cannot be considered nonselective or global CNS depressants like barbiturates and others.

Treatment of insomnia is the most important use of this class of drugs.

Alcohol and opium have been the oldest hypnotics and continue to be used for this purpose as self-medication by people. Bromides introduced in 1857 are now obsolete, so are chloral hydrate (1869) and paraldehyde (1882). Fischer and von Mering introduced barbitone in 1903 and phenobarbitone in 1912. Barbiturates reigned supreme till 1960s when benzodiazepines started eroding their position and have now totally replaced them. In the mean time, a number of other sedative-hypnotics (glutethimide, methyprilon, methaqualone) were introduced but none was significantly different from barbiturates; all are redundant now. Some non-BZD hypnotics have become available over the past two decades, and a novel melatonin receptor agonist ramelteon has been introduced.

Sleep

The duration and pattern of sleep varies considerably among individuals. Age has an important effect on quantity and depth of sleep. It has been recognized that sleep is an architectured cyclic process (Fig. 29.1). The different phases of sleep and their characteristics are—

Stage 0 (awake) From lying down to falling asleep and occasional nocturnal awakenings; constitutes 1–2% of sleep time. EEG shows α activity when eyes are closed and β activity when eyes are open. Eye movements are irregular or slowly rolling.

Stage 1 (dozing) α activity is interspersed with θ waves. Eye movements are reduced but there may be bursts of rolling. Neck muscles relax. Occupies 3–6% of sleep time.

Stage 2 (unequivocal sleep) θ waves with interspersed spindles, K complexes can be evoked on sensory stimulation; little eye movement; subjects are easily arousable. This comprises 40–50% of sleep time.

Stage 3 (deep sleep transition) EEG shows θ, δ and spindle activity, K complexes can be evoked with strong stimuli only. Eye movements are few; subjects are not easily arousable; comprises 5–8% of sleep time.

Stage 4 (cerebral sleep) δ activity predominates in EEG, K complexes cannot be evoked. Eyes are practically fixed; subjects are difficult to arouse. Night terror may occur at this time. It comprises 10–20% of sleep time.

During stage 2, 3 and 4 heart rate, BP and respiration are steady and muscles are relaxed. Stages 3 and 4 together are called slow wave sleep (SWS).

REM sleep (paradoxical sleep) EEG has waves of all frequency, K complexes cannot be elicited. There are marked, irregular and darting eye movements; dreams and nightmares

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The EEG waves have been divided into—
α: high amplitude, 8–14 c.p.s. (cycles per second)
β: low amplitude, 15–35 c.p.s.
θ: low amplitude, 4–7 c.p.s.
δ: high amplitude, 0.5–3 c.p.s.
K complex: deep negative wave followed by positive wave and a few spindles.

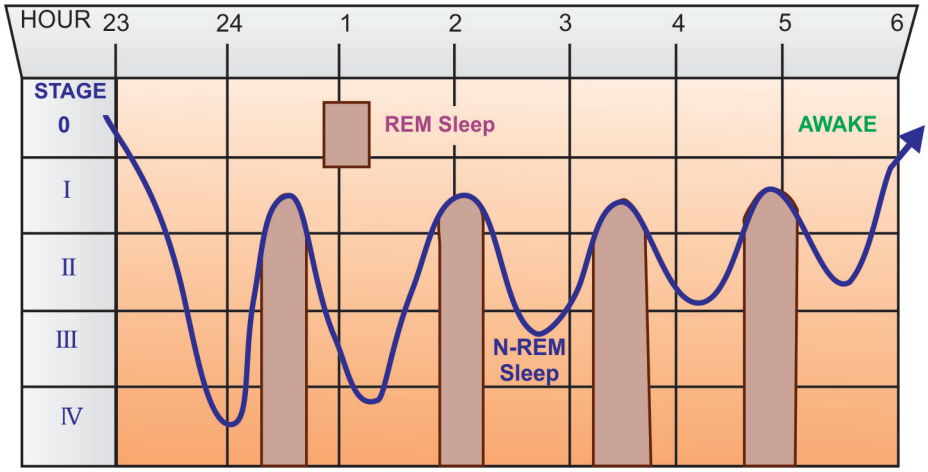


Fig. 29.1: A normal sleep cycle

occur, which may be recalled if the subject is aroused. Heart rate and BP fluctuate; respiration is irregular. Muscles are fully relaxed, but irregular body movements occur occasionally. Erection occurs in males. About 20–30% of sleep time is spent in REM.

Normally stages 0 to 4 and REM occur in succession over a period of 80–100 min. Then stages 1–4–REM are repeated cyclically.

CLASSIFICATION

1. *Barbiturates*

Long acting	*Short acting*	*Ultra-short acting*
Phenobarbitone	Butobarbitone	Thiopentone
	Pentobarbitone	Methohexitone

2. *Benzodiazepines*

Hypnotic	*Antianxiety*	*Anticonvulsant*
Diazepam	Diazepam	Diazepam
Flurazepam	Chlordiazepoxide	Lorazepam
Nitrazepam	Oxazepam	Clonazepam
Alprazolam	Lorazepam	Clobazam
Temazepam	Alprazolam	
Triazolam		

3. *Newer nonbenzodiazepine hypnotics*

Zopiclone Zolpidem Zaleplon

Chloral hydrate, Triclophos, Paraldehyde, Glutethimide, Methyprylon, Methaqualone and Meprobamate are historical sedative-hypnotics no longer used. They are described in earlier editions of this book.

In addition some antihistaminics (promethazine, diphenhydramine), some neuroleptic/antidepressants (chlorpromazine, amitriptyline), some anticholinergic (hyoscine) and opioids (morphine, pethidine) have significant sedative action, but are not reliable for treatment of insomnia.

BARBITURATES

Barbiturates have been popular hypnotics and sedatives of the last century upto 1960s, but are not used now to promote sleep or to calm patients. However, they are described first because they are the prototype of CNS depressants.

Barbiturates are substituted derivatives of barbituric acid (malonyl urea). Barbituric acid as such is not a hypnotic but compounds with alkyl or aryl substitution on C5 are. Replacement of O with S at C2 yields *thiobarbiturates* which are more lipid-soluble and more potent. Barbiturates have variable lipid solubility, the more soluble ones are more potent and shorter acting. They are insoluble in water but their sodium salts dissolve yielding highly alkaline solution.

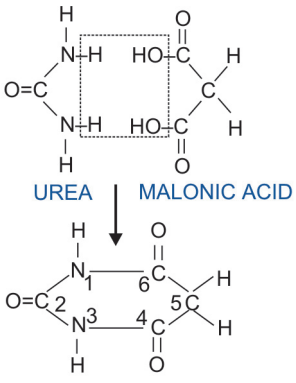
PHARMACOLOGICAL ACTIONS

Barbiturates are general depressants for all excitable cells, the CNS is most sensitive where the effect is almost global, but certain areas are more susceptible.

1. CNS Barbiturates produce dose-dependent effects:

sedation → sleep → anaesthesia → coma.

Hypnotic dose shortens the time taken to fall asleep and increases sleep duration. The sleep is arousable, but the subject may feel confused and unsteady if waken early. Night awakenings are reduced. REM and stage 3, 4 sleep are decreased; REM-NREM sleep cycle is disrupted. The effects on sleep become progressively less marked if the drug is taken every night consecutively. A rebound increase in REM sleep and nightmares is often noted when the drug is discontinued after a few nights of use and it takes several nights for normal pattern to be restored (Fig. 29.2). Hangover (dizziness, distortions of mood, irritability and lethargy) may occur in the morning after a nightly dose.



Condensation of malonic acid and urea to produce barbituric acid

Sedative dose (smaller dose of a longer acting barbiturate) given at daytime can produce drowsiness, reduction in anxiety and excitability. However, they do not have selective antianxiety action. Barbiturates can impair learning, short-term memory and judgement. They have no analgesic action; small doses may even cause hyperalgesia. Euphoria may be experienced by addicts.

Barbiturates have anticonvulsant property. The 5-phenyl substituted compounds (phenobarbitone) have higher anticonvulsant : sedative ratio, i.e. they have specific anticonvulsant action independent of general CNS depression.

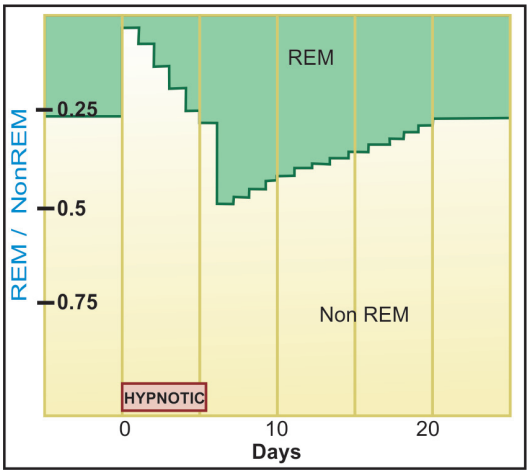


Fig. 29.2: Effect of hypnotic use for 6 consecutive nights on the ratio of REM / Non-REM sleep duration

Higher dose of a barbiturate induces a predominance of slow, high voltage EEG activity. Progressive burst suppression occurs if dose is increased further. Barbiturates depress all areas of the CNS, but reticular activating system is the most sensitive; its depression is primarily responsible for inability to maintain wakefulness.

Mechanism of action Barbiturates appear to act primarily at the GABA : BZD receptor–Cl^- channel complex (*see* Fig. 29.3) and potentiate GABAergic inhibition by increasing the lifetime of Cl^- channel opening induced by GABA (contrast BZDs which enhance frequency of Cl^- channel opening). They do not bind to the BZD receptor, but bind to another site on the same macromolecular complex to exert the GABA-facilitatory action. The barbiturate site appears to be located on α or β subunit, because presence of only these subunits is sufficient for their response. Presence of γ subunit is not necessary as is the case with BZDs. They also enhance BZD binding to its receptor. At high concentrations, barbiturates directly increase Cl^- conductance (GABA-mimetic action; contrast BZDs which have only GABA-facilitatory action) and inhibit Ca^{2+} dependent release of neurotransmitters. In addition they depress glutamate induced neuronal depolarization through AMPA

receptors (a type of excitatory amino acid receptors). At very high concentrations, barbiturates depress voltage sensitive Na^+ and K^+ channels as well. A dose-dependent effect on multiple neuronal targets appears to confer the ability to produce any grade of CNS depression.

2. Other systems

Respiration is depressed by relatively higher doses. Neurogenic, hypercapneic and hypoxic drives to respiratory centre are depressed in succession. Barbiturates donot have selective antitussive action.

CVS Hypnotic doses of barbiturates produce a slight decrease in BP and heart rate. Toxic doses produce marked fall in BP due to vasomotor centre depression, ganglionic blockade and direct decrease in cardiac contractility. Reflex tachycardia can occur, though pressor reflexes are depressed. However, the dose producing cardiac arrest is about 3 times larger than that causing respiratory failure.

Skeletal muscle Hypnotic doses have little effect but anaesthetic doses reduce muscle contraction by action on neuromuscular junction.

Smooth muscles Tone and motility of bowel is decreased slightly by hypnotic doses; more profoundly during intoxication. Action on bronchial, ureteric, vesical and uterine muscles is not significant.

Kidney Barbiturates tend to reduce urine flow by decreasing BP and increasing ADH release. Oliguria attends barbiturate intoxication.

PHARMACOKINETICS

Barbiturates are well absorbed from the g.i. tract. They are widely distributed in the body. The rate of entry into CNS is dependent on lipid solubility. Highly-lipid soluble thiopentone has practically instantaneous entry, while less lipid-soluble ones (pentobarbitone) take longer; phenobarbitone enters very slowly. Plasma protein binding varies with the compound, e.g. thiopentone 75%, phenobarbitone 20%. Barbiturates cross placenta and are secreted in milk; can produce effects on the foetus and suckling infant.

Three processes are involved in termination of action of barbiturates: the relative importance of each varies with the compound.

(a) *Redistribution* It is important in the case of highly lipid-soluble thiopentone. After i.v. injection, consciousness is regained in 6–10 min due to redistribution (*see* Ch. 2) while the ultimate disposal occurs by metabolism (t½ of elimination phase is 9 hours).

(b) *Metabolism* Drugs with intermediate lipid-solubility (short-acting barbiturates) are primarily metabolized in liver by oxidation, dealkylation and conjugation. Their plasma t½ ranges from 12–40 hours.

(c) *Excretion* Barbiturates with low lipid-solubility (long-acting agents) are significantly excreted unchanged in urine. The t½ of phenobarbitone is 80–120 hours. Alkalinization of urine increases ionization and excretion. This is most significant in the case of long-acting agents.

Barbiturates induce several hepatic microsomal enzymes and increase the rate of their own metabolism as well as that of many other drugs.

USES

Except for phenobarbitone in epilepsy (Ch. 30) and thiopentone in anaesthesia (Ch. 27) no other barbiturate is used now. As hypnotic and anxiolytic they have been superseded by BZDs. They are occasionally employed as adjuvants in psychosomatic disorders.

Phenobarbitone 30–60 mg oral OD–TDS; 100–200 mg i.m./i.v.
GARDENAL 30, 60 mg tab, 20 mg/5 ml syr; LUMINAL 30 mg tab; PHENOBARBITONE SOD 200 mg /ml inj.

ADVERSE EFFECTS

Side effects Hangover was common after the use of barbiturates as hypnotic. On repeated use they accumulate in the body—produce tolerance and dependence. Mental confusion, impaired performance and traffic accidents may occur (also *see* Ch. 30).

Idiosyncrasy In an occasional patient barbiturates produce excitement. This is more common in the elderly.
Precipitation of porphyria in susceptible individuals is another idiosyncratic reaction.

Hypersensitivity Rashes, swelling of eyelids, lips, etc.—more common in atopic individuals.

Tolerance and dependence Both cellular and pharmacokinetic (due to enzyme induction) tolerance develops on repeated use. However, fatal dose is not markedly increased: addicts may present with acute barbiturate intoxication. There is partial cross tolerance with other CNS depressants.

Psychological as well as physical dependence occurs and barbiturates have considerable abuse liability. This is one of the major disadvantages. Withdrawal symptoms are—excitement, hallucinations, delirium, convulsions; deaths have occurred.

Acute barbiturate poisoning Mostly suicidal, sometimes accidental. It is infrequently encountered now due to inavailability of barbiturates. However, the principles of treatment apply to any CNS depressant poisoning.

Manifestations are due to excessive CNS depression—patient is flabby and comatose with shallow and failing respiration, fall in BP and cardiovascular collapse, renal shut down, pulmonary complications, bullous eruptions.

Lethal dose depends on lipid solubility. It is 2–3 g for the more lipid-soluble agents (short-acting barbiturates) and 5–10 g for less lipid-soluble phenobarbitone.

Treatment

1. Gastric lavage; leave a suspension of activated charcoal in the stomach to prevent absorption of the drug from intestines.
2. Supportive measures: such as, patent airway, assisted respiration, oxygen, maintenance of blood volume by fluid infusion and use of vasopressors—dopamine may be preferred for its renal vasodilating action.
3. Alkaline diuresis: with sodium bicarbonate 1 mEq/kg i.v. with or without mannitol is helpful only in the case of long-acting barbiturates which are eliminated primarily by renal excretion.
4. Haemodialysis and haemoperfusion (through a column of activated charcoal or other adsorbants) is highly effective in removing long-acting as well as short-acting barbiturates.

There is no specific antidote for barbiturates. In the past, analeptics like metrazol, bemegride, etc. have been used in an attempt to awaken the patient. This is dangerous, may precipitate convulsions while the patient is still comatose—mortality is increased. The emphasis now is on keeping the patient alive till the poison has been eliminated.

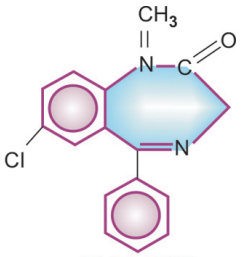
Interactions

1. Barbiturates induce several CYP isoenzymes, including glucuronyl transferase, and increase the metabolism of many drugs and reduce their effectiveness—warfarin, steroids (including contraceptives), tolbutamide, griseofulvin, chloramphenicol, theophylline.
2. Additive action with other CNS depressants—alcohol, antihistamines, opioids, etc.
3. Sodium valproate increases plasma concentration of phenobarbitone.
4. Phenobarbitone competitively inhibits as well as induces phenytoin and imipramine metabolism: complex interaction.
5. Phenobarbitone decreases absorption of griseofulvin from the g.i.t.

BENZODIAZEPINES (BZDs)

Chlordiazepoxide and diazepam were introduced around 1960 as antianxiety drugs. Since then this class has proliferated and has replaced barbiturates as hypnotic and sedative as well, because—

1. BZDs produce a lower degree of neuronal depression than barbiturates. They have a high therapeutic index. Ingestion of even 20 hypnotic doses does not usually endanger life—there is no loss of consciousness (though amnesia occurs) and patient can be aroused; respiration is mostly not so depressed as to need assistance.



DIAZEPAM

2. Hypnotic doses do not affect respiration or cardiovascular functions. Higher doses produce mild respiratory depression and hypotension which is problematic only in patients with respiratory insufficiency or cardiac/haemodynamic abnormality.
3. BZDs have practically no action on other body systems. Only on i.v. injection the BP falls (may be marked in an occasional patient) and cardiac contractility decreases. Fall in BP in case of diazepam and lorazepam is due to reduction in cardiac output while that due to midazolam is due to decrease in peripheral resistance. The coronary arteries dilate on i.v. injection of diazepam.
4. BZDs cause less distortion of sleep architecture; rebound phenomena on discontinuation of regular use are less marked.
5. BZDs do not alter disposition of other drugs by microsomal enzyme induction.
6. They have lower abuse liability: tolerance is mild, psychological and physical dependence, drug seeking and withdrawal syndrome are less marked.
7. A specific BZD antagonist *flumazenil* is available which can be used in case of poisoning.

CNS actions The overall action of all BZDs is qualitatively similar, but there are prominent differences in selectivity for different facets of action, and in their time-course of action. Different members are used for different purposes. In contrast to barbiturates, they are not general depressants, but exert relatively selective anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects in different measures. Even when apparently anaesthetic dose of diazepam is administered i.v., some degree of awareness is maintained, though because of anterograde amnesia (interference with establishment of memory trace) the patient does not clearly recollect the events on recovery.

Antianxiety: Some BZDs exert relatively selective antianxiety action (*see* Ch. 33) which is probably not dependent on their sedative property. With chronic administration relief of anxiety is maintained, but drowsiness wanes off due to development of tolerance.

Sleep: While there are significant differences among different BZDs, in general, they hasten onset of sleep, reduce intermittent awakening and increase total sleep time (specially in those who have a short sleep span). Time spent in stage 2 is increased while that in stage 3 and 4 is decreased. They tend to shorten REM phase, but more REM cycles may occur, so that effect on total REM sleep is less marked than with barbiturates. Nitrazepam has been shown to actually increase REM sleep. Night terrors and body movements during sleep are reduced and stage shifts to stage 1 and 0 are lessened. Most subjects wake up with a feeling of refreshing sleep. Some degree of tolerance develops to the sleep promoting action of BZDs after repeated nightly use.

Muscle relaxant: BZDs produce centrally mediated skeletal muscle relaxation without impairing voluntary activity (*see* Ch. 25). Clonazepam and diazepam have more marked muscle relaxant property. Very high doses depress neuromuscular transmission.

Anticonvulsant: Clonazepam, diazepam, nitrazepam, lorazepam and flurazepam have more prominent anticonvulsant activity than other BZDs. Diazepan and lorazepam are highly effective for short-term use in status-epilepticus, but their utility in long-term treatment of epilepsy is limited by development of tolerance to the anticonvulsant action.

Given i.v., diazepam (but not others) causes analgesia. In contrast to barbiturates, BZDs do not produce hyperalgesia.

Other actions Diazepam decreases nocturnal gastric secretion and prevents stress ulcers. BZDs do not significantly affect bowel movement.

Short-lasting coronary dilatation is produced by i.v. diazepam.

Site and mechanism of action

Benzodiazepines act preferentially on midbrain ascending reticular formation (which maintains wakefulness) and on limbic system (thought and mental functions). Muscle relaxation is produced by a primary medullary site of action and ataxia is due to action on cerebellum.

BZDs act by enhancing presynaptic/postsynaptic inhibition through a specific BZD receptor which is an integral part of the $GABA_A$ receptor–Cl^- channel complex. The subunits of this complex form a pentameric transmembrane anion channel (Fig. 29.3) gated by the primary ligand (GABA), and modulated by secondary ligands which include BZDs. Only the α and β subunits are required for GABA action, and most likely the binding site for GABA is located on the β subunit, while the α/γ subunit interface carrys the BZD binding site. The modulatory BZD receptor increases the frequency of Cl^- channel opening induced by submaximal concentrations of GABA. The BZDs also enhance GABA binding to $GABA_A$ receptor. The $GABA_A$ antagonist bicuculline antagonizes BZD action in a noncompetitive manner. It is noteworthy that the BZDs do not themselves increase Cl^- conductance; have only GABA

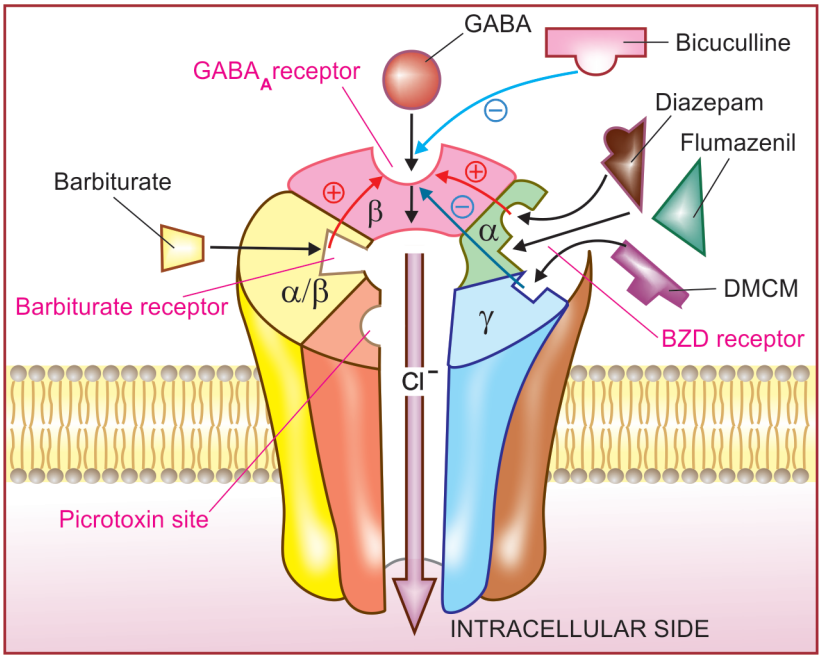


Fig. 29.3: Schematic depiction of $GABA_A$-benzodiazepine receptor-chloride channel complex
The chloride channel is gated by the primary ligand GABA acting on $GABA_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates $GABA_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl^- channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl^- channel directly as well. Bicuculline blocks $GABA_A$ receptor, while picrotoxin blocks the Cl^- channel directly

facilitatory but no GABA mimetic action. This probably explains the lower ceiling CNS depressant effect of BZDs.

The BZD receptor exhibits a considerable degree of constitutive activation. As such, it is capable of fine tuning GABA action in either direction. While the BZD-agonists enhance GABA induced hyperpolarization (due to influx of Cl^- ions), and decrease firing rate of neurones, other compounds called *BZD-inverse agonists* like dimethoxyethyl-carbomethoxy-β-carboline (DMCM) inhibit GABA action and are convulsants. The competitive BZD-antagonist flumazenil blocks the sedative action of BZDs as well as the convulsant action of DMCM.

The $GABA_A$-BZD receptor-Cl^- channel complex is composed of five α, β, γ, and in some cases δ, ε, θ or π subunits as well. Several isoforms of α, β and γ subunits have been cloned. The subunit composition of the complex differs at different sites, i.e. there are multiple subtypes of BZD receptor. The ($\alpha_1 2\ \beta_2\ 2\ \gamma_2$) pentamer appears to be the most commonly expressed BZD receptor isoform.

Based on studies conducted in genetically mutated mice, it has been suggested that BZD receptor isoforms containing the α_1 subunit are involved in mediating sedative, hypnotic, and amnesic actions of BZDs, while those containing α_2 subunits mediate anxiolytic and muscle relaxant actions. Diazepam has similar affinity for BZD receptor containing different (α_1 or α_2, or α_3 or α_5) subunits, and has broad spectrum action. Receptor inhomogeneity may provide an explanation for the pharmacological diversity of other BZDs. The newer non-BZD hypnotics zaleplon, Zolpidem, etc. have high affinity for α_1 subunit isoform of BZD receptor and exert selective hypnotic-amnesic effect, but have little antiseizure or muscle relaxant property.

At high concentrations BZDs also potentiate the depressant action of adenosine by blocking its uptake. Certain actions of BZDs are countered by the adenosine antagonist theophylline. Thus, BZDs could be acting through other mechanisms as well.

Drugs affecting $GABA_A$-receptor gated chloride channel		
• GABA	:	Endogenous agonist at $GABA_A$ receptor → promotes Cl^- influx
• Muscimol	:	Agonist at $GABA_A$ site
• Bicuculline	:	Competitive antagonist at $GABA_A$ receptor
• Picrotoxin	:	Blocks Cl^- channel noncompetitively; acts on picrotoxin sensitive site
• Barbiturates	:	Agonist at an allosteric site; prolong GABA action; and open Cl^- channel
• Alcohol, Inhalational anaesthetics, Propofol	:	Open Cl^- channel directly; allosteric facilitation of GABA
• Benzodiazepines	:	Agonist at an allosteric BZD site → facilitate GABA action
• β-Carboline (DMCM)	:	Inverse agonist at BZD site → impede GABA action
• Flumazenil	:	Competitive antagonist at BZD site

PHARMACOKINETICS

There are marked pharmacokinetic differences among BZDs because they differ in lipid-solubility by > 50 fold. These differences are important factors governing their choice for different uses. Oral absorption of some is rapid while that of others is slow. Absorption from i.m. sites is irregular except for lorazepam. Plasma protein binding also varies markedly (flurazepam 10% to diazepam 99%). BZDs are widely distributed in the body. The more lipid soluble members enter brain rapidly and have a two phase plasma concentration decay curve; first due to distribution to other tissues and later due to elimination. A relatively short duration of action is obtained with single dose of a drug that is rapidly redistributed, even though it may have a long elimination t½. Using the elimination t½ alone to predict duration of action may be misleading. However, elimination t½ determines duration of action in case of drugs whose elimination is by far the dominant feature or when the drug is given repeatedly.

Benzodiazepines are metabolized in liver mainly by CYP3A4 and CYP2C19 to dealkylated and hydroxylated metabolites, some of which may be active. The biological effect half-life of these drugs may be much longer than the plasma t½ of the administered compound. The phase I metabolites and certain BZDs themselves are conjugated with glucuronic acid. Some BZDs (e.g. diazepam) undergo enterohepatic circulation. BZDs and their phase I metabolites are excreted in urine as glucuronide conjugates. BZDs cross placenta and are secreted in milk.

Drugs with a long t½ or those which generate active metabolites cumulate on nightly use; their action may then extend into the next day. Some features of BZDs used as hypnotic are given in Table 29.1.

BZDs may be categorized according to their pharmacokinetic profile into:

I. *Slow elimination of parent drug or active metabolite*

Flurazepam Produces an active metabolite which has a long t½. Residual effects are likely next morning; cumulation occurs on daily ingestion peaking after 3–5 days. It is suitable for patients who have frequent nocturnal awakenings and in whom some day time sedation is acceptable.

NINDRAL, FLURAZ 15 mg cap.

II. *Relatively slow elimination but marked redistribution*

Diazepam It is the oldest and all purpose BZD, used as anxiolytic, hypnotic, muscle

TABLE 29.1 Some pharmacokinetic and clinical features of benzodiazepines used as hypnotics

Drug	t½ (hr)*	Redistribution$	Hypnotic dose (mg)	Clinical indications
I. LONG ACTING				
Flurazepam	50–100	–	15–30	Chronic insomnia, short-term insomnia with anxiety; Frequent nocturnal awakening; Night before operation
Diazepam	30–60	+	5–10	
Nitrazepam	30	±	5–10	
II. SHORT ACTING				
Alprazolam	12	+	0.25–0.5	Individuals who react unfavourably to unfamiliar surroundings or unusual timings of sleep. Sleep onset difficulties.
Temazepam	8–12	+	10–20	
Triazolam	2–3	±	0.125–0.25	

* t½ of elimination phase, including that of active metabolite
$ + indicates that redistribution contributes to termination of action of single dose

relaxant, premedicant, anaesthetic and for emergency control of seizures due to its broad spectrum activity. It generates active metabolites (desmethyl-diazepam, oxazepam). On occasional use it is free of residual effects. With regular use accumulation occurs and prolonged anxiolytic effect may be obtained. It is less likely to cause rebound insomnia on discontinuation of chronic use. Withdrawal phenomena are mild. VALIUM 2, 5, 10 mg tab., 10 mg/2 ml inj., CALMPOSE 2.5, 5, 10 mg tab, 2 mg/5 ml syr, 10 mg/2 ml inj, PLACIDOX 2, 5, 10 mg tab, 10 mg/2 ml inj.

Nitrazepam Dose to dose equipotent as diazepam. Accumulation and residual effects can be avoided only if ingestion is occasional. Good for patients with frequent nocturnal awakenings, when some day time sedation is acceptable. SEDAMON, HYPNOTEX, NITRAVET 5 mg tab., 5, 10 mg cap.

III. *Relatively rapid elimination and marked redistribution*

Alprazolam The primary indication of this potent and intermediate acting BZD is anxiety disorder (*see* Ch. 33), but it is also being employed as night-time hypnotic with few residual effects the next day. Discontinuation after regular use has produced relatively marked withdrawal phenomena.

Temazepam It is an intermediate acting BZD. Absorption is slow in case of tablet but fast when used in soft gelatin capsule. Good for sleep onset difficulty, free of residual effects. Accumulation can occur on daily ingestion. Does not produce active metabolites.

IV. *Ultrarapid elimination*

Triazolam Very potent, peak effect occurs in < 1 hour; good for sleep induction but poor for maintaining it. Patient may wake up early in the morning and feel anxious. This may be a withdrawal phenomenon. Rebound insomnia may occur when it is discontinued after a few nights of use. It does not accumulate on repeated nightly use and no residual effects are noted in the morning. However, higher doses can alter sleep architecture, produce anterograde amnesia and anxiety the following day. Some cases of paranoia and other psychiatric disturbances have been noted. For this reason, it has been withdrawn from U.K., but is employed in other countries for elderly patients, shift workers, travellers, etc.

Midazolam Extremely rapid absorption—peak in 20 min. It can cause problems in the elderly (ataxia, blackouts); more liable for abuse. Therefore, it is not available now for oral use as a hypnotic. It is mainly used as an i.m. premedicant or an i.v. anaesthetic (*see* p. 383).

ADVERSE EFFECTS

Benzodiazepines are relatively safe drugs. Side effects of hypnotic doses are dizziness, vertigo, ataxia, disorientation, amnesia, prolongation of reaction time—impairment of psychomotor skills (should not drive). Hangover is less common, but may be noted if larger doses are used, especially of longer acting drugs. Weakness, blurring of vision, dry mouth and urinary incontinence are sometimes complained. Older individuals are more susceptible to

psychomotor side effects. Like any hypnotic, BZDs can aggravate sleep apnoea.

Paradoxical stimulation, irritability and sweating may occur in an occasional patient, especially with flurazepam. Some patients experience increase in nightmares and behavioural alterations, especially with flurazepam and nitrazepam.

Tolerance to the sedative effects develops gradually, but there is little tendency to increase the dose. Cross tolerance to alcohol and other CNS depressants occurs.

The dependence producing liability of BZDs is low. They are weak reinforcers (less pleasurable) and seldom abused alone. Drug abusers find them rather bland and prefer other CNS depressants. Withdrawal syndrome is generally mild; may be more intense in case of ultrarapid elimination drugs. Anxiety, insomnia, restlessness, malaise, loss of appetite, bad dreams is all that occurs in most cases. Agitation, panic reaction, tremors and delirium are occasional; convulsions are rare. Drug seeking behaviour is not prominent.

An earlier report of increased birth defects on use of diazepam during pregnancy has been disputed. Administration during labour may cause flaccidity and respiratory depression in the neonate.

INTERACTIONS

BZDs synergise with alcohol and other CNS depressants leading to excessive impairment. Concurrent use with sod. valproate has provoked psychotic symptoms.

Drug interactions due to displacement from protein binding or microsomal enzyme induction are not significant.

Since CYP 3A4 isoenzyme plays important role in metabolism of several BZDs, their action can be prolonged by CYP 3A4 inhibitors like ketoconazole, erythromycin and others. Cimetidine, isoniazid and oral contraceptives also retard BZD metabolism.

NON-BENZODIAZEPINE HYPNOTICS

This lately developed group of hypnotics are chemically different from BZDs, but act as agonists on a specific subset of BZD receptors. Their action is competitively antagonized by the BZD antagonist flumazenil, which can be used to treat their overdose toxicity. The non-BZD hypnotics act selectively on α_1 subunit containing BZD receptors and produce hypnotic-amnesic action with only weak antianxiety, muscle relaxant and anticonvulsant effects. They have lower abuse potential than hypnotic BZDs. Given their shorter duration of action, they are being preferred over BZDs for the treatment of insomnia.

Zopiclone This is the first of the non-BZD hypnotics, which acts as an agonist at a subtype of BZD receptor involved in the hypnotic action. The effect on sleep resemble those of BZDs, but it does not alter REM sleep and tends to prolong stages 3 and 4. It is reported not to disturb sleep architecture, but some degree of next morning impairment can occur. Zopiclone has been used to wean off insomniacs taking regular BZD medication. Its t½ is 5–6 hours.

Zopiclone is indicated for short term (< 2 weeks) treatment of insomnia. Side effects are metallic or bitter after-taste, impaired judgement and alertness, psychological disturbances, dry mouth and milder dependence. Safety in overdose is similar to BZDs.

ZOPITRAN, ZOPICON, ZOLIUM, 7.5 mg tab, one tab at bedtime for not more than 2–4 weeks (elderly 3.75 mg).

Eszopiclone The active (S) enantiomer of zopiclone has recently been approved. It produces little tolerance and physical dependence, and is considered suitable for treatment of short-term as well as chronic insomnia.

Zolpidem This structurally non-BZD, but selective BZD receptor agonist has pronounced hypnotic effect. Sleep latency is shortened, sleep duration is prolonged in insomniacs, but anticonvulsant, muscle relaxant and antianxiety effects are not evident. Its advantages are: relative lack of effect on sleep stages (REM suppression is slight); minimal residual day time sedation

or fading of hypnotic action on repeated nightly use; no/little rebound insomnia on discontinuation; near absence of tolerance and low abuse potential combined with safety in overdose like BZDs.

Zolpidem is nearly completely metabolized in liver (t½ 2 hr), and has short duration of action. It is indicated for short-term (1–2 weeks) use in sleep onset insomnia as well as for intermittent awakenings. Because the plasma t½ is short, next day sedation is minimal, but morning sedation or prolongation of reaction-time can occur if it is taken late at night. Side effects are few. Even large doses do not markedly depress respiration. Currently, it is one of the most commonly prescribed hypnotics.
Dose: 5–10 mg (max 20 mg) at bedtime; ½ dose in elderly and liver disease patients.
NITREST, ZOLDEM, DEM 5, 10 mg tabs.

Zaleplon This is the shortest acting of the newer non-BZD hypnotics that selectively act on a subset of BZD receptors containing the α_1 subunit which appear to mediate the hypnotic action. It is rapidly absorbed; oral bioavailability is ~30% due to first pass metabolism; is rapidly cleared by hepatic metabolism with a t½ of 1 hour. No active metabolite is produced. As such it is effective only in sleep-onset insomnia; does not prolong total sleep time or reduce the number of awakenings. Because of brevity of action, it can be taken late at night (> 4 hour before waking time) without causing morning sedation. Surprisingly, despite very short action, no daytime anxiety or rebound insomnia has been observed, and hypnotic effect does not fade on nightly use. However, its use should be limited to 1–2 weeks. The hypnotic efficacy of zaleplon is rated similar to zolpidem. Like the latter, effect on sleep stages and REM sleep are less than that of BZDs. Tolerance and dependence is unusual.
Dose: 5–10 mg (max 20 mg) at bed time.
ZAPLON, ZALEP, ZASO 5, 10 mg tabs.

USES

Currently, BZDs are one of the most frequently prescribed drugs. They have also been combined with many other categories of drugs with a view to improve efficacy by relieving attendant anxiety.

1. As hypnotic A hypnotic should not be casually prescribed for every case of insomnia. Understanding the pattern and cause of insomnia in the specific patient is important, and use of a variety of other measures can avoid unnecessary hypnotic medication. When indicated, BZDs or the newer non-BZDs like zolpidem, zaleplon are the hypnotic of choice. A wide range of compounds have been developed to suit specific requirements. Some important points are outlined below:

- A hypnotic may be used to shorten sleep latency, to reduce nocturnal awakenings, or to provide anxiolytic effect the next day when insomnia is accompanied with marked element of anxiety.
- In the use of hypnotics, consideration must be given to onset and duration of action of the drug. The most suitable pharmacokinetic profile drug should be chosen for a given case.
- Next morning impairment is largely related to the dose and pharmacokinetic profile of the drug. The next day effects are either due to prolonged sedation (longer acting drugs) or rebound anxiety (shorter acting drugs).
- Any hypnotic (probably except zolpidem-like drugs) becomes ineffective after regular use for a few days; may actually be harmful.
- Though effect of the drug on EEG stages of sleep, including REM sleep, could be physiologically relevant, most important is the subject's own assessment of having slept restfully and waking up feeling fresh with no impairment the following day. The subjective impression that quality of sleep was poor is the major criterion of insomnia. This probably correlates more closely with effect of the hypnotic on the *cyclic alternating pattern (CAP)* of sleep.
- Insomnia arises under a variety of circumstances. It could be a long-term (months-years), short-term (weeks) or transient (a day or two, mostly situational) problem.

Chronic insomnia (> 3 weeks) Uncertainty exists about the use of hypnotics in this situation. The patient may have a personality disorder, but often there is no specific stress factor. He may have used hypnotics for long periods or may be alcoholic or have some somatic disease, e.g. gastroesophageal reflux, pain, COPD, etc. which interfere with sleep. Measures like aerobic exercise, training at mental relaxation, avoiding anxiety about past/future performance while in bed, attempting sleep when sleepiness is maximum, avoiding napping at daytime, maintaining regular sleep-wake timings and other sleep-hygiene measures, coffee/alcohol restriction, treatment of concurrent somatic illness, psychotherapy and controlled sleep curtailment may succeed. Good nightly sleep improves the quality of day-time wakefulness. Patients of obstructive sleep apnoea have poor sleep and feel sleepy during the day. All hypnotics aggravate sleep apnoea and are contraindicated.

Intermittent use of a hypnotic, say once every 3 days, may be tried. Risk of tolerance and abuse are maximum among chronic insomniacs. A slowly eliminated drug is preferable because rebound insomnia and withdrawal symptoms are least marked with such drugs.

Short-term insomnia (3–21 days) Emotional problem (occupational stress, bereavement) and physical illness are the usual causes. Patient may have induction difficulty or may be waking up early. Cautious use of low doses of an appropriate drug for the type of sleep disturbance may be made. Generally a hypnotic, free of residual effects should be selected, but when anxiety is a dominant feature, a BZD whose action extends into the next day may be better. Short acting drugs are preferable in the elderly. Intermittent hypnotic use should be limited to 2–3 weeks.

Transient insomnia (1–3 days) Due to alterations in the circumstances of sleep, e.g. unusual noise, on an overnight train, new place, unusual pattern of work, shift workers, intercontinental travel–jetlag, etc. A rapidly eliminated hypnotic or one with marked distribution is to be preferred to avoid residual effects the next morning. However, night before surgery—a long acting drug is better.

2. Other uses

(a) As anxiolytic and for day-time sedation (*see* Ch. 33).
(b) As anticonvulsant, especially emergency control of status epilepticus, febrile convulsions, tetanus, etc. (*see* Ch. 30).
(c) As centrally acting muscle relaxant (*see* Ch. 25).
(d) For preanaesthetic medication, i.v. anaesthesia and conscious sedation (*see* Ch. 27).
(e) Before ECT, electrical cardioversion of arrhythmias, cardiac catheterization, endoscopies, in obstetrics and many minor procedures—diazepam i.v. has gained popularity because of its calming-amnesic-analgesic and muscle relaxant properties and relative safety.
(f) Alcohol withdrawal in dependent subjects.
(g) Along with analgesics, NSAIDs, spasmolytics, antiulcer and as adjuvants to treat 'gas' or nonspecific dyspeptic symptoms.

Fixed dose combinations of sedative/hypnotic/anxiolytic drugs with analgesic-antipyretics has been banned in India.

BENZODIAZEPINE ANTAGONIST

Flumazenil It is a BZD analogue which has little intrinsic activity (practically no effect on normal subjects), but competes with BZD agonists as well as inverse agonists for the BZD receptor and reverses their depressant or stimulant effects respectively.

Flumazenil abolishes the hypnogenic, psychomotor, cognitive and EEG effects of BZDs. At higher doses it has some week BZD agonist-like as well as inverse agonist-like activity in animal models, but these are of no clinical significance.

Flumazenil is absorbed orally; oral bioavailability is ~16%, but it is not used orally. On i.v. injection, action of flumazenil starts in

seconds and lasts for 1–2 hr; elimination t½ is 1 hr, due to rapid metabolism.

Uses

1. *To reverse BZD anaesthesia* Patients anaesthetized/sedated with a BZD wakeup, get oriented and regain motor control within 1 min of an i.v. injection of 0.3–1 mg of flumazenil. Resedation generally occurs within 1 hour (more with diazepam than with midazolam): supplemental doses of flumazenil may be given. This may allow early discharge of patients after diagnostic procedures and facilitates postanaesthetic management.

2. *BZD overdose* Majority of patients of BZD overdose require only supportive measures like patent airway, maintenance of BP, cardiac and renal function (by fluid transfusion, etc.). In addition, flumazenil 0.2 mg/min may be injected i.v. till the patient regains consciousness. Practically all patients intoxicated with a BZD alone respond within 5 min. However, reversal of respiratory depression is incomplete. Flumazenil blocks the hypnotic effect of zolpidem-like non-BZDs as well. In mixed CNS depressant poisoning, whatever sedation is not abolished by 5 mg of flumazenil should be taken to be due to a non-BZD/non-Zolpidem-like depressant. It thus helps in differential diagnosis of such patients.

Adverse effects Flumazenil is safe and well tolerated.

Agitation, discomfort, tearfulness, anxiety, coldness and withdrawal seizures are the occasional side effects.

Melatonin It is the principal hormone of the pineal gland which is secreted at night and has been found to play an important role in entraining (synchronizing) the sleep-wakefulness cycle with the circadian rhythm. Two subtypes of melatonin receptor MT_1 and MT_2 have been identified in the brain. Both are GPCRs and are believed to carry out the function of facilitating sleep onset and fixing its timing in relation to the circadian clock. Though high doses (80 mg) of melatonin administered orally can induce sleep, low doses (2–10 mg) do not depress the CNS, but probably increase the propensity of falling asleep. Started before the flight it has been shown to reduce jet-lag symptoms and to hasten reentrainment with day-night cycle of the new place in intercontinental travellers. Beneficial effects in shift workers and in individuals with delayed sleep phase syndrome have also been reported. Elderly insomniacs have reported subjective improvement in sleep quality. However, melatonin is not a dependable hypnotic; has little effect on latency and duration of sleep, especially in non-elderly insomniacs. A meta-analysis has concluded that it is no more effective than placebo in the short-term for sleep disorders. Though it does not have the disadvantages of conventional hypnotics, its long-term safety is not known. Use may therefore be restricted to treatment of jet-lag, shift workers and elderly insomniacs.

Since melatonin secretion declines with age, it has been argued that melatonin supplementation might retard ageing. Though there is no proof of benefit, melatonin (2–5 mg/day) is being consumed as a health food in USA and some other countries. It has also been tried in cluster headache. In India it is marketed as a remedy for disturbed biorhythms and sleep disorders.

MELOSET 3 mg tab, ZYTONIN, ETERNEX melatonin 3 mg + pyridoxine 10 mg tab; one tab at evening daily.

Ramelteon It is a MT_1 as well as MT_2 melatonin receptor agonist introduced in USA and now approved in India as well, as a new class of hypnotic for sleep onset insomnia, that does not produce the usual BZD-like side effects. Administered in a dose of 8 mg ½ hour before going to bed, it is shown to hasten sleep onset as well as increase sleep duration, without causing next morning sedation or impairment.

In clinical trial on chronic insomnia patients, continuous nightly treatment with ramelteon maintained its effect to shorten sleep latency and was found to be free of rebound phenomena on stoppage. No dependence producing potential has been noted so far. It is rapidly absorbed orally, undergoes extensive first pass metabolism in liver, so that bioavailability is low and elimination t½ is 1–3 hours.

Ramelteon appears to be a promizing novel hypnotic, provided its efficacy is established.

ROZEREM 8 mg tab: 1 tab 1/2 hour before going to bed.

☞ PROBLEM DIRECTED STUDY

29.1 A 70-year-old man consults his family physician for the problem of failing to fall asleep occasionally (3–4 times in a month) for the past few months. He usually sleeps well and has a 6–7 hour sleep duration. However, on certain nights he keeps lying in bed for 2–3 hours before getting sleep. Such episodes are unpredictable, and he cannot relate them to any disturbance, anxiety, worry or physical illness. He has tried relaxing, getting up and walking around or reading, but nothing helps. As a result, next day he feels lethargic, impaired, unable to concentrate and has poor creativity. He requests a sleeping pill that he can take after failing to fall asleep.

(a) Can he be prescribed a hypnotic for occasional use? If so, which drug would be suitable for late night intake without next morning sedation?

(see Appendix-1 for solution)

Chapter 30 Antiepileptic Drugs

Epilepsies These are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. These episodes are unpredictable and their frequency is highly variable. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread and postictal depression of these regions. Recognised from the dawn of history as 'disease of lightening', it was correctly described by JH Jackson little over a century ago. Epilepsies have been classified variously; major types are described below.

I. Generalised seizures

1. *Generalised tonic-clonic seizures* (GTCS, major epilepsy, grand mal): commonest, lasts 1–2 min.
The usual sequence is aura—cry—unconsciousness—tonic spasm of all body muscles—clonic jerking followed by prolonged sleep and depression of all CNS functions.

2. *Absence seizures* (minor epilepsy, petit mal): prevalent in children, lasts about 1/2 min.
Momentary loss of consciousness, patient apparently freezes and stares in one direction, no muscular component or little bilateral jerking. EEG shows characteristic 3 cycles per second spike and wave pattern.

3. *Atonic seizures* (Akinetic epilepsy): Unconsciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall.

4. *Myoclonic seizures* Shock-like momentary contraction of muscles of a limb or the whole body.

5. *Infantile spasms (Hypsarrhythmia)* Seen in infants. Probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deterioration. Diffuse changes in the interseizure EEG are noted.

II. Partial seizures

1. *Simple partial seizures* (SPS, cortical focal epilepsy): lasts 1/2–1 min. Often secondary. Convulsions are confined to a group of muscles or localized sensory disturbance depending on the area of cortex involved in the seizure, without loss of consciousness.

2. *Complex partial seizures* (CPS, temporal lobe epilepsy, psychomotor): attacks of bizarre and confused behaviour and purposeless movements, emotional changes lasting 1–2 min along with impairment of consciousness. An aura often precedes. The seizure focus is located in the temporal lobe.

3. *Simple partial or complex partial seizures secondarily generalized* The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness.

Most of the cases of epilepsy are primary (idiopathic), some may be secondary to trauma/surgery on the head, intracranial tumour, tuberculoma, cysticercosis, cerebral ischaemia, etc. Treatment is symptomatic and the same whether epilepsy is primary or secondary.

Experimental models These models for testing antiepileptic drugs have also shed light on the etiopathogenesis of epilepsy.

1. *Maximal electroshock seizures* Brief high intensity shock is applied to the head of a rodent (just as in ECT): produces tonic flexion—tonic extension—clonic convulsions. The tonic phase (especially extensor) is selectively abolished by drugs effective in GTCS. Activity in this model represents action on spread of seizure discharge.

2. *Pentylenetetrazol (PTZ) clonic seizures* Injection of PTZ in rats or mice produces clonic convulsions which are prevented by drugs effective in myoclonic and absence seizures. Activity in this model represents action on seizure focus itself.

3. *Chronic focal seizures* Produced by application of alumina cream on the motor cortex of monkey.

4. *Kindled seizures* Brief bursts of weak electrical impulses are applied to the brain (especially amygdala) intermittently over days. After-discharges increase progressively and tonic-clonic seizures are produced after 10–15 shocks. With time spontaneous seizures set in, usually after >100 shocks. This indicates that seizures have a self perpetuating and reinforcing effect: more neuronal circuits are facilitated and recruited in the seizure process. Kindling is probably involved in the genesis of clinical epilepsy.

CLASSIFICATION

1.	*Barbiturate*	Phenobarbitone
2.	*Deoxybarbiturate*	Primidone
3.	*Hydantoin*	Phenytoin
		Fosphenytoin
4.	*Iminostilbene*	Carbamazepine
		Oxcarbazepine
5.	*Succinimide*	Ethosuximide
6.	*Aliphatic carboxylic acid*	Valproic acid (sodium valproate)
		Divalproex
7.	*Benzodiazepines*	Clonazepam
		Diazepam
		Lorazepam
		Clobazam
8.	*Phenyltriazine*	Lamotrigine
9.	*Cyclic GABA analogues*	Gabapentin
		Pregabalin
10.	*Newer drugs*	Topiramate
		Zonisamide
		Levetiracetam
		Vigabatrin
		Tiagabine
		Lacosamide

Felbamate, rufinamide and few other newer antiseizure drugs have been introduced in some countries as second line/add-on drugs for refractory partial seizures.

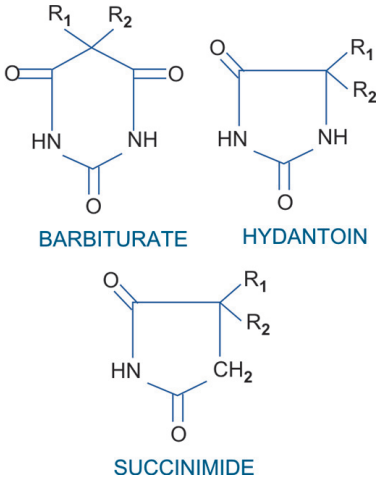


Fig. 30.1: Chemical structures of classical anticonvulsant drugs

Chemistry Most of the older anticonvulsants have close structural similarity. This is depicted in Fig. 30.1. However, benzodiazepines, carbamazepine, valproic acid and the newer drugs are chemically diverse. Presence of a phenyl substitution confers activity against tonic-clonic seizures.

Phenobarbitone (*see* Ch. 29)

Phenobarbitone was the first efficacious antiepileptic introduced in 1912. The mechanism of CNS depressant action of barbiturates is described on p. 399. The same may apply to anticonvulsant action. Enhancement of $GABA_A$ receptor mediated synaptic inhibition appears to be most important mechanism. However, phenobarbitone has specific anticonvulsant activity which is not entirely dependent on general CNS depression. Quantitative differences in the different facets of action (GABA-facilitatory, GABA-mimetic, antiglutamate, Ca^{2+} entry reduction) have been noted for phenobarbitone compared to hypnotic barbiturates. The higher anticonvulsant: hypnotic ratio of phenobarbitone may be due to its minimal effect on Ca^{2+} channels and glutamate release compared to hypnotic barbiturates. With continued use of phenobarbitone sedation wanes off but not anticonvulsant action. It has a wide spectrum of anticonvulsant property—raises seizure threshold as well as limits spread and suppresses kindled seizures.

Phenobarbitone has slow oral absorption and a long plasma t½ (80–120 hours), is metabolized in liver as well as excreted unchanged by kidney. Steady-state concentrations are reached after 2–3 weeks, and a single daily dose can be used for maintenance.

The major drawback of phenobarbitone as an antiepileptic is its sedative action. Long term administration (as needed in epilepsy) may produce additional side effects like—behavioral abnormalities, diminution of intelligence, impairment of learning and memory, hyperactivity in children, mental confusion in older people.

Rashes, megaloblastic anaemia and osteomalacia (similar to that with phenytoin) occur in some patients on prolonged use.

Uses Phenobarbitone is one of the cheapest and least toxic antiepileptics.

It has broad spectrum efficacy in generalized tonic-clonic (GTC), simple partial (SP) and complex partial (CP) seizures in a dose of 60 mg 1–3 times a day in adults; in children (3–5 mg/kg/day); However, it has become less popular than carbamazepine, phenytoin or valproate because of its dulling and behavioural side effects.

Status epilepticus: Phenobarbitone sod. may be injected i.m. or i.v. but response is slow to develop.

It is not effective in absence seizures.

GARDENAL 30, 60 mg tabs, 20 mg/5 ml syr; LUMINAL 30 mg tab, PHENOBARBITONE SODIUM 200 mg/ml inj.

Primidone A deoxybarbiturate, converted by liver to phenobarbitone and phenylethyl malonamide (PEMA). Its antiepileptic activity is mainly due to these active metabolites because t½ of primidone (6–14 hr) is less than that of its active metabolites. About 1/3 primidone is excreted unchanged by kidney. Dose to dose primidone is less potent, but antiepileptic efficacy is similar to phenobarbitone. It is infrequently used now in GTCS and partial epilepsy, mainly as an adjuvant to phenytoin or carbamazepine.

Adverse effects are similar to phenobarbitone. In addition, anaemia, leukopenia, psychotic reaction and lymph node enlargement occur rarely.

Dose: 250–500 mg BD, children 10–20 mg/kg/day.

MYSOLINE 250 mg tab.

Phenytoin (Diphenylhydantoin)

It was synthesized in 1908 as a barbiturate analogue, but shelved due to poor sedative property. Its anticonvulsant activity was specifically tested in 1938 in the newly developed electroshock seizure model and since then it is a major antiepileptic drug.

Phenytoin is not a CNS depressant; some sedation occurs at therapeutic doses, but this does not increase further with dose; rather toxic doses produce excitement and muscular rigidity. The most outstanding action is abolition of tonic phase of maximal electroshock seizures, with no effect on or prolongation of clonic phase. It limits spread of seizure activity. Threshold for PTZ convulsions is not raised. Tonic-clonic epilepsy is suppressed but paroxysmal focal EEG discharge and 'aura' persist.

Mechanism of action Phenytoin has a stabilizing influence on neuronal membrane—prevents repetitive detonation of normal brain cells during '*depolarization shift*' that occurs in epileptic patients and consists of a synchronous and unusually large depolarization over which action potentials are superimposed. This is achieved by prolonging the inactivated state of voltage sensitive neuronal Na^+ channel (Fig. 30.2) that governs the refractory period of the neurone. As a result high frequency discharges are inhibited with little effect on normal low frequency discharges which allow Na^+ channels to recover even when their inactivation is prolonged. This effect has been noted at therapeutic concentration of phenytoin, while other effects like reduction in Ca^{2+} influx, inhibition of glutamate and facilitation of GABA responses have been demonstrated at higher/toxic concentrations. Intracellular accumulation of Na^+ that occurs during repetitive firing is prevented.

Therapeutic concentrations have no effect on resting membrane potential: normal synaptic transmission is not impaired. Phenytoin, in contrast to phenobarbitone and valproate, does not interfere with kindling. Its ability to selectively inhibit high frequency firing confers efficacy in trigeminal neuralgia and cardiac arrhythmias as well.

Pharmacokinetics Absorption of phenytoin by oral route is slow, mainly because of its poor aqueous solubility. Bioavailability of different market preparations may differ. It is widely distributed in the body and is 80–90% bound to plasma proteins.

Phenytoin is metabolized in liver by hydroxylation involving CYP2C9 and 2C19 as well as by glucuronide conjugation. The kinetics of metabolism is *capacity limited*; changes from first order to zero order over the therapeutic

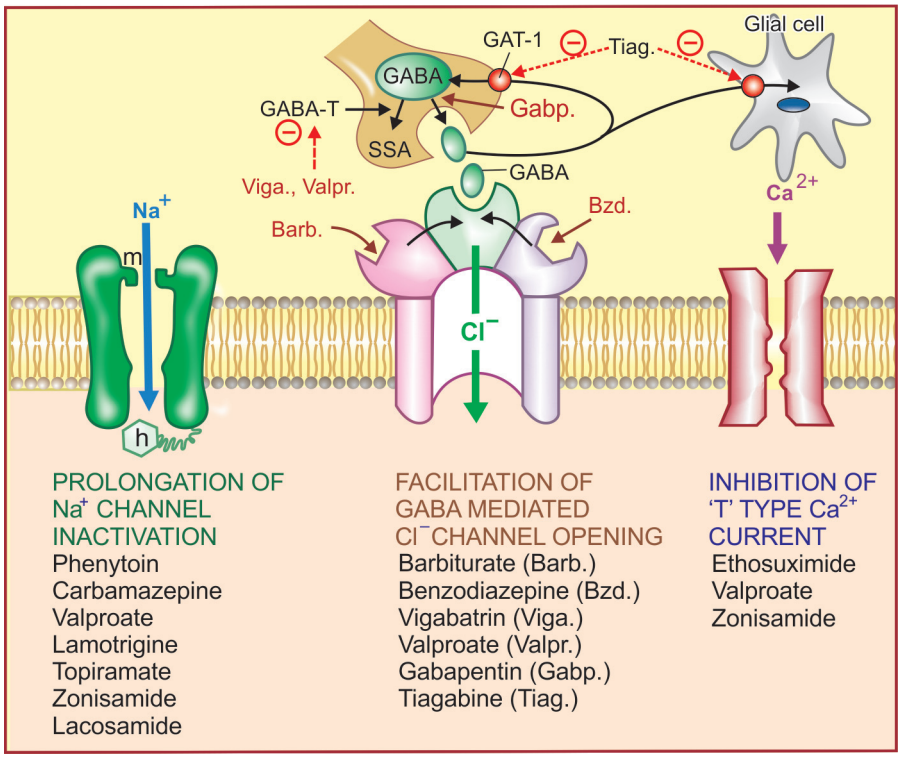


Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase;
SSA: Succinic semialdehyde; GAT-1: GABA transporter

range. As a result small increments in dose produce disproportionately high plasma concentrations. The t½ (12–24 hours at therapeutic levels), progressively increases (upto 60 hr) when plasma concentration rises above 10 µg/ml because metabolizing enzymes get saturated. Monitoring of plasma concentration is very helpful in tailoring dosage. Only 5% unchanged phenytoin is excreted in urine.

Adverse effects After prolonged use numerous side effects are produced at therapeutic plasma concentration; others occur as a manifestation of toxicity due to overdose.

At therapeutic levels

- Gum hypertrophy: Commonest (20% incidence), more in younger patients. It is due to overgrowth of gingival collagen fibres. This can be minimized by maintaining oral hygiene.
- Hirsutism, coarsening of facial features (troublesome in young girls), acne.
- Hypersensitivity reactions are—rashes, DLE, lymphadenopathy; neutropenia is rare but requires discontinuation of therapy.
- Megaloblastic anaemia: Phenytoin decreases folate absorption and increases its excretion.
- Osteomalacia: Phenytoin interferes with metabolic activation of vit D and with calcium absorption/metabolism.
- It can inhibit insulin release and cause hyperglycaemia.
- Used during pregnancy, phenytoin can produce *'foetal hydantoin syndrome'* (hypoplastic phalanges, cleft palate, hare lip, microcephaly), which is probably caused by its areneoxide metabolite.

At high plasma levels (dose related toxicity)

(a) Cerebellar and vestibular manifestations: ataxia, vertigo, diplopia, nystagmus are the most characteristic features.

(b) Drowsiness, behavioral alterations, mental confusion, hallucinations, disorientation and rigidity.

(c) Epigastric pain, nausea and vomiting. These can be minimised by taking the drug with meals.

(d) Intravenous injection can cause local vascular injury → intimal damage and thrombosis of the vein → edema and discolouration of the injected limb. Rate of injection should not exceed 50 mg/min. Tissue necrosis occurs if the solution extravasates.

(e) Fall in BP and cardiac arrhythmias occur only on i.v. injection which, therefore, must be given under continuous ECG monitoring.

Interactions Phenytoin is a potent inducer of CYP2C8/9, CYP3A4/5 and some other CYPs. It competitively inhibits CYP2C9/19.

- Phenobarbitone competitively inhibits phenytoin metabolism, while by enzyme induction both enhance each other's degradation—unpredictable overall interaction.
- Carbamazepine and phenytoin induce each other's metabolism.
- Valproate displaces protein bound phenytoin and decreases its metabolism: plasma level of unbound phenytoin increases.
- Chloramphenicol, isoniazid, cimetidine and warfarin inhibit phenytoin metabolism—can precipitate its toxicity.
- Phenytoin competitively inhibits warfarin metabolism.
- Phenytoin induces microsomal enzymes and increases degradation of steroids (failure of oral contraceptives), doxycycline, theophylline.
- A number of acidic drugs displace it from protein binding sites. However, rise is free phenytoin level enhances its clearance. Thus, concentration of free form does not change much.
- Sucralfate binds phenytoin in g.i. tract and decreases its absorption.

Uses Phenytoin is a first line antiepileptic drug, but less commonly used now because side effects are frequent and marginal overdose causes steep rise in plasma concentration, producing neurotoxicity. Indications are:

1. Generalized tonic-clonic, simple and complex partial seizures. It is ineffective in absence seizures.

Dose: 100 mg BD, maximum 400 mg/day; Children 5–8 mg/kg/day.

2. Status epilepticus: occasionally used by slow i.v. injection (fosphenytoin has replaced it).
3. Trigeminal neuralgia: second choice drug to carbamazepine.

DILANTIN 25 mg, 100 mg cap., 100 mg/4 ml oral suspension, 100 mg/2 ml inj; EPSOLIN 100 mg tab, 100 mg/2 ml inj; EPTOIN 50, 100 mg tab, 25 mg/ml syr; FENTOIN-ER 100 mg extended release cap.

Fosphenytoin This water soluble prodrug of phenytoin has been introduced to overcome the difficulties in i.v. administration of phenytoin, which it has replaced for use in status epilepticus. In the body, it is rapidly converted to phenytoin; its doses are expressed as phenytoin equivalents (PE). On i.v. injection it is less damaging to the intima; only minor vascular complications are produced and it can be injected at a faster rate (150 mg/min), but like phenytoin sod., it requires ECG monitoring. While phenytoin cannot be injected in a drip of glucose solution (because it gets precipitated), fosphenytoin can be injected with both saline and glucose.

FOSOLIN 50 mg/ml in 2 ml, 10 ml inj.

Carbamazepine

Chemically related to imipramine, it was introduced in the 1960s for trigeminal neuralgia. Now it is a first line antiepileptic drug. Its pharmacological actions resemble phenytoin, but important differences have been noted in experimental studies. Carbamazepine modifies maximal electroshock seizures as well as raises threshold to PTZ and electroshock convulsions. It also

inhibits kindling. Though its action on Na^+ channels (prolongation of inactivated state) is similar to phenytoin, the profile of action on neuronal systems in brain is different.

Carbamazepine exerts a lithium-like therapeutic effect in mania and bipolar mood disorder. It also has antidiuretic action, probably by enhancing ADH action on renal tubules.

Pharmacokinetics Oral absorption of carbamazepine is slow and variable because of poor water solubility. It is 75% bound to plasma proteins and metabolized in liver by oxidation to an active metabolite (10-11 epoxy carbamazepine) as well as by hydroxylation and conjugation to inactive ones. It is a substrate as well as inducer of CYP3A4 and CYP2C9. Initially its plasma t½ is 20–40 hours but, decreases to 10–20 hr on chronic medication due to autoinduction of metabolism.

Adverse effects Carbamazepine produces dose-related neurotoxicity—sedation, dizziness, vertigo, diplopia and ataxia. Vomiting, diarrhoea, worsening of seizures are also seen with higher doses. Acute intoxication causes coma, convulsions and cardiovascular collapse.

Hypersensitivity reactions are rashes, photosensitivity, hepatitis, lupus like syndrome, rarely agranulocytosis and aplastic anaemia. Some degree of leucopenia due to hypersensitivity is more common.

Water retention and hyponatremia can occur in the elderly because it enhances ADH action. Increased incidence of minor foetal malformations has been reported. Its combination with valproate doubles teratogenic frequency.

Interactions Carbamazepine is an enzyme inducer; can reduce efficacy of haloperidol, oral contraceptives, lamotrigine, valproate and topiramate. Metabolism of carbamazepine is induced by phenobarbitone, phenytoin, and *vice versa*. Erythromycin, fluoxetine, isoniazid inhibit metabolism of carbamazepine.

Uses Carbamazepine is the most effective drug for CPS and also the most commonly used drug for GTCS and SPS.

Trigeminal and related neuralgias: Carbamazepine is the drug of choice. These neuralgias are characterized by attacks of high intensity electric shock-like or stabbing pain set off by even trivial stimulation of certain trigger zones in the mouth or on the face. Drugs benefit by interrupting temporal summation of afferent impulses (by a selective action on high frequency nerve impulses). Carbamazepine is not an analgesic, but has a specific action (almost diagnostic) in these neuralgias. About 60% patients respond well. Phenytoin, lamotrigine and baclofen are less efficacious alternatives. Gabapentin can be tried in nonresponders.

Carbamazepine is not useful in diabetic, traumatic and other forms of neuropathic pain.

Manic depressive illness and acute mania: as an alternative to lithium (*see* Ch. 32).

Dose: 200–400 mg TDS; Children 15–30 mg/kg/day.
TEGRETOL, MAZETOL 100, 200, 400 mg tab, 100 mg/5 ml syr; CARBATOL 100, 200, 400 mg tab.
MAZETOL SR, TEGRITAL CR 200, 400 mg sustained release/continuous release tabs. to avoid high peaks and low troughs in plasma concentration. These are the preferred formulations.

Oxcarbazepine This newer congener of carbamazepine is rapidly converted to an active metabolite that is only glucuronide conjugated but not oxidized. Toxic effects due to the epoxide metabolite are avoided. Drug interactions and autoinduction of own metabolism are less marked, because it is a weak enzyme inducer. Risk of hepatotoxicity is estimated to be lower than carbamazepine; but that of hyponatraemia is more. Indications are the same as for carbamazepine, but it may be better tolerated. Dose to dose it is 1½ times less potent.
OXETOL, OXCARB, OXEP 150, 300, 600 mg tabs.

Ethosuximide

The most prominent action of ethosuximide is antagonism of PTZ induced clonic seizures at doses which produce no other discernable action. It raises seizure threshold but does not modify maximal electroshock seizures or inhibit kindling. Clinically it is effective only in absence seizures.

The primary action appears to be exerted on thalamocortical system which is involved in the generation of absence seizures. The EEG in absence seizures shows characteristic bilaterally synchronous 3 Hz spike and wave rhythm generated by reciprocal activation and oscillation of impulses between thalamus and neocortex through reverberatory synaptic connections. Thalamic neurones exhibit prominent 'T' (transient) current which is low threshold Ca^{2+} current (due to inward flow of Ca^{2+} through T type Ca^{2+} channels) that acts as the pacemaker and amplifies repetitive spikes. Ethosuximide selectively suppresses T current without affecting other types of Ca^{2+} or Na^{+} currents. It also does not potentiate GABA at therapeutic concentrations. This correlates well with its selective action in absence seizures.

Ethosuximide is rather slowly but completely absorbed, not protein bound, evenly distributed in body, and largely metabolized in liver by hydroxylation and glucuronidation, and excreted in urine—about ¼th in the unchanged form. Plasma t½ averages 48 hours in adults and 32 hours in children.

Adverse effects Dose-related side effects are gastrointestinal intolerance, tiredness, mood changes, agitation, headache, drowsiness and inability to concentrate.
Hypersensitivity reactions like rashes, DLE and blood dyscrasias are rare. No liver or kidney damage.

Use The only indication for ethosuximide is absence seizures; in that also it has been superseded by valproate.
Dose: 20–30 mg/kg/day; ZARONTIN 250 mg/5 ml syr.

Valproic acid (Sodium valproate)

It is a branched chain aliphatic carboxylic acid with a broad spectrum anticonvulsant action. It is more potent in blocking PTZ seizures than in modifying maximal electroshock. Establishment of chronic experimental seizure foci and kindling are also prevented. Remarkably, at anticonvulsant doses, valproate produces little sedation or other central effects. Likewise, it is effective in partial seizures and GTCS as well as absence seizures.
Valproate appears to act by multiple mechanisms:
(i) A phenytoin-like frequency-dependent prolongation of Na^{+} channel inactivation.
(ii) Weak attenuation of Ca^{2+} mediated 'T' current (ethosuximide like).
(iii) Augmentation of release of inhibitory transmitter GABA by inhibiting its degradation (by GABA-transaminase) as well as probably by increasing its synthesis from glutamic acid. However, responses to exogenously applied GABA are not altered.

Pharmacokinetics Oral absorption of valproic acid is good. It is 90% bound to plasma proteins; completely metabolized in liver by oxidation mainly by CYP2C9 and 2C19 (some metabolites are active) and glucuronide conjugation, and then excreted in urine. Plasma t½ is 10–15 hours; but anticonvulsant effects are longer lasting.

Adverse effects The toxicity of valproate is relatively low.
Anorexia, vomiting, loose motions and heart burn are common but mild. Drowsiness, ataxia and tremor are dose-related side effects. However, cognitive and behavioral effects are not prominent.
Alopecia, curling of hair, weight gain and increased bleeding tendency have been observed.
Rashes and thrombocytopenia are infrequent hypersensitivity phenomena.
Asymptomatic rise in serum transaminase is often noted; monitoring of liver function is advised.
A rare but serious adverse effect is fulminant hepatitis; occurs only in children (especially below 3 yr). Those with hepatic disease or who receive other anticonvulsant or hepatotoxic drug are at greater risk. Pancreatitis is also reported. Long-term use of valproate in young girls has been associated with higher incidence of polycystic ovarian disease and menstrual irregularities.
Used during pregnancy, it has produced spina bifida and other neural tube defects in the offspring; should be avoided.

Dose: Adults—start with 200 mg TDS, maximum 800 mg TDS; children—15–30 mg/kg/day.
VALPARIN CHRONO 200, 300, 500 mg tabs, 200 mg/5 ml syr; ENCORATE 200, 300, 500 mg regular and controlled release tabs, 200 mg/5 ml syr, 100 mg/ml inj.

Uses Valproic acid is the drug of choice for absence seizures.

It is an alternative/adjuvant drug for GTCS, SPS and CPS.

Myoclonic and atonic seizures—control is often incomplete, but valproate is the drug of choice.

Mania and bipolar illness: as alternative to lithium. It has also been used for panic attacks.

Valproate has some prophylatic efficacy in migraine.

Interactions

- Valproate increases plasma levels of phenobarbitone and lamotrigine by inhibiting their metabolism.
- It displaces phenytoin from protein binding site and decreases its metabolism → phenytoin toxicity.
- Valproate inhibits hydrolysis of active epoxide metabolite of carbamazepine.
- Concurrent administration of clonazepam and valproate is contraindicated because absence status may be precipitated.
- Foetal abnormalities are more common if valproate and carbamazepine are given concurrently.

Divalproex (Semisodium valproate) It is the coordination compound of valproic acid with sodium valproate (1:1). Oral absorption is slower, but bioavailability is the same. Gastric tolerance may be better.

DIPROEX, VALANCE, 125, 250, 500 mg tabs; DEPAKOTE 250, 500 mg tabs.

Clonazepam

It is a benzodiazepine with prominent anticonvulsant properties: blocks PTZ seizures at doses which produce mild sedation. Efficacy in modifying maximal electroshock seizures is low. Though in experimental models of chronic epilepsy it inhibits spread rather than the focus itself, it is singularly ineffective in GTCS. Production of generalized seizures by kindling is suppressed, but local after-discharges persist.

Benzodiazepines potentiate GABA induced Cl^- influx to produce sedation and the same mechanism has been held responsible for the anticonvulsant property, but the sites of action in the brain may be different. At large doses, high frequency discharges are inhibited akin to phenytoin.

Pharmacokinetics Oral absorption of clonazepam is good. It is 85% bound to plasma proteins, completely metabolized in liver and excreted in urine; t½ averages 24 hours. It does not produce any active metabolite.

Adverse effects The most important side effect of clonazepam is sedation and dullness. This can be minimized by starting at low dose; some tolerance develops with chronic therapy. Lack of concentration, irritability, temper and other behavioral abnormalities may occur in children. Motor disturbances and ataxia are dose-related adverse effects. Salivation and increased respiratory secretions may be complained of.

Uses Clonazepam has been primarily employed in absence seizures. It is also useful as an adjuvant in myoclonic and akinetic epilepsy and may afford some benefit in infantile spasms. However, its value is limited by development of tolerance to the therapeutic effect within six months or so. It has also been used to suppress acute mania.

Dose: adults 0.5–5 mg TDS, children 0.02–0.2 mg/kg/day.

LONAZEP, CLONAPAX, RIVOTRIL 0.5, 1.0, 2.0 mg tab.

Clobazam It is a 1,5 benzodiazepine (diazepam and others are 1,4 benzodiazepines) introduced first as anxiolytic and later found to possess useful antiepileptic efficacy in partial, secondarily generalized tonic-clonic as well as absence and atonic seizures, including some refractory cases. Sedation and psychomotor retardation are less prominent, but side effect profile is similar to other BZDs. It appears to act by facilitating GABA action.

Oral bioavailability of clobazam is ~90% and elimination t½ 18 hrs, but an active metabolite is produced which has longer t½ (>35 hr). It is generally used as adjuvant to other antiepileptic drugs like phenytoin, carbamazepine or valproate in refractory epilepsy.

Dose: start with 10–20 mg at bedtime, can be increased upto 60 mg/day; FRISIUM, LOBAZAM, CLOZAM, 5, 10, 20 mg cap.

Diazepam (*see* Ch. 29)

It has anticonvulsant activity in a variety of models but is not used for long term therapy of epilepsy because of prominent sedative action and rapid development of tolerance to the antiepileptic effect. However, it is a first line drug

for emergency control of convulsions, e.g. status epilepticus, tetanus, eclampsia, convulsant drug poisoning, etc.

For this purpose 0.2–0.5 mg/kg slow i.v. injection is followed by small repeated doses as required; maximum 100 mg/day. Thrombophlebitis of injected vein is not uncommon. Marked fall in BP and respiratory depression can occur; resuscitative measures should be at hand before the drug is injected.

Rectal instillation of diazepam is now the preferred therapy for febrile convulsions in children.

Lorazepam 0.1 mg/kg injected i.v. at a rate not exceeding 2 mg/min is better suited than diazepam in status epilepticus or for emergency control of convulsions of other etiology, because of lesser local thrombophlebitic complications and more sustained action than that of diazepam which is rapidly redistributed.

Lamotrigine A new anticonvulsant having carbamazepine-like action profile: modifies maximal electroshock and decreases electrically evoked as well as photic after-discharge duration. Prolongation of Na^+ channel inactivation and suppression of high frequency firing has been demonstrated. In addition, it may directly block voltage sensitive Na^+ channels, thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters, mainly glutamate and aspartate. This may account for its broader-spectrum of antiseizure efficacy. However, it does not antagonize PTZ seizures or block NMDA type of glutamate receptors.

Lamotrigine is a broad-spectrum antiepileptic. Initially found useful as add-on therapy in refractory cases of partial seizures and GTCS, it has now been shown effective as monotherapy as well. Absence and myoclonic or akinetic epilepsy cases have also been successfully treated. Reduction in seizure frequency or complete control is obtained as frequently as with carbamazepine.

Lamotrigine is well absorbed orally and metabolized completely in liver. Its t½ is 24 hr, but is reduced to ~16 hr in patients receiving phenytoin, carbamazepine or phenobarbitone. On the contrary valproate inhibits glucuronidation of lamotrigine and doubles its blood level, but valproate levels are lowered by lamotrigine. Reduce the dose of lamotrigine to half in patients taking valproate. However, metabolism of other anticonvulsants and oral contraceptives is not altered.

Side effects are sleepiness, dizziness, diplopia, ataxia and vomiting. In some comparative trials lamotrigine has been found to be better tolerated than carbamazepine or phenytoin. Negative effect on cognitive function is not reported. Rash may be a severe reaction, particularly in children, requiring withdrawal.
Dose: 50 mg/day initially, increase upto 300 mg/day as needed; not to be used in children.
LAMETEC, LAMITOR, LAMIDUS 25, 50, 100 mg tabs.

Gabapentin This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at $GABA_A$ receptor. It modifies maximal electroshock as well as inhibits PTZ induced clonic seizures.

Gabapentin and its newer congener pregabalin exert a specific analgesic effect in neuropathic pain. Recently they have been found to modulate a subset of neuronal voltage sensitive Ca^{2+} channels which contain $\alpha 2\delta$-1 subunits. It is postulated that decreased entry of Ca^{2+} into the presynaptic neurone through these channels could reduce glutamate release, lowering neuronal excitability. However, whether $\alpha 2\delta$-1 Ca^{2+} channel modulation or the GABA enhancing action is responsible for the anticonvulsant/analgesic effect of gabapentin and pregabalin, is not known.

Added to a first line drug, gabapentin reduces seizure frequency in refractory partial seizures with or without generalization. Though gabapentin monotherapy as well has been found effective in SPS and CPS, it is mostly employed as add-on drug. Gabapentin is considered to be a first line drug for neuralgic pain due to diabetic neuropathy and postherpetic neuralgia. It has some prophylactic effect in migraine and is an alternative drug for phobic states.

Gabapentin is well absorbed orally and excreted unchanged in urine with a t½ of 6 hrs. No drug interactions have been noted, and no change in dose of primary antiepileptic drug is required when gabapentin is added. Side effects are mild sedation, tiredness, dizziness and unsteadiness.

Dose: Start with 300 mg OD, increase to 300–600 mg TDS as required; NEURONTIN 300 mg, 400 mg cap, GABANTIN, GABAPIN 100, 300, 400 mg cap.

Pregabalin This newer congener of gabapentin has similar pharmacodynamic, pharmacokinetic properties and clinical indications in seizure disorders. It has been particularly used for neuropathic pain, such as diabetic neuropathy, postherpetic neuralgia, complex regional pain syndrome (CRPS) and certain other types of chronic pain. Sedative side effects are claimed to be less prominent, but poor concentration, rashes and allergic reactions have been complained.

Dose: 75–150 mg BD, max 600 mg/day

PREGABA, NEUGABA, TRUEGABA 75, 150 mg caps.

Topiramate This weak carbonic anhydrase inhibitor has broad spectrum anticonvulsant activity in maximal electroshock, PTZ induced clonic seizures and in kindling model. It appears to act by multiple mechanisms, *viz* phenytoin like prolongation of Na^+ channel inactivation, GABA potentiation by a postsynaptic effect, antagonism of certain glutamate receptors and neuronal hyperpolarization through certain K^+ channels.

Topiramate is indicated as monotherapy as well as for supplementing primary antiepileptic drug in refractory SPS, CPS and GTCS. Promising results have been obtained in myoclonic epilepsy. Topiramate is readily absorbed orally and mainly excreted unchanged in urine with an average t½ of 24 hours. Adverse effects are impairment of attention, sedation, ataxia, word finding difficulties, poor memory, weight loss, paresthesias and renal stones.

Recently, topiramate has been approved for prophylaxis of migraine; may be used when β blockers/other prophylactics are contraindicated or are not effective.

Dose: Initially 25 mg OD, increase weekly upto 100–200 mg BD as required.

TOPEX, EPITOP, TOPAMATE, NEXTOP 25, 50, 100 mg tabs.

Zonisamide Another newer anticonvulsant with weak carbonic anhydrase inhibitory action that modifies maximal electroshock seizures and inhibits kindled seizures, but does not antagonize PTZ. Prolongation of Na^+ channel inactivation resulting in suppression of repetitive neuronal firing has been observed. It has also been found to suppress T-type of Ca^{2+} currents in certain neurones.

Zonisamide is well absorbed orally and mainly excreted unchanged in urine with a t½ of > 60 hours. A small fraction is oxidized and conjugated with glucuronic acid. It is indicated as add-on drug in refractory partial seizures. Side effects are somnolence, dizziness, headache, irritability and anorexia. Metabolic acidosis and renal stones can occur. Zonisamide is to be avoided in patients sensitive to sulfonamides.

Dose: 25–100 mg BD. Not to be given to children.

ZONISEP, ZONICARE, ZONIT 50, 100 mg cap.

Levetiracetam A unique anticonvulsant which suppresses kindled seizures, but is ineffective against maximal electroshock or PTZ. Clinical efficacy has been demonstrated both as adjuvant medication as well as monotherapy in refractory partial seizures with or without generalization. The mechanism of action is not known. None of the major anticonvulsant mechanisms appear to be applicable. However, it may modify synaptic release of glutamate/GABA by binding to a specific synaptic protein labelled 'SV_2A'. This may or may not account for the antiepileptic property.

Levetiracetam is completely absorbed orally, partly hydrolysed, but mainly excreted unchanged in urine with a t½ of 6–8 hours. It is neither oxidized by CYP enzymes nor induces or inhibits them. As such, it is free of drug interactions. Few side effects like sleepiness, dizziness, weakness and rarely behavioural changes are reported. Driving may be impaired. Because of good tolerability, levetiracetam is being increasingly used in CPS, GTCS and myoclonic epilepsy, mainly as add-on drug. It is not approved for use in children below 4 years.

Dose: 0.5 g BD, increase upto 1.0 g BD (max 3 g/day), children 4-15 year 10–30 mg/kg/day.

LEVOREXA, TORLEVA, LEVTAM 0.25, 0.5, 1.0 g tabs.

Tiagabine This newer anticonvulsant potentiates GABA mediated neuronal inhibition by depressing GABA transporter GAT-1 which removes synaptically released GABA into neurones and glial cells. Maximal electroshock and kindled seizures are suppressed. Currently it is approved only for add-on therapy of partial seizures with or without secondary generalization, when not adequately controlled by standard antiepileptic drugs alone. Side effects are mild sedation, nervousness, asthenia, amnesia and abdominal pain.

Vigabatrin (γ vinyl GABA) It is an inhibitor of GABA-transaminase, the enzyme which degrades GABA. Anticonvulsant action may be due to increase in synaptic GABA concentration. It is effective in many patients with refractory epilepsy, especially CPS with or without generalization. It is approved only for adjuvant medication.

Visual field contraction and production of behavioural changes, depression or psychosis has restricted its use to only as a reserve drug.

Lacosamide This recently approved (in 2010 in India) antiseizure drug is indicated in adults only for add-on therapy of partial seizures with or without generalization. It acts by enhancing Na^+ channel inactivation and suppressing repetitive firing of neurones. Lacosamide is metabolized by CYP2C19 and excreted in urine. No alteration in dose of companion antiepileptic drug is needed, because it neither induces nor inhibits drug metabolizing enzymes. Adverse effects are ataxia, vertigo, diplopia, tremour, depression and cardiac arrhythmia.
Dose: Initially 50 mg BD, increase upto 200 mg BD.

TREATMENT OF EPILEPSIES

Antiepileptic drugs suppress seizures, but do not cure the disorder; the disease may fadeout though after years of successful control. The aim of drugs is to control and totally prevent all seizure activity at an acceptable level of side effects. With the currently available drugs, this can be achieved in about half of the patients. Another 20–30% attain partial control, while the rest remain refractory. The cause of epilepsy should be searched in the patient; if found and treatable, an attempt to remove it should be made. Some general principles of symptomatic treatment with antiepileptic drugs are:

(i) Choice of drug (Table 30.1) and dose is according to the seizure type(s) and need of the individual patient.

(ii) Initiate treatment early, because each seizure episode increases the propensity to further attacks, probably by a process akin to kindling. Start with a single drug, preferably at low dose—gradually increase dose till full control of seizures or side effects appear. If full control is not obtained at maximum tolerated dose of one drug, substitute another drug. Use combinations when all reasonable monotherapy fails. Combining drugs with different mechanisms of action, such as those which prolong Na^+ channel inactivation with those facilitating GABA appears more appropriate. Pharmacokinetic interactions

TABLE 30.1 Choice of antiseizure drugs

	Type of seizure	*First choice drugs*	*Second choice drugs*	*Alternative/Add-on drugs*
1.	Generalised tonic-clonic/ simple partial with or without generalization	Carbamazepine, Phenytoin	Valproate, Phenobarbitone	Lamotrigine, Gabapentin, Topiramate, Primidone, Levetiracetam
2.	Complex partial with or without generalization	Carbamazepine, Valproate, Phenytoin	Gabapentin, Lamotrigine, Levetiracetam	Clobazam, Zonisamide, Topiramate
3.	Absence	Valproate	Ethosuximide, Lamotrigine	Clobazam, Clonazepam
4.	Myoclonic	Valproate	Lamotrigine, Topiramate	Levetiracetam, Clonazepam
5.	Atonic	Valproate	Clonazepam, Clobazam	Lamotrigine
6.	Febrile seizures	Diazepam (rectal)	—	—
7.	Status epilepticus	Lorazepam (i.v.), Diazepam (i.v.)	Fosphenytoin (i.v.) Phenobarbitone (i.v., i.m.)	Gen. anaesthetics

among anticonvulsants are common; dose adjustment guided by therapeutic drug monitoring is warranted.

(iii) A single tonic-clonic seizure in a subject with no predisposing factor for development of epilepsy (history of head injury, family history of epilepsy, neurological abnormality, abnormal EEG or brain scan) may not merit initiation of antiepileptic therapy.

(iv) Therapy should be as simple as possible. A seizure diary should be maintained.

(v) All drug withdrawals should be gradual (except in case of toxicity. Abrupt stoppage of therapy without introducing another effective drug can precipitate status epilepticus. Prolonged therapy (may be life-long, or at least 3 years after the last seizure) is needed. Stoppage of therapy may be attempted in selected cases. Features favourable to withdrawal are:

- childhood epilepsy,
- absence of family history,
- primary generalized tonic-clonic epilepsy,
- recent onset at start of treatment,
- absence of cerebral disorder and normal inter-seizure EEG.

Even with these features recurrence rates of 12–40% have been reported.

(vi) Dose regulation may be facilitated by monitoring of steadystate plasma drug levels. Monitoring is useful because:

(a) Therapeutic range of concentrations has been defined for many older drugs.
(b) There is marked individual variation in the plasma concentration attained with the same daily dose.
(c) Compliance among epileptic patients is often poor.

Plasma levels given in Table 30.2 are to serve as rough guides:

(vii) When women on antiepileptic therapy conceive, antiepileptic drugs should not be stopped. Though, most antiseizure drugs increase the incidence of birth defects, discontinuation of therapy carries a high risk of status epilepticus. Fits occurring during pregnancy themselves increase birth defects and may cause mental retardation in the offspring (anoxia occurs during seizures). An attempt to reduce the dose of drugs should be cautiously made. It may be advisable to substitute valproate.

Prophylactic folic acid supplementation in 2nd and 3rd trimester along with vit. K in the last month of pregnancy is recommended, particularly in women receiving antiepileptic drugs to minimise neural tube defects and bleeding disorder respectively in the neonate.

(viii) Individual seizure episodes do not require any treatment. During an attack of tonic-clonic seizures, the first priority is to prevent injury due to fall or biting. The patient should be put in prone

TABLE 30.2 **Plasma half life, therapeutic and toxic plasma concentration range of some important antiepileptic drugs**

Drug	*Half life (hr)*	*Plasma concentration (μg/ml)*	
		Therapeutic	*Toxic*
Phenobarbitone	80–120	10–30	> 30 mild > 60 severe
Phenytoin	12–36	10–20	> 20 mild > 35 severe
Carbamazepine	10–40	5–10	> 12
Ethosuximide	30–50	50–100*	>200
Valproate	10–15	40–100*	–
Clonazepam	20–40	0.01–0.1*	–

* Poorly correlated with response.

or lateral position and a gag should be placed between the teeth. The head should be turned and patency of airway ensured. The attack usually passes off in 2–3 min, but the patient may not be roadworthy for a couple of hours.

1. Generalised tonic-clonic and simple partial seizures In large comparative trials, considering both efficacy and toxicity, carbamazepine and phenytoin have scored highest, phenobarbitone was intermediate, while primidone was lowest among the older drugs. Carbamazepine was the best in partial seizures, while valproate was equally effective in secondarily GTCS. Valproate is a good second line drug but should be used cautiously in young children for fear of hepatic toxicity. Carbamazepine is preferred in young girls because of cosmetic side effects of phenytoin.

Lamotrigine, gabapentin and topiramate have emerged as good alternatives. Levetiracetam is another close contender. Clonazepam is a short-term alternative. Newer drugs are mostly used as add-on therapy in cases with incomplete/poor response. They are being increasingly used for monotherapy as well, either to initiate therapy or as alternative medication, particularly when drug interactions are to be avoided. The newer drugs generally are less sedating and produce fewer side effects. However, experience with them is less extensive and comparative trials are few.

Complete control can be obtained in upto 90% patients with generalized seizures, but in only 50% or less patients with partial seizures.

Phenobarbitone, phenytoin, valproate and carbamazepine have been used to treat early post-head injury seizures. Phenobarbitone and phenytoin are often prescribed empirically for prophylaxis of late-onset (8 days to 2 yrs later) post-traumatic epilepsy, but risk/benefit ratio of such use is not clear. Decision has to be taken on individual basis.

2. Complex partial seizures This type of epilepsy is difficult to control completely; relapses are more common on withdrawal. Carbamazepine is the preferred drug, but phenytoin or valproate may have to be added to it. The newer drugs levetiracetam, lamotrigine, gabapentin, topiramate or zonisamide may be added in refractory cases.

3. Absence seizures Ethosuximide and valproate are equally efficacious, but the latter is more commonly used because it would also prevent kindling and emergence of GTCS. Valproate is clearly superior in mixed absence and GTCS, which is more common than pure absence seizures. Lamotrigine has emerged as a good alternative. Clonazepam is a second line drug limited by its sedative property and development of tolerance. Clobazam is an alternative with promise of more sustained response.

4. Myoclonic and atonic seizures Valproate is the preferred drug and lamotrigine is an effective alternative. Topiramate may be added in case of poor response. Levetiracetam is generally added in nonresponsive cases.

5. Febrile convulsions Some children, especially under 5 years age, develop convulsions during fever. Seizures may recur every time with fever and few may become chronic epileptics. Every attempt should be made to see that they do not develop fever, but when they do, temperature should not be allowed to rise by using paracetamol and external cooling.

The best treatment of febrile convulsions is rectal diazepam 0.5 mg/kg given at the onset of convulsions. The i.v. preparation can be used where the rectal formulation is not available. A rectal solution (5 mg in 2.5 ml) in tubes is available in the UK and some other countries. Seizures generally stop in 5 min; if not, another dose may be given. The drug is repeated 12 hourly for 4 doses. If fever is prolonged a gap of 24–48 hr is given before starting next series of doses.

In recurrent cases or those at particular risk of developing epilepsy—intermittent prophylaxis with diazepam (oral or rectal) started at the onset of fever is recommended. Chronic prophylaxis with phenobarbitone advocated earlier has been abandoned, because of poor efficacy and behavioural side effects.

6. Infantile spasms (hypsarrhythmia) Therapy is unsatisfactory, antiepileptic drugs are generally useless. Corticosteroids afford symptomatic relief. Valproate and clonazepam have adjuvant value. Vigabatrin has some efficacy.

7. Status epilepticus When seizure activity occurs for >30 min, or two or more seizures occur without recovery of consciousness, the condition is called *status epilepticus*. Recurrent tonic-clonic convulsions without recovery of consciousness in between is an emergency; fits have to be controlled as quickly as possible to prevent death and permanent brain damage.

- *Lorazepam* 4 mg (0.1 mg/kg in children) injected i.v. at the rate of 2 mg/min, repeated once after 10 min if required, is the first choice drug now. It is effective in 75–90% cases and produces a more sustained anticonvulsant effect (lasting 6–12 hours) than diazepam, because of lower lipid solubility and slower redistribution. Moreover, thrombophlebitis of injected vein is less likely with lorazepam.
- *Diazepam* 10 mg (0.2–0.3 mg/kg) injected i.v. at 2 mg/min, repeated once after 10 min if required, has been the standard therapy till recently. However, its anticonvulsant effect starts fading after 20 min, and many supplemental doses may be required. It is also more damaging to the injected vein.
- *Fosphenytoin* 100–150 mg/min i.v. infusion to a maximum of 1000 mg (15–20 mg/kg) under continuous ECG monitoring is a slower acting drug which should be given if the seizures recur or fail to respond 20 min after onset, despite lorazepam/diazepam. It may also be employed to continue anticonvulsant cover after the seizures have been controlled by the BZD.
- *Phenytoin sod.* It should be used only when fosphenytoin is not available, because it can be injected only at the rate of 25–50 mg/min and causes more marked local vascular complications.
- *Phenobarbitone sod.* 50–100 mg/min i.v. injection to a maximum of 10 mg/kg is another slower acting drug which can be used as alternative to fosphenytoin. It is also employed to maintain seizure free state over short term before definitive oral therapy is instituted.
- Refractory cases who fail to respond to lorazepam and fosphenytoin within 40 min of seizure onset may be treated with i.v. midazolam/propofol/thiopentone anaesthesia, with or without curarization and full intensive care.
- General measures, including maintenance of airway (intubation if required), oxygenation, fluid and electrolyte balance, BP, normal cardiac rhythm, euglycaemia and care of the unconscious must be taken.

☞ PROBLEM DIRECTED STUDY

30.1 A young lady aged 25 years comes for consultation along with her husband for having suffered two episodes of fits lasting 2–3 min each over the past one week. Just before each fit, she experienced flickering in her right arm. Description of the fit given by the husband corresponds to generalized tonic-clonic seizures. She gave the history of having met a car accident about one year back in which she received head injury. There is no family history of epilepsy. General physical and neurological examination revealed no abnormality. Investigations, including EEG and MRI scan of the brain, were ordered.

(a) What instructions should be given to the husband regarding care to be taken, if and when, the next fit occurs?

(b) Should antiepileptic drug/drugs be started right away, or therapy be delayed till findings of the investigations become available or till more fits occur?

(c) In case antiseizure therapy has to be started right away, should a single drug or a combination of drugs be given? Which drug(s) would be the most appropriate for this patient?

(see Appendix-1 for solution)

Chapter 31 Antiparkinsonian Drugs

These are drugs that have a therapeutic effect in parkinsonism.

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

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

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

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

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

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

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

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

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

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

CLASSIFICATION

I. *Drugs affecting brain dopaminergic system*

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

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

II. *Drugs affecting brain cholinergic system*

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

(b) *Antihistaminics :* Orphenadrine, Promethazine.

LEVODOPA

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

ACTIONS

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

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

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

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

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

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

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

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

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

Gradual tolerance develops to both cardiac stimulant and hypotensive actions.

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

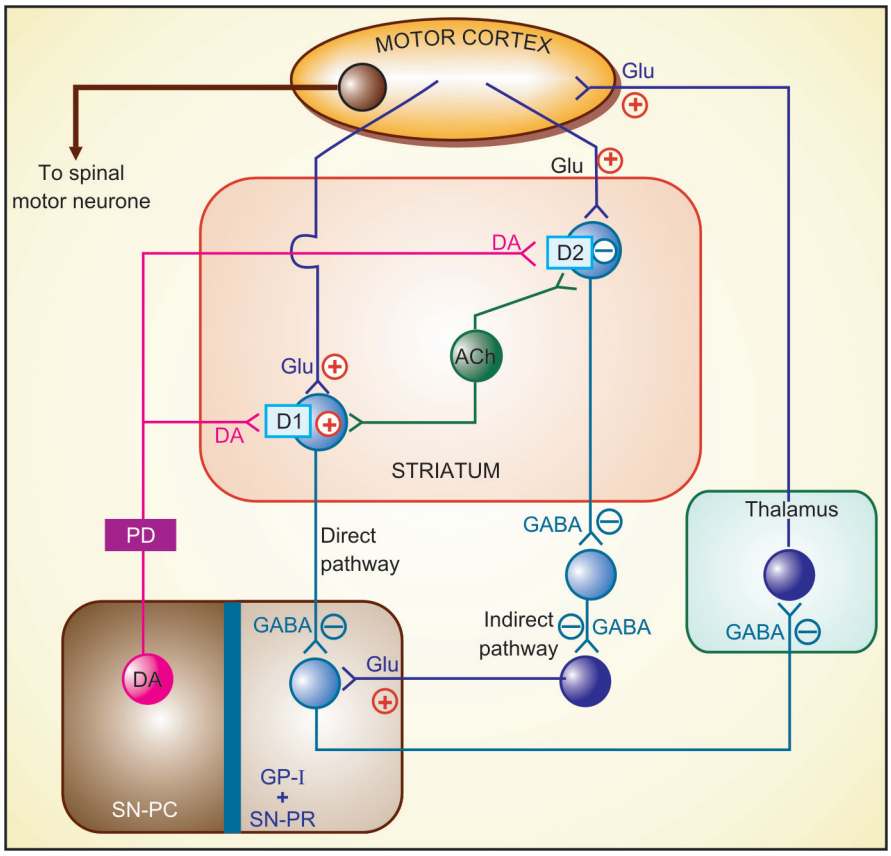


Fig. 31.1: Simplified scheme of side loop circuits in the basal ganglia that provide modulatory input to the motor cortex. The striatal GABAergic neurones receive side-loop excitatory glutamatergic (Glu) input from the motor cortex and modulatory dopaminergic (DA) projections from the substantia nigra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

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

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

PHARMACOKINETICS

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

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

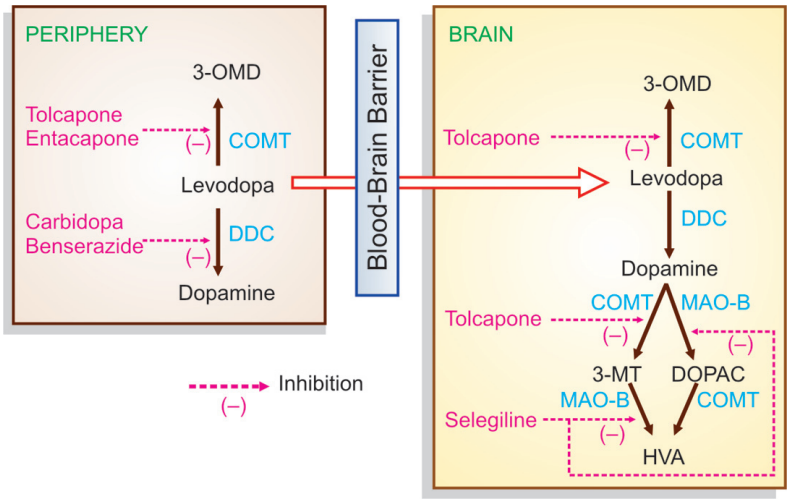


Fig. 31.2: Metabolic pathways of levodopa in the periphery and the brain.
3-OMD—3-O-methyldopa; COMT—Catechol-O-methyl transferase; MAO—monoamine oxidase; 3-MT—3-methoxytyramine; DOPAC—3,4 dihydroxy phenylacetic acid; HVA—Homovanillic acid (3-methoxy-4-hydroxy phenylacetic acid), DDC—Dopa decarboxylase

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

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

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

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

ADVERSE EFFECTS

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

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

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

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

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

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

5. *Alteration in taste sensation*

After prolonged therapy

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

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

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

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

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

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

LEVOPA, BIDOPAL 0.5 g tab.

Interactions

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

PERIPHERAL DECARBOXYLASE INHIBITORS

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

Benefits of the combination are—

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

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

Problems not resolved or accentuated are—

1. Involuntary movements
2. Behavioural abnormalities

} may even be more pronounced and appear earlier.

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

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

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

Preparations and dose

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

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

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

DOPAMINERGIC AGONISTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MAO-B INHIBITOR

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

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

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

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

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

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

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

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

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

COMT INHIBITORS

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

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

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

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

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

GLUTAMATE (NMDA receptor) ANTAGONIST (Dopamine facilitator)

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

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

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

Side effects are accentuated when it is combined with anticholinergics.

CENTRAL ANTICHOLINERGICS

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

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

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

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

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

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

Some general points

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

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

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

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

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

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

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

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

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

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

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

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

☞ PROBLEM DIRECTED STUDY

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

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

(see Appendix-1 for solution)

Chapter 32 Drugs Used in Mental Illness: Antipsychotic and Antimanic Drugs

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

During the past 60 years psychiatric treatment has witnessed major changes due to advent of drugs which can have specific salutary effect in mental illnesses. The trend has turned from custodial care towards restoring the individual patient to his place in the community. All that could be done before 1952 was to dope and quieten agitated and violent patients. The introduction of *chlorpromazine* (CPZ) in that year has transformed the lives of schizophrenics; most can now be rehabilitated to productive life. *Reserpine* was discovered soon after. Though it is a powerful pharmacological tool to study monoaminergic systems in brain and periphery, its clinical use in psychiatry lasted only few years. Next came the *tricyclic* and *MAO inhibitor antidepressants* in 1957–58 and covered another group of psychiatric patients. Many novel and atypical antipsychotics, selective serotonin reuptake inhibitors (SSRIs) and other antidepressants have been introduced since the 1980s. Meprobamate (1954) aroused the hope that anxiety could be tackled without producing marked sedation. This goal has been realised more completely by the development of *Chlordiazepoxide* (1957) and other *benzodiazepines* in the 1960s. *Buspirone* is a significant later addition.

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

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

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

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

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

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

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

(iii) *Mood (affective) disorders* The primary symptom is change in mood state; may manifest as:

Mania—elation or irritable mood, reduced sleep, hyperactivity, uncontrollable thought and speech, may be associated with reckless or violent behaviour, or

Depression—sadness, loss of interest and pleasure, worthlessness, guilt, physical and mental slowing, melancholia, self-destructive ideation.

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

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

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

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

(c) *Obsessive-compulsive disorder* Limited abnormality of thought or behaviour; recurrent intrusive thoughts or ritual-like behaviours which the patient realizes are abnormal or stupid, but is not able to overcome even on voluntary effort. The obsessions generate considerable anxiety and distress.
(d) *Reactive depression* due to physical illness, loss, blow to self-esteem or bereavement, but is excessive or disproportionate.
(e) *Post-traumatic stress disorder* Varied symptoms following distressing experiences like war, riots, earthquakes, etc.
(f) *Hysterical* Dramatic symptoms resembling serious physical illness, but situational, and always in the presence of others; the patient does not feign but actually undergoes the symptoms, though the basis is only psychic and not physical.

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

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

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

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

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

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

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

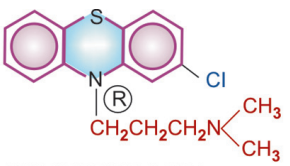
Tranquillizer It is an old term meaning "a drug which reduces mental tension and produces calmness without inducing sleep or depressing mental faculties." This term was used to describe the effects of reserpine or chlorpromazine. However, it has been interpreted differently by different people; some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

ANTIPSYCHOTIC DRUGS (Neuroleptics)

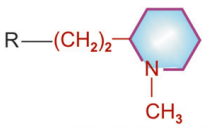
These are drugs having a salutary therapeutic effect in psychoses.

CLASSIFICATION

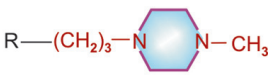
1. *Phenothiazines*
   - *Aliphatic side chain*: Chlorpromazine, Triflupromazine
   - *Piperidine side chain*: Thioridazine
   - *Piperazine side chain*: Trifluoperazine, Fluphenazine
2. *Butyrophenones*: Haloperidol, Trifluperidol, Penfluridol
3. *Thioxanthenes*: Flupenthixol
4. *Other heterocyclics*: Pimozide, Loxapine
5. *Atypical antipsychotics*: Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole, Ziprasidone, Amisulpiride, Zotepine



CHLORPROMAZINE
(aliphatic side chain)



THIORIDAZINE
(piperidine side chain)



TRIFLUOPERAZINE
(piperazine side chain)

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

PHARMACOLOGICAL ACTIONS

1. CNS Effects differ in normal and psychotic individuals.

In normal individuals CPZ produces indifference to surroundings, paucity of thought, psychomotor slowing, emotional quietening, reduction in initiative and tendency to go off to sleep from which the subject is easily arousable. Spontaneous movements are minimized but slurring of speech, ataxia or motor incoordination does not occur. This has been referred to as the 'neuroleptic syndrome' and is quite different from the sedative action of barbiturates and other similar drugs. Accordingly the typical antipsychotics which exert CPZ-like action, have potent dopamine D2 receptor blocking property and produce extrapyramidal motor side effects. They are also called *'Neuroleptic drugs'*. The effects are perceived as 'neutral' or 'unpleasant' by most normal individuals.

In a psychotic CPZ reduces irrational behaviour, agitation and aggressiveness and controls psychotic symptomatology. Disturbed thought and behaviour are gradually normalized, anxiety is relieved. Hyperactivity, hallucinations and delusions are suppressed.

All phenothiazines, thioxanthenes and butyrophenones have the same antipsychotic efficacy, but potency differs in terms of equieffective doses. The aliphatic and piperidine side chain phenothiazines (CPZ, triflupromazine, thioridazine) have low potency, produce more sedation and cause greater potentiation of hypnotics, opioids, etc. The sedative effect is produced promptly, while antipsychotic effect takes weeks to develop. Moreover, tolerance develops to the sedative but not to the antipsychotic effect. Thus, the two appear to be independent actions.

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

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

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

Mechanism of action All antipsychotics (except clozapine-like atypical ones) have potent dopamine D2 receptor blocking action. Antipsychotic potency has shown good correlation with their capacity to bind to D2 receptor. Phenothiazines and thioxanthenes also block D1, D3 and D4 receptors, but there is no correlation of such blockade with their antipsychotic potency. Blockade of dopaminergic projections to the temporal and prefrontal areas constituting the 'limbic system' and in mesocortical areas is probably responsible for the antipsychotic action. This contention is

strengthened by the observation that drugs which increase DA activity (amphetamines, levodopa, bromocriptine) induce or exacerbate schizophrenia. A *'dopamine theory of schizophrenia'* has been propounded envisaging DA overactivity in limbic area to be responsible for the disorder. Accordingly, blockade of DA overactivity in limbic area produces the antipsychotic effect, while that in basal ganglia produces the parkinsonian adverse effects. The delayed onset of these effects may be explained by initial adaptive increase in the firing of DA neurones and DA turnover, which gradually subsides and a state of persistent inactivation supervenes as the drug is continued, corresponding to the emergence of the therapeutic effect as well as the extrapyramidal side effects.

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

The DA hypothesis fails to explain the antipsychotic activity of clozapine and other atypical antipsychotics which have weak D2 blocking action. However, they have significant 5-HT_2 and α_1 adrenergic blocking action, and some are relatively selective for D4 receptors. Thus, antipsychotic property may depend on a specific profile of action of the drugs on several neurotransmitter receptors. Positron emission tomography (PET) studies of D2 and other receptor occupancy in brains of antipsychotic drug treated patients have strengthened this concept.

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

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

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

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

thioridazine > CPZ > triflupromazine > trifluoperazine = haloperidol.

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

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

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

High doses of CPZ directly depress the heart and produce ECG changes (Q-T prolongation and suppression of T wave). CPZ exerts some antiarrhythmic action, probably due to membrane stabilization. Arrhythmia may occur in overdose, especially with thioridazine.

5. Skeletal muscle Neuroleptics have no direct effect on muscle fibres or neuromuscular transmission. However, they reduce certain types of spasticity: the site of action being in the basal ganglia or medulla oblongata. Spinal reflexes are not affected.

6. Endocrine Neuroleptics consistently increase prolactin release by blocking the inhibitory action of DA on pituitary lactotropes. This may result in galactorrhoea and gynaecomastia.

They reduce gonadotropin secretion, but amenorrhoea and infertility occur only occasionally. ACTH release in response to stress is diminished. As a result corticosteroid levels fail to increase under such circumstances. Release of GH is also reduced but this is not sufficient to cause growth retardation in children or to be beneficial in acromegaly. Decreased release of ADH may result in an increase in urine volume. A direct action on kidney tubules may add to it, but Na^+ excretion is not affected.

Though in general, antipsychotic drugs do not affect blood sugar level, CPZ and few others have the potential to impair glucose tolerance or aggravate diabetes, as well as elevate serum triglycerides. This is often associated with weight gain, which may be a causative factor along with accentuation of insulin resistance.

Tolerance and dependence

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

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

PHARMACOKINETICS

Oral absorption of CPZ is somewhat unpredictable and bioavailability is low. More consistent effects are produced after i.m. or i.v. administration. It is highly bound to plasma as well as tissue proteins; brain concentration is higher than plasma concentration. Volume of distribution, therefore, is large (20 L/kg). It is metabolized in liver, mainly by CYP 2D6 into a number of metabolites.

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

The broad features of pharmacokinetics of other neuroleptics are similar.

DISTINCTIVE FEATURES OF NEUROLEPTICS

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

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

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

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

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

ANATENSOL DECANOATE, PROLINATE 25 mg/ml inj.

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

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

4. *Haloperidol* It is a potent antipsychotic with pharmacological profile resembling that of piperazine substituted phenothiazines. It produces few autonomic effects, is less epileptogenic, does not cause weight gain, jaundice is rare. It is the preferred drug for acute schizophrenia, Huntington's disease and Gilles de la Tourette's syndrome. It is metabolised by CYP3A4 and 2D6 both. Elimination t½ averages 24 hours.

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

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

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

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

8. *Pimozide* It is a selective DA antagonist with little α adrenergic or cholinergic blocking activity. Because of long duration of action (several days; elimination t½ 48–60 hours) after a single oral dose, it is considered good for maintenance therapy but not when psychomotor agitation is prominent. Incidence of dystonic reactions is low, but it tends to prolong myocardial APD and carries risk of arrhythmias. It has been particularly used in Gilles de la Tourett's syndrome and in ticks.

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

ATYPICAL (Second generation) ANTIPSYCHOTICS

These are newer (second generation) antipsychotics that have weak D2 blocking but potent 5-HT_2 antagonistic activity. Extrapyramidal side effects are minimal, and they tend to improve the impaired cognitive function in psychotics.

1. *Clozapine* It is the first atypical antipsychotic; pharmacologically distinct from CPZ and related drugs in that it has only weak D2 blocking action, produces few/no extrapyramidal symptoms; tardive dyskinesia is rare and prolactin level does not rise. Both positive and negative symptoms of schizophrenia are improved and clozapine is the most effective drug in refractory schizophrenia, i.e. patients not responding to typical neuroleptics may respond to it. The differing pharmacological profile may be due to its relative selectivity for D4 receptors (which are sparse in basal ganglia) and additional 5-HT_2 as well as α adrenergic blockade. It is quite sedating, moderately potent anticholinergic, but paradoxically induces hypersalivation. Significant H_1 blocking property is present.

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

Clozapine is used as a reserve drug in refractory schizophrenia.

2. *Risperidone* Another compound whose antipsychotic activity has been ascribed to a combination of D2 + 5-HT_2 receptor blockade. In addition it has high affinity for α_1, α_2 and H_1 receptors: blockade of these may contribute to efficacy as well as side effects like postural hypotension. However, BP can rise if it is used with a SSRI. Risperidone is more potent D2 blocker than clozapine; extrapyramidal side effects are less only at low doses (<6 mg/day). Prolactin levels rise disproportionately during risperidone therapy, but it is less epileptogenic than clozapine, though frequently causes agitation. Weight gain and incidence of new-onset

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

3. *Olanzapine* This atypical antipsychotic; resembles clozapine in blocking multiple monoaminergic (D2, 5-HT_2, α_1, α_2) as well as muscarinic and H_1 receptors. Both positive and negative symptoms of schizophrenia tend to benefit. A broader spectrum of efficacy covering schizo-affective disorders has been demonstrated, and it is approved for use in mania.

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

4. *Quetiapine* This new short-acting (t½ 6 hours) atypical antipsychotic requires twice daily dosing. It blocks 5-HT_{1A}, 5-HT_2, D2, α_1, α_2 and H_1 receptors in the brain, but D2 blocking activity is low: extrapyramidal and hyperprolactinaemic side effects are minimal. However, it is quite sedating (sleepiness is a common side effect), and major portion of daily dose is given at night. Postural hypotension can occur, especially during dose titration. Urinary retention/incontinence are reported in few patients. Weight gain and rise in blood sugar are moderate, and it causes some degree of QTc prolongation, risking arrhythmia only at high doses. Quetiapine has not been found to benefit negative symptoms of schizophrenia, but there is evidence of efficacy in acute mania as well as in bipolar depression, because of which it is frequently selected for maintenance therapy. It is metabolized mainly by CYP3A4; can interact with macrolides, antifungals, anticonvulsants, etc.

5. *Aripiprazole* This atypical antipsychotic is unique in being a partial agonist at D2 and 5-HT_{1A} receptor, but antagonist at 5-HT_2 receptor. The high affinity but low intrinsic activity of aripiprazole for D2 receptor impedes dopaminergic transmission by occupying a large fraction of D2 receptors but activating them minimally. It is not sedating, may even cause insomnia. Extrapyramidal side effects, hyperprolactinaemia and hypotension are not significant. Little tendency to weight gain and rise in blood sugar has been noted. A moderate prolongation of Q-Tc interval occurs at higher doses. Frequent side effects are nausea, dyspepsia, constipation and light-headedness, but not antimuscarinic effects.

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

6. *Ziprasidone* Another atypical antipsychotic with combined D2 + 5-$HT_{2A/2C}$ + H_1 + α_1 blocking activity. Antagonistic action at 5-HT_{1D} + agonistic activity at 5-HT_{1A} receptors along with moderately potent inhibition of 5-HT and NA reuptake indicates some anxiolytic and antidepressant property as well. Like other atypical antipsychotics, ziprasidone has low propensity to cause extrapyramidal side effects or hyperprolactinaemia. It is mildly sedating, causes modest hypotension and little weight gain or blood sugar elevation. Nausea and vomiting are the common side effects but it lacks antimuscarinic effects. More importantly, a dose-related prolongation of Q-T interval occurs imparting potential to induce serious cardiac arrhythmias, especially in the presence of predisposing factors/drugs.

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

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

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

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

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

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

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

Dose: Initially 25 mg TDS; increase upto 100 mg TDS.

ZOLEPTIL, NIPOLEPT 25, 50 mg tabs.

ADVERSE EFFECTS

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

I. Based on pharmacological actions (dose related)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

II. Hypersensitivity reactions These are not dose related.

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

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

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

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

INTERACTIONS

1. Neuroleptics potentiate all CNS depressants—hypnotics, anxiolytics, alcohol, opioids and antihistaminics. Overdose symptoms may occur.
2. Neuroleptics block the actions of levodopa and direct DA agonists in parkinsonism.
3. Antihypertensive action of clonidine and methyldopa is reduced, probably due to central α_2 adrenergic blockade.
4. Phenothiazines and others are poor enzyme inducers—no significant pharmacokinetic interactions occur. Enzyme inducers (barbiturates, anticonvulsants) can reduce blood levels of neuroleptics.

USES

1. Psychoses

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

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

- Agitated, combative and violent—haloperidol, quetiapine, CPZ, thioridazine.

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

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

Mania Antipsychotics are required in high doses for rapid control of acute mania, and mania patients tolerate them very well. CPZ or haloperidol may be given i.m.—act in 1–3 days. Lithium or valproate may be started simultaneously or after the acute phase. Such combination therapy is more effective. The antipsychotic may be continued for months or may be withdrawn gradually after 1–3 weeks when lithium has taken effect. Now, oral therapy with one of the atypical antipsychotics olanzapine/risperidone/aripiprazole/quetiapine is mostly used to avoid extrapyramidal side effects, especially for cases not requiring urgent control.

Organic brain syndromes Antipsychotic drugs have limited efficacy in dementia and delirium associated with psychotic features. They may be used in low doses on a short-term basis. One of the potent drugs is preferred to avoid mental confusion, hypotension and precipitation of seizures. Moreover, low potency drugs (CPZ, thioridazine) have significant antimuscarinic property which may worsen delirium and dementia. Haloperidol, risperidone, ripiprazole or ziprasidone are mostly selected.

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

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

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

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

3. As antiemetic The typical neuroleptics are potent antiemetics. They control a wide range of drug and disease induced vomiting at doses

much lower than those needed in psychosis. However, they should not be given unless the cause of vomiting has been identified. Though effective in morning sickness, they should not be used for this condition. They are ineffective in motion sickness: probably because dopaminergic pathway through the CTZ is not involved. With the availability of 5-HT_3 antagonists and other antiemetics, use of neuroleptics for control of vomiting has declined.

4. Other uses

(a) *To potentiate hypnotics, analgesics and anaesthetics:* such use is rarely justified now.

(b) *Intractable hiccough* may respond to parenteral CPZ.

(c) *Tetanus* CPZ is an alternative drug to relieve skeletal muscle spasm.

(d) *Alcoholic hallucinosis, Huntington's disease and Gilles de la Tourette's syndrome* are rare indications.

ANTIMANIC AND MOOD STABILIZING DRUGS (Drugs for bipolar disorder)

LITHIUM CARBONATE

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

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

Actions and mechanism

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

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

(a) Li^+ partly replaces body Na^+ and is nearly equally distributed inside and outside the cells (contrast Na^+ and K^+ which are unequally distributed); this may affect ionic fluxes across brain cells or modify the property of cellular membranes. However, relative to Na^+ and K^+ concentration, the concentration of Li^+ associated with therapeutic effect is very low.

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

(c) The above hypothesis cannot explain why Li^+ has no effect on people not suffering from mania. An attractive hypothesis has been put forward based on the finding that lithium in therapeutic concentration range inhibits hydrolysis of inositol-1-phosphate by inositol monophosphatase. As a result, the supply of free inositol for regeneration of membrane phosphatidylinositides, which are the source of IP_3 and DAG, is reduced (Fig. 32.1). The hyperactive neurones involved in the manic state may be preferentially affected, because supply of inositol from extracellular sources is meagre. Thus, lithium may ignore normally operating receptors, but 'search out' and selectively, though indirectly, dampen signal transduction in the overactive receptors functioning through phosphatidyl inositol hydrolysis. In support of this hypothesis, it has been recently demonstrated that valproate, which has Li^+ like effect in mania and bipolar disorder, also reduces intraneuronal

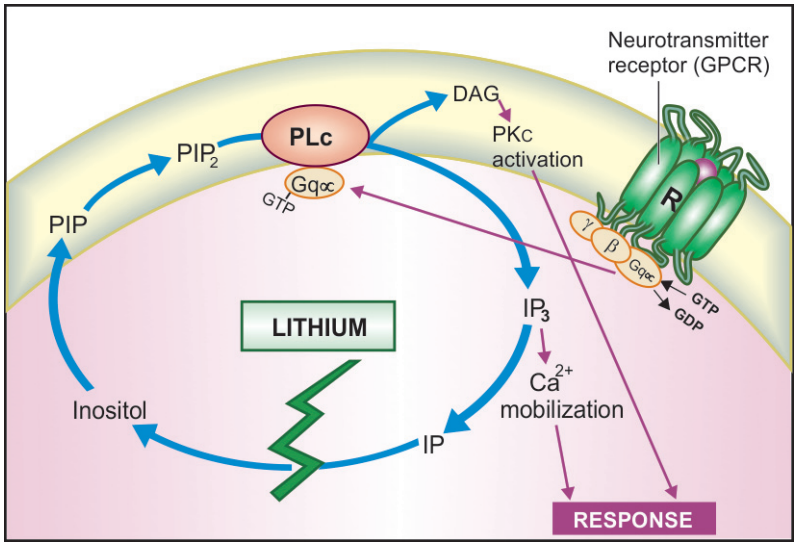


Fig. 32.1: Proposed mechanism of antimanic action of lithium
PIP—Phosphatidyl inositol phosphate; PIP_2—Phosphatidyl inositol bisphosphate; IP_3—Inositol trisphosphate; IP—Inositol-1-phosphate; PLc—Phospholipase C; DAG—Diacylglycerol; PKc—Protein Kinase C; Gq—Coupling Gq protein; R—Neurotransmitter receptor

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

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

2. *Other actions* Lithium inhibits the action of ADH on distal tubules in the kidney and causes a diabetes insipidus like state.

An insulin-like action on glucose metabolism is exerted.

Leukocyte count is increased by lithium therapy.

Lithium inhibits release of thyroid hormones resulting in feedback stimulation of thyroid through pituitary. Majority of Li^+ treated patients remain in a state of compensated euthyroidism, but few get decompensated and become clinically hypothyroid.

Pharmacokinetics and control of therapy

Lithium is slowly but well absorbed orally and is neither protein bound nor metabolized. It first distributes in extracellular water, then gradually enters cells and penetrates into brain, ultimately attaining a rather uniform distribution in total body water. The CSF concentration of Li^+ is about half of plasma concentration. Apparent volume of distribution at steady-state averages 0.8 L/kg.

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

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

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

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

Adverse effects Side effects are common, but are mostly tolerable. Toxicity occurs at levels only marginally higher than therapeutic levels.

1. Nausea, vomiting and mild diarrhoea occur initially, can be minimized by starting at lower doses.
2. Thirst and polyuria are experienced by most, some fluid retention may occur initially, but clears later.
3. Fine tremors are noted even at therapeutic concentrations.
4. CNS toxicity manifests as plasma concentration rises producing coarse tremors, giddiness, ataxia, motor incoordination, nystagmus, mental confusion, slurred speech, hyper-reflexia. Overdose symptoms are regularly seen at plasma concentration above 2 mEq/L. In acute intoxication these symptoms progress to muscle twitchings, drowsiness, delirium, coma and convulsions. Vomiting, severe diarrhoea, albuminuria, hypotension and cardiac arrhythmias are the other features.

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

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

Lithium can cause dermatitis and worsen acne.

Interactions

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

Use

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

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

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

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

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

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

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

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

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

ALTERNATIVES TO LITHIUM

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

1. *Sodium valproate* A reduction in manic relapses is noted when valproate is used in bipolar disorder. It is now a first line treatment of acute mania in which high dose valproate acts faster than lithium and is an alternative to antipsychotic ± benzodiazepine. It can be useful in those not responding to lithium or not tolerating it. Patients with rapid cycling pattern may particularly benefit from valproate therapy. A combination of lithium and valproate may succeed in cases resistant to monotherapy with either drug. Valproate has a favourable tolerability profile, and now its use as prophylactic in bipolar disorder has exceeded that of lithium. Combination of valproate with an atypical antipsychotic has high efficacy in acute mania. *Divalproex*, a compound of valproate, is more commonly used due to better gastric tolerance. Dosage guidelines are the same as for epilepsy.

2. *Carbamazepine* Soon after its introduction as antiepileptic, carbamazepine (CBZ) was found to prolong remission in bipolar disorder. Its efficacy in mania and bipolar disorder has now been confirmed. However, it is less popular than valproate as an alternative to lithium. Carbamazepine is less effective than lithium or valproate in acute mania. Moreover, acute mania requires rapidly acting drug, while effective doses of carbamazepine have to be gradually built up. Initiation of therapy with high doses needed for efficacy produce neurotoxicity and are poorly tolerated. Compared to lithium and valproate, efficacy of carbamazepine for long-term prophylaxis of bipolar disorder and suicides is less well established. Nevertheless, it is a valuable alternative/adjunct to lithium. The dose and effective plasma concentration range is the same as for treatment of epilepsy.

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

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

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

HALLUCINOGENS (Psychotomimetics, Psychedelics, Psychodysleptics, Psychotogens)

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

INDOLE AMINES

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

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

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

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

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

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

PHENYLALKYL AMINES

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

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

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

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

ARYLCYCLOHEXYL AMINES

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

CANNABINOIDS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

☞ PROBLEM DIRECTED STUDY

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

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

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

(see Appendix-1 for solution)

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

Major depression and mania are two extremes of *affective disorders* which refer to a pathological change in mood state. *Major depression* is characterized by symptoms like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation or agitation, change in appetite and/or sleep, melancholia, suicidal thoughts, etc. It may be a *unipolar* or a *bipolar disorder* in which cycles of mood swings from mania to depression occur over time. The mood change may have a psychotic basis with delusional thinking or occur in isolation and induce anxiety. On the other hand, pathological anxiety may lead to depression. Anxiety and depression are the leading psychiatric disorders now.

ANTIDEPRESSANTS

These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other, and many of them have other associated properties. Over the past three decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines, and on pre/post-junctional aminergic/cholinergic receptors have become available so that a cogent classification is difficult. The following working classification may be adopted.

CLASSIFICATION

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

II. *Tricyclic antidepressants (TCAs)*
A. *NA + 5-HT reuptake inhibitors*
Imipramine, Amitriptyline, Trimipramine, Doxepin, Dothiepin, Clomipramine
B. *Predominantly NA reuptake inhibitors*
Desipramine, Nortriptyline, Amoxapine, Reboxetine

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

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

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

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

MAO INHIBITORS

MAO is a mitochondrial enzyme involved in the oxidative deamination of biogenic amines (Adr, NA, DA, 5-HT). Two isoenzyme forms of MAO have been identified.

MAO-A: Preferentially deaminates 5-HT and NA, and is inhibited by clorgyline, moclobemide.

MAO-B: Preferentially deaminates phenylethylamine and is inhibited by selegiline.

Dopamine is degraded equally by both isoenzymes.

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

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

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

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

Nonselective MAO Inhibitors

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

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

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

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

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

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

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

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

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

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

Reversible inhibitors of MAO-A (RIMAs)

Moclobemide It is a reversible and selective MAO-A inhibitor with short duration of action; full MAO activity is restored within 1–2 days of stopping the drug. Because of competitive enzyme inhibition, tyramine is able to displace it from the enzyme, so that potentiation of pressor response to ingested amines is minor, and dietary restrictions are not required. Clinical trials have shown moclobemide to be an efficacious antidepressant, comparable to TCAs, except in severe cases. It lacks the anticholinergic, sedative, cognitive, psychomotor and cardiovascular adverse effects of typical TCAs and is safer in overdose. This makes it a particularly good option in elderly patients and in those with heart disease.

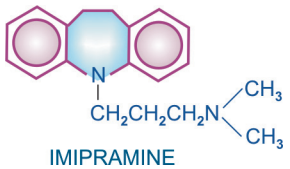
Dose: 150 mg BD–TDS (max 600 mg/day)
RIMAREX, TRIMA 150, 300 mg tabs.

Adverse effects are nausea, dizziness, headache, insomnia, rarely excitement and liver damage. Chances of interaction with other drugs and alcohol are remote, but caution is advised while coprescribing pethidine, SSRIs and TCAs.

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

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Imipramine, an analogue of CPZ was found during clinical trials (1958) to selectively benefit depressed but not agitated psychotics. In contrast to CPZ, it inhibited NA and 5-HT



IMIPRAMINE

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

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

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

PHARMACOLOGICAL ACTIONS

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

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

1. CNS Effects differ in normal individuals and in the depressed.

In normal individuals It induces a peculiar clumsy feeling, tiredness, light-headedness, sleepiness, difficulty in concentrating and thinking, unsteady gait. These effects tend to provoke anxiety. There is no mood elevation or euphoria; effects are rather unpleasant and may become more so on repeated administration.

In depressed patients Little acute effects are produced, except sedation (in the case of drugs which have sedative property). After 2–3 weeks of continuous treatment, the mood is gradually elevated, patients become more communicative and start taking interest in self and surroundings. Thus, TCAs are not euphorients but only antidepressants. In depressed patients who have preponderance of REM sleep, this phase is suppressed and awakenings during night are reduced. The EEG effects of low doses are similar to hypnotics but high doses cause desynchronization. Sedative property varies among different compounds (*see* Table 33.1). The more sedative ones are suitable for depressed patients showing anxiety and agitation. The less sedative or stimulant ones are better for withdrawn and retarded patients.

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

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

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

Reuptake inhibition results in increased concentration of the amines in the synaptic cleft in both CNS and periphery. Tentative conclusions drawn are:

- Inhibition of DA uptake correlates with stimulant action; but is not primarily involved in antidepressant action.
- Inhibition of NA and 5-HT uptake is associated with antidepressant action.

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

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

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

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

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

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

3. CVS Effects on cardiovascular function are prominent, occur at therapeutic concentrations and may be dangerous in overdose.

Tachycardia: due to anticholinergic and NA potentiating actions.

Postural hypotension: due to inhibition of cardiovascular reflexes and α_1 blockade.

ECG changes and cardiac arrhythmias: T wave suppression or inversion is the most consistent change. Arrhythmias occur in overdose mainly due to interference with intraventricular conduction. The NA potentiating + ACh blocking actions along with direct myocardial depression compound the proarrhythmic potential. Older patients are more susceptible. The SSRIs, SNRIs and atypical antidepressants are safer in this regard.

Tolerance and dependence

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

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

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

PHARMACOKINETICS

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

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

TABLE 33.1 **Comparative properties and preparations of tricyclic and related antidepressants**

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

below and above this range, beneficial effects are suboptimal.

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

ADVERSE EFFECTS

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

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

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

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

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

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

INTERACTIONS

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

5. *Phenobarbitone* competitively inhibits as well as induces imipramine metabolism. Carbamazepine and other enzyme inducers enhance metabolism of TCAs.
6. SSRIs inhibit metabolism of several drugs (*see* later) including TCAs—dangerous toxicity can occur if the two are given concurrently.
7. By their anticholinergic property, TCAs delay gastric emptying and retard their own as well as other drug's absorption. However, *digoxin* and *tetracyclines* may be more completely absorbed. When used together, the anticholinergic action of neuroleptics and TCAs may add up.
8. *MAO inhibitors*—dangerous hypertensive crisis with excitement and hallucinations has occurred when given with TCAs.

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

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

Dose: 4 mg BD or 8 mg OD.

NAREBOX 4, 8 mg tab.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

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

- Frequent anticholinergic, cardiovascular and neurological side effects.
- Relatively low safety margin. They are hazardous in overdose; fatalities are common.
- Lag time of 2–4 weeks before antidepressant action manifests.
- Significant number of patients respond incompletely and some do not respond.

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

The relative safety and better acceptability of SSRIs has made them 1st line drugs in depression and allowed their extensive use in anxiety, phobias, OCD and related disorders. The SSRIs produce little or no sedation, do not interfere with cognitive and psychomotor function or produce anticholinergic side effects. They are devoid of α adrenergic blocking action—postural hypotension does not occur, making them suitable for elderly patients. They have practically no seizure precipitating propensity and do not inhibit cardiac conduction—overdose arrhythmias are not a problem. Prominent side effects are gastrointestinal; all SSRIs frequently produce nausea (due to 5-HT_3 receptor stimulation), but tolerance develops over time. Loose motions are due to 5-HT uptake blockade in the gut and activation of 5-HT receptors on enteric plexus neurones. Weight gain is not a problem with SSRIs, but they more commonly interfere with ejaculation or orgasm. A new constellation of mild side effects, *viz.* nervousness, restlessness, insomnia, anorexia, dyskinesia and headache is associated with them, but patient acceptability is good. Increased incidence of

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

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

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

Fluoxetine A bicyclic compound, is the first SSRI to be introduced, and the longest acting. Its plasma t½ is 2 days and that of its active demethylated metabolite is 7–10 days. It has been approved for use in children 7 years or older for depression and OCD on the basis of similar efficacy and side effect profile as in adults, but should be given to children only when psychotherapy fails. Agitation and dermatological reactions are more frequent than other SSRIs. Because of slower onset of antidepressant effect, it is considered less suitable for patients needing rapid effect, but is more appropriate for poorly compliant patients. Its stimulant effect could worsen patients showing agitation.

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

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

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

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

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

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

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

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

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

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

SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS (SNRIs)

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

2. Duloxetine A newer SNRI similar to venlafaxine. It is neither sedative, nor anticholinergic, nor antihistaminic, nor α blocker. Side effects, including g.i. and sexual problems are milder, but some agitation, insomnia and rise in BP can occur. Antidepressant efficacy is comparable to TCAs. Duloxetine is also indicated in panic attacks, diabetic neuropathic pain, fibromyalgia and stress urinary incontinence in women (because it increases urethral tone).

ATYPICAL ANTIDEPRESSANTS

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

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

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

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

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

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

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

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

Dose: 100 mg BD at breakfast and lunch.

SURVECTOR 100 mg tab.

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

USES

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

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

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

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

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

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

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

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

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

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

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

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

ANTIANXIETY DRUGS

Anxiety It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat. Some degree of anxiety is a part of normal life. Treatment is needed when it is disproportionate to the situation and excessive. Some psychotics and depressed patients also exhibit pathological anxiety.

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

Antianxiety drugs These are an ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of anxiety, produce a restful state of mind without interfering with normal mental or physical functions. The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They:

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

CLASSIFICATION

1. *Benzodiazepines*	Diazepam Chlordiazepoxide Oxazepam Lorazepam, Alprazolam
2. *Azapirones*	Buspirone, Gepirone, Ispapirone
3. *Sedative antihistaminic*	Hydroxyzine
4. β *blocker*	Propranolol

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

BENZODIAZEPINES

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

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

At antianxiety doses, cardiovascular and respiratory depression is minor.

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

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

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

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

Adverse effects of BZDs noted in their use as hypnotics are described in Ch. 29. *Side effects* that occur in their use to relieve anxiety are—sedation, light-headedness, psychomotor and cognitive impairment, confusional state (especially in the elderly), increased appetite and weight gain, alterations in sexual function. Rashes are uncommon. Some women fail to ovulate while on regular use of BZDs. The major constraint in their long-term use for anxiety disorders is their potential to impair mental functions and to produce dependence.

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

1. Chlordiazepoxide It was the first BZD to be used clinically. Oral absorption is slow. A smooth long lasting effect is produced. It is preferred in chronic anxiety states. Chlordiazepoxide is often combined with other drugs in psychosomatic disorders, and has been the commonest BZD used to cover alcohol withdrawal. Its t½ is 6–12 hours, but active metabolites are produced which extend the duration of action. Its anticonvulsant action is weak.

Daily dose: 25–100 mg; LIBRIUM 10, 25 mg tabs; EQUILIBRIUM 10 mg tab.

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

Daily dose: 5–30 mg; VALIUM, PLACIDOX 2, 5, 10 mg tabs; CALMPOSE 5, 10 mg tab, 2 mg/5 ml Syr.

3. Oxazepam It is slowly absorbed; being relatively polar, its penetration in brain is also slow. The plasma t½ is about 10 hours. It is metabolized only by glucuronide conjugation, therefore no active metabolite is produced. Duration of action is relatively shorter making it preferable for the elderly and in those with liver disease. It has been used mainly in short lasting anxiety states.

Daily dose: 30–60 mg in 2–3 divided portions; SEREPAX 15, 30 mg tab.

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

Daily dose: 1–6 mg; LARPOSE, ATIVAN 1, 2 mg tab. CALMESE 1, 2 mg tabs, 4 mg/2 ml inj.

5. Alprazolam A high potency anxiolytic BZD which in addition has some mood elevating action in mild depression. As such, it is particularly useful in anxiety associated with depression. Good response has been obtained in panic disorders with severe anxiety and autonomic symptoms. Its plasma t½ is about 12 hours, but an active metabolite is produced. Alprazolam is also used as hypnotic. When administered daily as anxiolytic, some patients experience anxiety in between doses, which may be obviated by employing sustained release tablet. Withdrawal symptoms may be more marked on discontinuation than with other BZDs.

Dose: 0.25–1.0 mg TDS; upto 6 mg/day in panic disorder; ALPRAX 0.25, 0.5, 1.0 mg tabs., 0.5, 1.0, 1.5 mg SR tabs; ALZOLAM 0.25, 0.5, 1.0 mg tabs; 1.5 mg SR tab, ALPROCONTIN 0.5, 1.0, 1.5 mg CR tabs. RESTYL 0.25, 0.5, 1.0 mg tabs, RESTYL-SR 0.5, 1.0, 1.5 mg SR tabs.

OTHER ANTIANXIETY DRUGS

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

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

Buspirone relieves mild-to-moderate generalized anxiety, but is ineffective in severe cases, in those showing panic reaction and in OCD. The therapeutic effect develops slowly; maximum benefit may be delayed up to 2 weeks. The mechanism of anxiolytic action is not clearly known, but may be dependent on its selective partial agonistic action on 5-HT_{1A} receptors. By stimulating presynaptic 5-HT_{1A} autoreceptors, it reduces the activity of dorsal raphe serotonergic neurones. Antagonistic action at certain postsynaptic 5-HT_{1A} receptors has also been demonstrated. After chronic treatment, adaptive reduction in cortical 5-HT_2 receptors may occur. Buspirone has weak dopamine D2 blocking action but no antipsychotic or extrapyramidal effects. A mild mood elevating action has been noted occasionally, which may be due to facilitation of central noradrenergic system.

Buspirone is rapidly absorbed; undergoes extensive first pass metabolism; (bioavailability <5%), one metabolite is active and excretion occurs both in urine and faeces; t½ is 2–3.5 hrs. Side effects are minor: dizziness, nausea, headache, light-headedness, rarely excitement. It may cause rise in BP in patients on MAO inhibitors, but does not potentiate CNS depressants. Though most patients on buspirone remain alert, those operating machinery/motor vehicles should be cautioned.

Dose: 5–15 mg OD–TDS:
ANXIPAR, BUSPIN, BUSCALM 5, 10 mg tab.

Hydroxyzine An H_1 antihistaminic with sedative, antiemetic, antimuscarinic and spasmolytic properties. It is claimed to have selective anxiolytic action, but the accompanying sedation is quite marked. Hydroxyzine may be used in reactive anxiety or that associated with marked autonomic symptoms. Due to antihistaminic and sedative property, it is useful in pruritus and urticaria.

Daily dose 50–200 mg;
ATARAX 10, 25 mg tab, 10 mg/5 ml syr, 25 mg/2 ml inj.

β Blockers (*see* Ch. 10)

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

TREATMENT OF ANXIETY

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

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

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

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

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

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

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

Fixed dose combination of tranquillizers with vitamins has been banned.

☞ PROBLEM DIRECTED STUDY

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

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

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

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

(see Appendix-1 for solution)

Chapter 34 Opioid Analgesics and Antagonists

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

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

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

A. Opioid/narcotic/morphine-like analgesics.
B. Nonopioid/non-narcotic/aspirin-like/antipyretic or antiinflammatory analgesics (described in Ch. 14).

OPIOID ANALGESICS

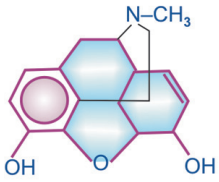
Opium A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule. It contains two types of alkaloids.

Phenanthrene derivatives

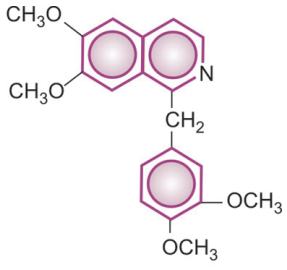
Morphine (10% in opium)
Codeine (0.5% in opium)
Thebaine (0.2% in opium), (Nonanalgesic)

Benzoisoquinoline derivatives

Papaverine (1%), Noscapine (6%) } Nonanalgesic



MORPHINE



PAPAVERINE

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

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

MORPHINE

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

PHARMACOLOGICAL ACTIONS

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

(a) *Analgesia* Morphine is a strong analgesic. Though dull, poorly localized visceral pain is

relieved better than sharply defined somatic pain; higher doses can mitigate even severe pain; degree of analgesia increasing with dose. Nociceptive pain arising from stimulation of peripheral pain receptors is relieved better than neuretic pain (such as trigeminal neuralgia) produced by inflammation of or damage to neural structures. The associated reactions to intense pain (apprehension, fear, autonomic effects) are also dampened. Suppression of pain perception is selective, without affecting other sensations or producing proportionate generalized CNS depression (contrast general anaesthetics).

Perception of pain and the emotional component (anxiety, fear, suffering, distress) induced by it are both altered so that pain is no longer as unpleasant or distressing, i.e. the patient tolerates pain better. The analgesic action of morphine has both spinal and supraspinal components. Intrathecal injection of morphine has been shown to cause segmental analgesia without affecting other modalities. It acts in the substantia gelatinosa of dorsal horn to inhibit release of excitatory transmitters (e.g. substance P) from primary afferents carrying pain impulses. The action appears to be exerted through interneurones which are involved in the 'gating' of pain impulses. Release of glutamate from primary pain afferents in the spinal cord and its postsynaptic action on dorsal horn neurones is inhibited by morphine. Action at supraspinal sites in medulla, periaqueductal gray matter, limbic and cortical areas may alter processing and interpretation of pain impulses. It also sends inhibitory impulses through descending pathways to the spinal cord. Several aminergic (5-HT, NA), GABAergic and other neuronal systems appear to be involved in the action of morphine. Simultaneous action at spinal and supraspinal sites greatly amplifies the analgesia.

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

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

(c) *Mood and subjective effects* These are prominent. Morphine has a calming effect; there is loss of apprehension, feeling of detachment, lack of initiative, limbs feel heavy and body warm, mental clouding and inability to concentrate occurs. In the absence of pain or apprehension, these are generally appreciated as unpleasant by normal people. However, patients in pain or anxiety, and especially addicts, perceive it as pleasurable floating sensation: refer it as 'high'. Rapid i.v. injection by addicts gives them a 'kick' or 'rush' which is intensely pleasurable—akin to orgasm. Thus, one has to learn to perceive the *euphoric* effect of morphine.

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

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

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

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

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

Morphine stimulates:

(a) *CTZ* Nausea and vomiting occur as side effects, especially if stomach is full and the patient stands or moves about. Thus, morphine appears to sensitize the CTZ to vestibular and other impulses. Larger doses depress vomiting centre directly: emetics should not be tried in morphine poisoning.

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

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

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

2. Neuro-endocrine Hypothalamic activation by afferent collaterals is dampened. Hypothalamic influence on pituitary is reduced. As a result FSH, LH, ACTH levels are lowered, while prolactin and GH levels are raised (these are under predominant inhibitory control). The sex hormone and cortisol levels are lowered. Some degree of tolerance may develop to this effect, but heavy abusers often suffer loss of libido, impotence, menstrual irregularities and infertility. Clinical hypocorticism is unusual. Morphine can release ADH and reduce urine volume.

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

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

4. GIT The enteric plexus neurones and g.i. mucosa are rich in opioid receptors. Morphine exerts marked effect on g.i. motility as well as on fluid dynamics across g.i. mucosa. Constipation is a prominent feature of morphine action. Several factors contribute:
(a) Action directly on intestines and in the CNS increases tone and segmentation but decreases propulsive movements. Tone of duodenum and colon may be increased to the level of spasm.
(b) Spasm of pyloric, ileocaecal and anal sphincters.
(c) Decrease in all gastrointestinal secretions due to reduction in movement of water and electrolytes from mucosa to the lumen. This is mainly a peripheral action through opioid receptors on

enteric plexus neurones, but also a central action. Absorption of fluid is increased due to stasis. (d) Central action causing inattention to defecation reflex.

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

5. Other smooth muscles

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

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

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

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

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

PHARMACOKINETICS

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

ADVERSE EFFECTS

1. *Side effects* Sedation, mental clouding, lethargy and other subjective effects which may even be dysphoric in some subjects; vomiting is occasional in recumbent patient; constipation is common and distressing. Respiratory depression, blurring of vision, urinary retention (especially in elderly male) are other side effects. BP may fall, especially in hypovolaemic patient and if he/she walks about.

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

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

4. *Acute morphine poisoning* It may be accidental, suicidal or seen in drug abusers. In the nontolerant adult, 50 mg of morphine i.m. produces serious toxicity. The human lethal dose is estimated to be about 250 mg. Manifestations are extensions of the pharmacological action.

Stupor or coma, flaccidity, shallow and occasional breathing, cyanosis, pinpoint pupil, fall in BP and shock; convulsions may be seen in few, pulmonary edema occurs at terminal stages, death is due to respiratory failure.

Treatment: consists of respiratory support (positive pressure respiration also opposes pulmonary edema formation) and maintenance of BP (i.v. fluids, vasoconstrictors). Gastric lavage should be done with pot. permanganate to remove unabsorbed drug. Lavage is indicated even when morphine has been injected. Being a basic drug it is partitioned to the acid gastric juice, ionizes there and does not diffuse back into blood.

Specific antidote: Naloxone 0.4–0.8 mg i.v. repeated every 2–3 min till respiration picks up, is the specific antagonist of choice because it acts rapidly, does not have any agonistic action and does not *per se* depress respiration (*see* p. 483). Due to short duration of action, naloxone should be repeated every 1–4 hours, according to the response.

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

Morphine produces pronounced psychological and physical dependence, its abuse liability is rated high. Recently the NMDA antagonists and nitric oxide synthase inhibitors have been found to block morphine tolerance and dependence in animals. Thus, the analgesic action of morphine can be dissociated from tolerance and dependence which contribute to its abuse. Concern about abuse has been a major limitation in the use of morphine, but appropriate medical use of morphine seldom progresses to dependence and abuse. Morphine abuse is higher among medical and paramedical personnel because they have easier access to the drug. Earlier, morphine addicts tended to be from the middle age group, but now younger individuals are also opting for it. Opium eating has been prevalent among natives in the orient.

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

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

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

PRECAUTIONS AND CONTRAINDICATIONS

Morphine is a drug of emergency, but due care has to be taken in its use.

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

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

5. Hypotensive states and hypovolaemia exaggerate fall in BP due to morphine.
6. Undiagnosed acute abdominal pain: morphine can aggravate certain conditions, e.g. diverticulitis, biliary colic, pancreatitis. Inflamed appendix may rupture. Morphine can be given after the diagnosis is established. Pentazocine, buprenorphine are less likely to aggravate biliary spasm.
7. Elderly male: chances of urinary retention are high.
8. Hypothyroidism, liver and kidney disease patients are more sensitive to morphine.
9. Unstable personalities: are liable to continue with its use and become addicted.

Interactions

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

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

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

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

CLASSIFICATION OF OPIOIDS

1. *Natural opium alkaloids:* Morphine, Codeine

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

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

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

Many others like—Levorphanol, Dextromoramide, Dipipanone, Alfentanil, Sufentanil, Remifentanil are not available in India.

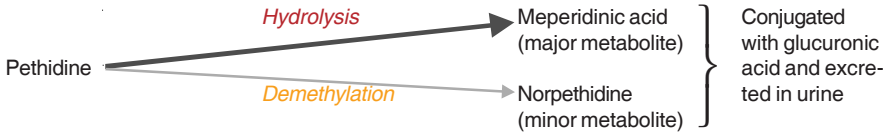
1. Codeine It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine. It is less potent than morphine (1/10th as analgesic), also less efficacious; is a partial agonist at μ opioid receptor with a low ceiling effect. The degree of analgesia is comparable to aspirin (60 mg codeine ~ 600 mg aspirin); can relieve mild to moderate pain only.

However, codeine is more selective cough suppressant (1/3rd as potent as morphine); subanalgesic doses (10–30 mg) suppress cough (*see* p. 220). Codeine has very low affinity for opioid receptors. The analgesic action has been ascribed to morphine generated by its demethylation by CYP2D6. Codeine fails to produce analgesia in subjects with polymorphic CYP2D6 who cannot demethylate codeine. However, receptors involved in the antitussive action appear to be distinct, because they bind codeine as well as morphine.

Codeine has good activity by the oral route (oral: parenteral ratio 1:2). A single oral dose acts for 4–6 hours. Constipation is a prominent side effect when it is used as analgesic. Codeine has been used to control diarrhoea (*see* Ch. 48). Other side effects are milder. The abuse liability is low. Though codeine phosphate is water soluble and can be injected, parenteral preparation is not available.

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

3. Heroin (Diamorphine, Diacetylmorphine) It is about 3 times more potent than morphine; more lipid soluble, therefore enters the brain more rapidly, but duration of action is similar. It is considered to be more euphorient (especially on i.v. injection) and highly addicting. Because of its high potency, it has been favoured in illicit drug trafficking. The sedative,



emetic and hypotensive actions are said to be less prominent. However, it has no outstanding therapeutic advantage over morphine and has been banned in most countries except U.K.

4. Pethidine (Meperidine)

Pethidine was synthesized as an atropine substitute in 1939, and has some actions like it. Though chemically unrelated to morphine, it interacts with μ opioid receptors and its actions are blocked by naloxone. Important differences in comparison to morphine are:

1. Dose to dose 1/10th in analgesic potency; however, analgesic efficacy approaches near to morphine and is greater than codeine.
2. After i.m. injection, the onset of action is more rapid but duration is shorter (2–3 hours).
3. It does not effectively suppress cough.
4. Spasmodic action on smooth muscles is less marked—miosis, constipation and urinary retention are less prominent.

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

5. It is equally sedative and euphoriant, has similar abuse potential. The degree of respiratory depression seen at equianalgesic doses is equivalent to that with morphine.
6. Tachycardia (due to antimuscarinic action) occurs instead of bradycardia.
7. It causes less histamine release and is safer in asthmatics.
8. It has local anaesthetic action: corneal anaesthesia is seen after systemic doses.
9. It is well absorbed, oral: parenteral activity ratio is higher (1/3 to 1/2). Pethidine is nearly completely metabolized in liver. The plasma t½ of pethidine is 2–3 hours. Acidification of urine increases excretion of unchanged pethidine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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