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.

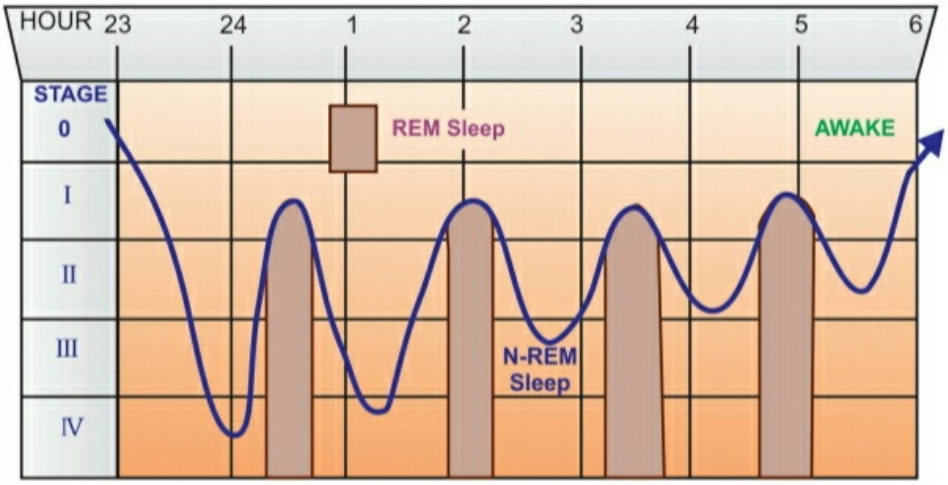


Fig. 29.1: A normal sleep cycle

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.

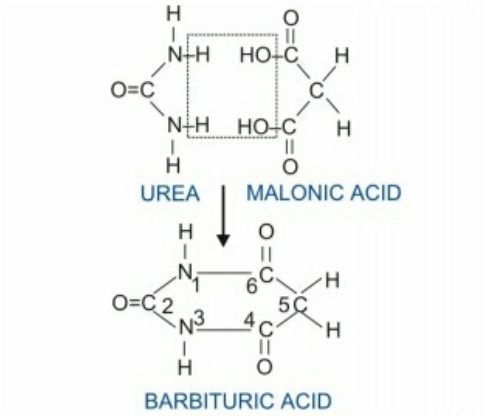
PHARMACOLOGICAL ACTIONS

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.

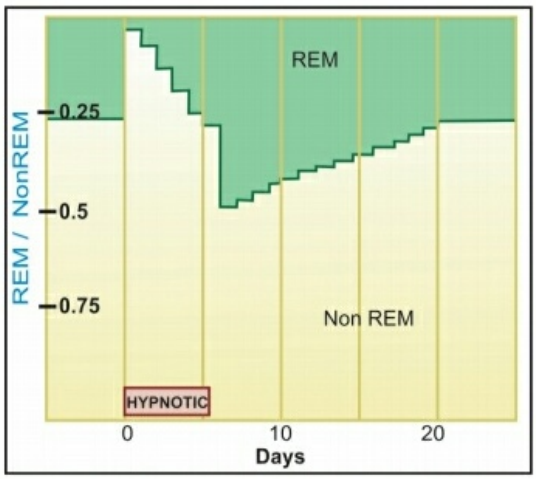


Fig. 29.2: Effect of hypnotic use for 6 consecutive nights on the ratio of REM / Non-REM sleep duration

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.

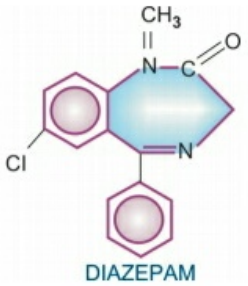
Interactions

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

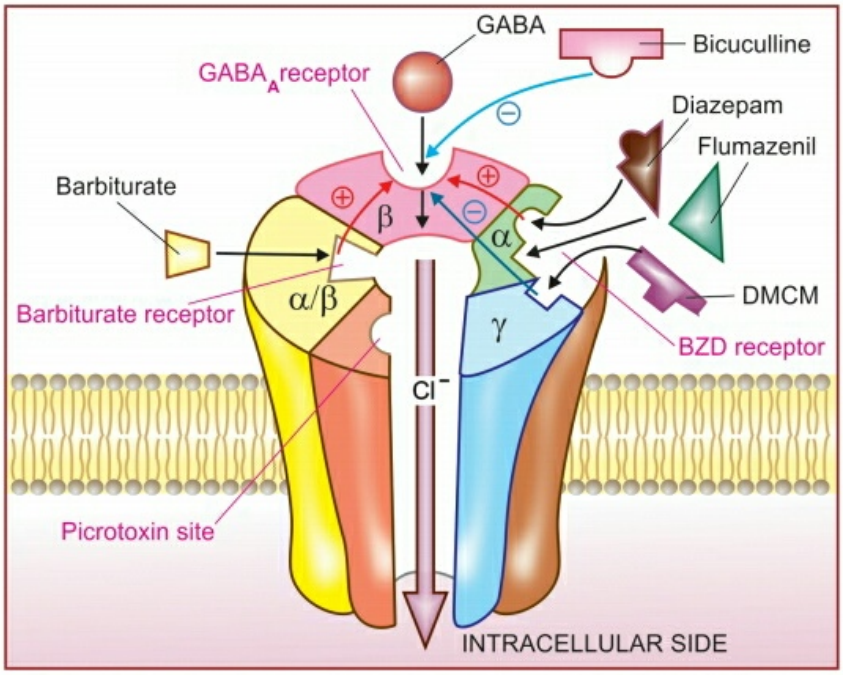


Fig. 29.3: Schematic depiction of $GABA_A$-benzodiazepine receptor-chloride channel complex
The chloride channel is gated by the primary ligand GABA acting on $GABA_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates $GABA_A$ 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
Diazepam	30–60	+	5–10	with anxiety; Frequent nocturnal awakening;
Nitrazepam	30	±	5–10	Night before operation
II. SHORT ACTING				
Alprazolam	12	+	0.25–0.5	Individuals who react unfavourably to
Temazepam	8–12	+	10–20	unfamiliar surroundings or unusual timings
Triazolam	2–3	±	0.125–0.25	of sleep. Sleep onset difficulties.

* 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)