ANXIOLYTIC
and
SEDATIVE-HYPNOTIC DRUGS

Anxiety disorders include:

- generalised anxiety disorder (an ongoing state of excessive anxiety lacking any clear reason)

- panic disorder (attacks of overwhelming fear occuring in association with somatic symptoms (sweating, tachycardia, chest pain)

- phobias (strong fears of specific things or situation (snakes, flying)

- postraumatic stress disorder (anxiety triggered by insistent recall of past stressful experiences

General Definitions

- **Sedative: Calm down, treat agitation**
- **Hypnotic: Induce sleep**
  - **go to sleep fast, feel refreshed tomorrow !!!**
- **Anxiolytic: Reduce anxiety**
  - **physical, emotional, cognitive**

SEDATIVE-HYPNOTIC DRUGS

- Major therapeutic use is to relieve anxiety

(anxiolytics/Sedatives) or induce sleep (hypnotics).

- Hypnotic effects can be achieved with most anxiolytic drugs just by increasing the dose.

- Sedatives/anxiolytics are among the most prescribed substances worldwide.

- An effective **sedative** (anxiolytic) agent should reduce anxiety and exert a calming effect with little or no effect on motor or mental functions.

- A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep that as far as possible resembles the natural sleep state.

TABLE 22–2 Clinical uses of sedative-hypnotics.

For relief of anxiety
For insomnia
For sedation and amnesia before and during medical and surgical procedures
For treatment of epilepsy and seizure states
As a component of balanced anesthesia (intravenous administration)
For control of ethanol or other sedative-hypnotic withdrawal states
For muscle relaxation in specific neuromuscular disorders
As diagnostic aids or for treatment in psychiatry

- The sedative-hypnotics produce dose-dependent CNS depressant effects.

Normal

↘

Relief from Anxiety

↘

SEDATION (↓activity, calming effect)

↘

HYPNOSIS (Produces drowsiness & sleep)

↘

Confusion, Delirium, Ataxia

↘

Surgical Anesthesia

↘

Depression of respiratory and vasomotor Center in the brainstem

↘

COMA

↘

DEATH

CHEMICAL CLASSIFICATION

1. **Benzodiazepines:** not to lead general anesthesia, rarely death.
2. **Barbiturates:** the older sedative-hypnotics, general depression of central nervous system. With such drugs, an increase in dose above that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, it may depress respiratory and vasomotor centers in the medulla, leading to coma and death.
3. **Other classes of drugs:** chloral hydrate, buspirone, et al.

SEDATIVE-HYPNOTICS

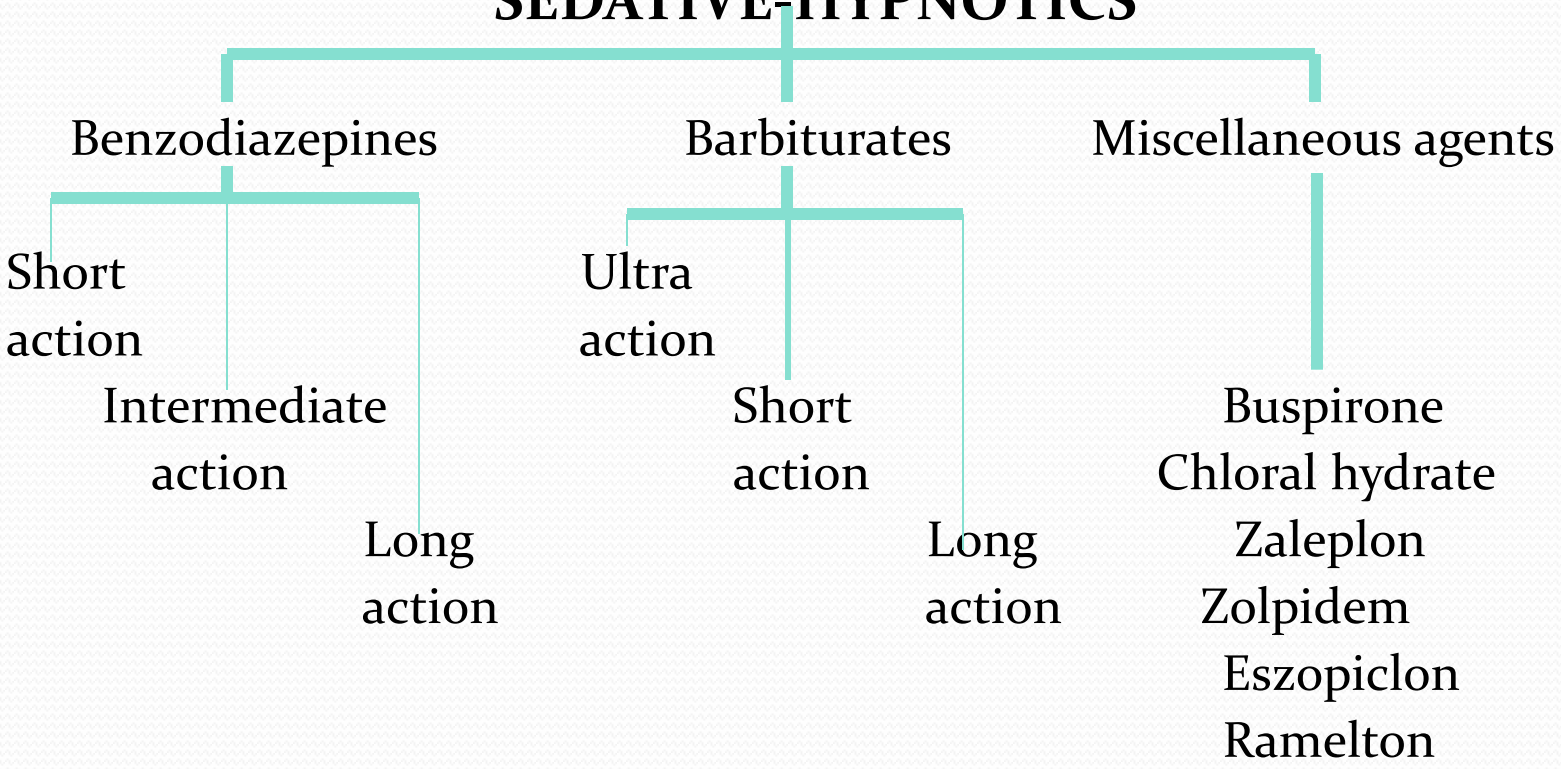


Figure 9.1
Summary of anxiolytic and hypnotic drugs. (Figure continues on next page.)

Sedatives: History

- Alcohol, the oldest known sedative
- 1900 Barbiturates: narrow therapeutic range
- 1960's Chlordiazepoxide [Librium]

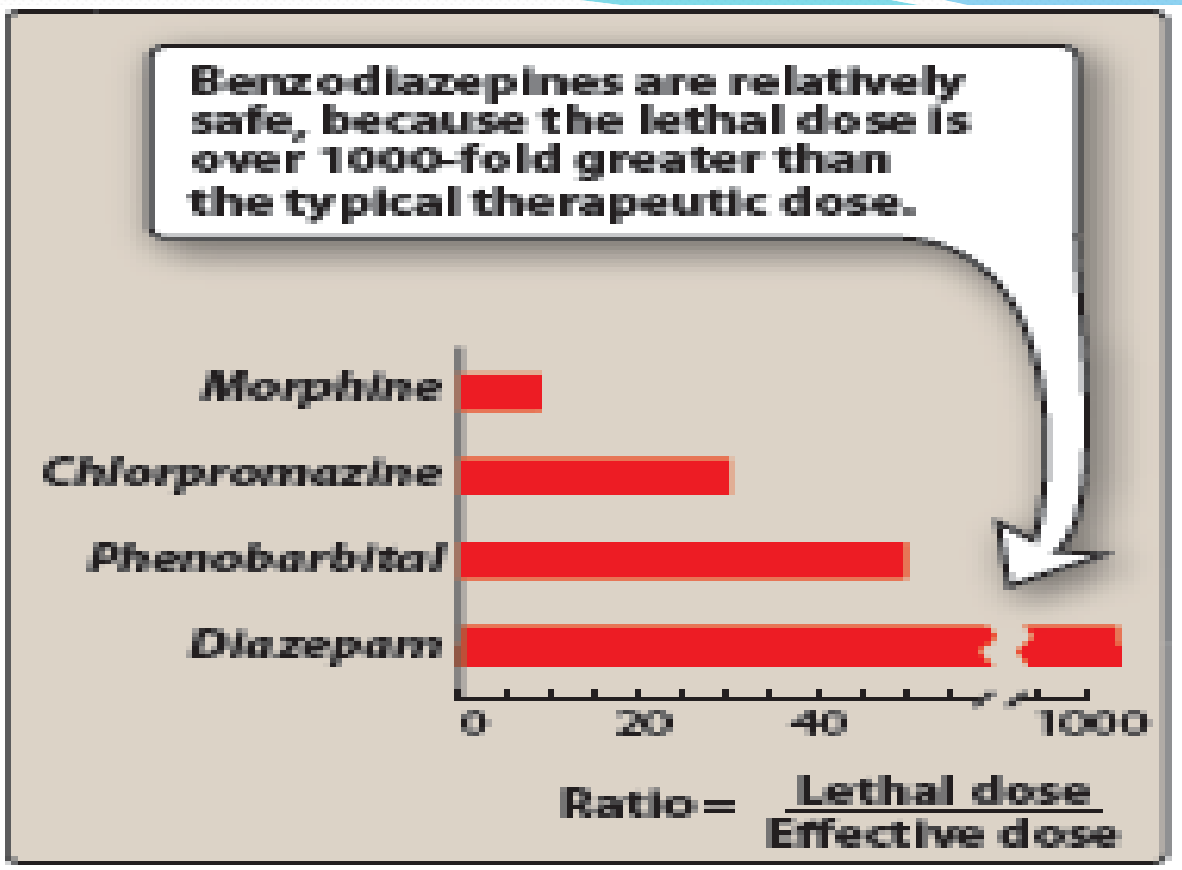


Figure 9.2
Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 14), *chlorpromazine* (a neuroleptic, see Chapter 13), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.

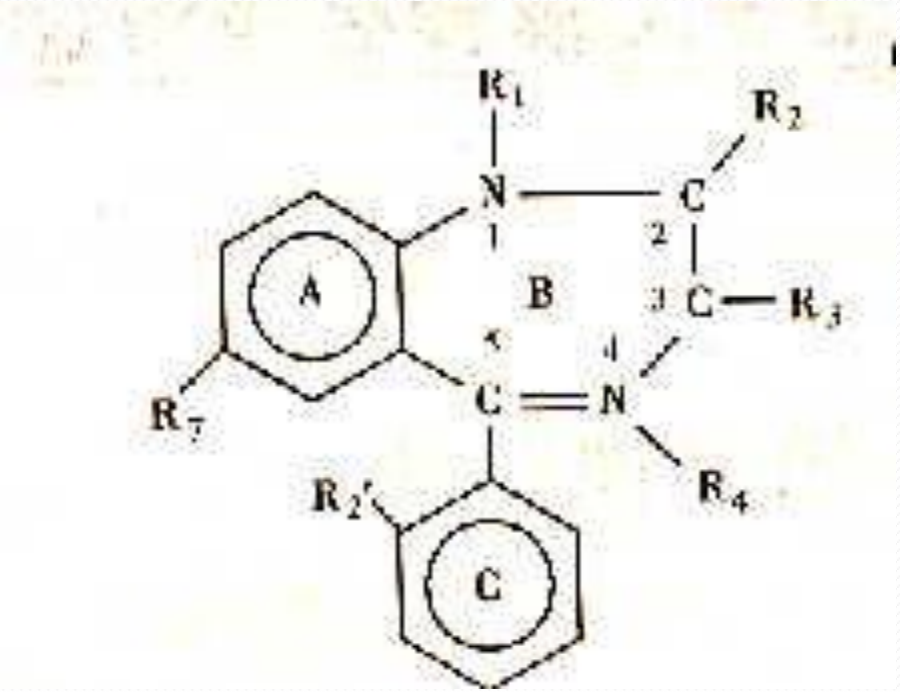
TABLE 34–1 • Contrasts Between Benzodiazepines and Barbiturates

Area of Comparison	Benzodiazepines	Barbiturates
Relative safety	High	Low
Maximal ability to depress CNS function	Low	High
Respiratory depressant ability	Low	High
Suicide potential	Low	High
Ability to cause physical dependence	Low*	High
Ability to cause tolerance	Low	High
Abuse potential	Low	High
Ability to induce hepatic drug metabolism	Low	High

*Although dependence is low in most patients, significant dependence *can* develop with long-term high-dose

Benzodiazepines

- The first benzodiazepine, **chlordiazepoxide**, was synthesised by accident in 1961.



Benzodiazepines

- They are basically similar in their pharmacological actions, though some degree of selectivity has been reported. From a clinical point of view, difference in pharmacokinetic behaviour are more important than difference in profile of activity.

Benzodiazepines-Anxiolytics

- chlordiazepoxide (Librium®)
- diazepam (Valium®)
- clonazepam (Klonopin®)
- clorazepate (Tranxene®)
- lorazepam (Ativan®)
- oxazepam (Serax®)
- alprazolam (Xanax®)
- Triazolam

PHARMACOKINETIC ASPECTS

- Lipid soluble
- Well absorbed when given orally;
- They bind strongly to plasma protein, and their high lipid solubility cause many of them to accumulate gradually in body fat. Distribution volumes is big.

- Metabolic transformation in the microsomal drug-metabolizing enzyme systems of the liver, eventually excreted as glucuronide conjugates in the urine.

- **<u>Biotransformation & Half-Life</u>:**
  - **Hepatic oxidation: long-t1/2, active metabolites**
  - **Glucuronidation: short-t1/2, no active metab.**

SEDATIVE-HYPNOTIC DRUGS

BENZODIAZEPINES

- Converted initially to *active metabolites* with long half-lives
- Diazepam and flurazepam
  - After several days of therapy accumulation of active metabolites can lead to excessive sedation

SEDATIVE-HYPNOTIC DRUGS

BENZODIAZEPINES

- Lorazepam and oxazepam
  - Undergo extrahepatic conjugation and do not form active metabolites

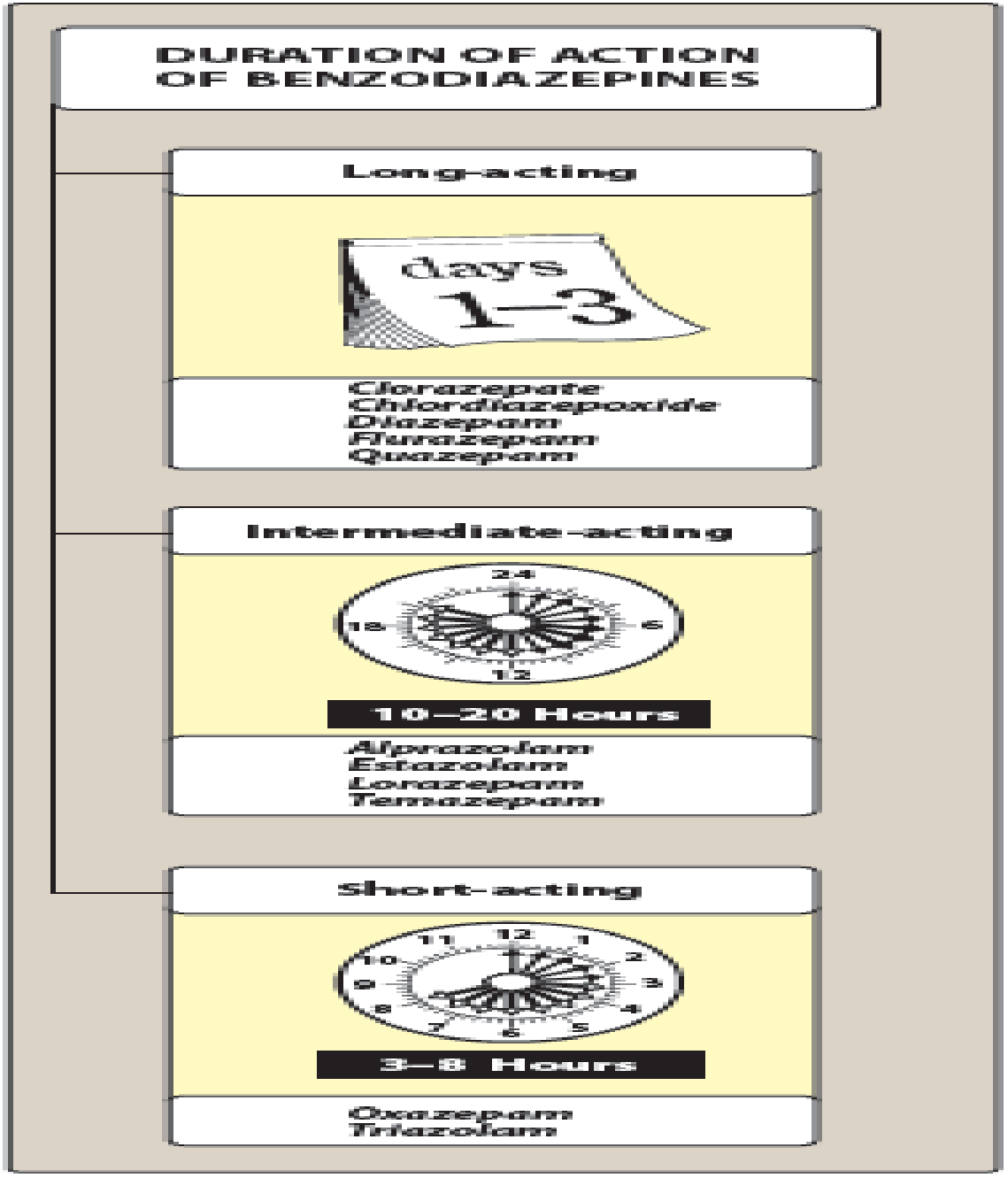


Figure 9.4
Comparison of the durations of action of the benzodiazepines.

- They vary greatly in duration of action, and can be roughly divided into
  - **Short-acting compounds**: triazolam, oxazepam(15-30min, t1/2 2-3 h)
  - **Medium-acting compounds**: estazolam, nitrazepam (40min, t1/2 5-8 h)
  - **Long-acting compounds**: diazepam, flurazepam(50h)

MECHANISM OF ACTION

- Benzodiazepines act very selectively on $GABA_A$-receptors, which mediate the fast inhibitory synaptic response produced by activity in GABA-ergic neurons.

- The effect of benzodiazepines is to enhance the response to GABA, by facilitating the opening of GABA-activated chloride channels (an increase in the frequency of channel opening, but no change in the conductance or mean open time).

- Effects: Sedative, Hypnotic, Anticonvulsant, Muscle-Relaxant

PHARMACOLOGICAL EFFECTS

1. Reduction of anxiety and aggression :

affects the hippocampus and nucleus amygdalae

2. Sedation and induction of sleep:

(1) the latency of sleep onset is decreased;

(2) the duration of stage 2 NREM sleep is increased;

(3) the duration of slow-wave sleep is decreased.

3. Anticonvulsant and antiseizure

clonazepam to treat epilepsy

diazepam (i.v.) status epilepticus to control life-threatening seizures

4. Reduction of muscle tone and coordination

may be clinically useful: increased muscle tone is a common feature of anxiety states and may contribute to pains (headache).

5. Other effects

- lead to temporary amnesia
- decrease the dosage of anesthetic;
- depress respiratory and cardiovascular fuction.

PHARMACOLOGICAL EFFECTS

Reasons for their extensive clinical use:

(1) great margin of safety;

(2) little effect on REM sleep;

(3) little hepatic microsomal drug-metabolizing enzymes;

(4) slight physiologic and psychologic dependence and withdrawal syndrome;

(5) less adverse effects such as residual drowsiness and incoordination movement.

TABLE 34–2 • Applications of the Benzodiazepines

Generic Name [Trade Name]	Approved Applications						
	GAD*	Insomnia	Seizures	Muscle Spasm, Spasticity	Alcohol Withdrawal	Induction of Anesthesia	Panic Disorder
Alprazolam [Xanax, Niravam]	✓						✓
Chlordiazepoxide [Librium]	✓				✓		
Clonazepam [Klonopin]			✓				✓
Clorazepate [Tranxene]	✓		✓		✓		
Diazepam [Valium, others]	✓		✓	✓	✓	✓	
Estazolam [ProSom]		✓					
Flurazepam [Dalmane]		✓					
Lorazepam [Ativan]	✓		✓		✓	✓	✓
Midazolam [Versed]						✓†	
Oxazepam [Serax]	✓				✓		
Quazepam [Doral]		✓					
Temazepam [Restoril]		✓					
Triazolam [Halcion]		✓					

*GAD = generalized anxiety disorder.

†Midazolam, in conjunction with an opioid analgesic, is also used to produce *conscious sedation,* a semiconscious state suitable for minor surgeries and endoscopic procedures.

ADVERSE DRUG REACTION

Acute toxicity:

Benzodiazepines in acute overdose are considerably less dangerous than other sedative-hypnotic drugs. Cause prolonged sleep,without serious depression of respiration or cardiovascular.

- Severe CNS & Respiratory Depression if combined with:
  - alcohol
  - barbiturates
  - narcotics
  - tricyclic antidepressants

ADVERSE DRUG REACTION

- **Side-effects during therapeutic use:**
- CNS depression: drowsiness, sedation, psychomotor impairment, ataxia, confusion,
- Disorientation, impaired coordination, irritability
- Impairment in memory and recall
- Respiratory depression
- Precaution: liver disease, glaucoma,
- Main disadvantages are interaction with alcohol and CNS depressant,
- long-lasting hangover and the development of dependence.

ADVERSE DRUG REACTION

Tolerance and dependence:

- Tolerance
  - Decrease in response to the medication effects(appears to represent a change at the receptor level)

ADVERSE DRUG REACTION

Tolerance and dependence:

- Dependence
  - Physical Dependence: when medication is stopped, withdrawal or discontinuation symptoms occur

stopping BZ treatment after weeks and months causes an increase in symptoms of anxiety, together with tremor and dizziness.

Benzodiazepine Withdrawal

- Symptoms: insomnia, anxiety, autonomic instability (increased heart rate and BP, tremor), muscle cramps, confusion, seizures, irritability, ataxia
- Time frame for emergence of symptoms corresponds to half-life of the benzodiazepine
  - Example: alprazolam has high risk of withdrawal- due to short half-life

Benzodiazepine Overdose

- Treatment Options
  - Supportive and symptomatic care
  - Gastric lavage
  - Activated Charcoal
  - IV hydration and maintain adequate airway
  - IV Flumazenil (Romazicon®): Benzodiazepine antagonist

Flumazenil (Romazicon®)

- Benzodiazepine antagonist that competitively binds to benzodiazepine receptors
- 0.2 mg IV over 30 seconds, then 0.5 mg at 1 minute interval, up to 3 mg
- Rapid response: 1-2 min, up to 10 min
- Duration: 1-5 hours

Flumazenil (Romazicon®)

- Use with caution if patient ingest TCA and benzodiazepine due to risk of seizures
- Monitor patients respiratory rate and cardiac status
- SE: Agitation, confusion, sweating, nausea/vomiting, blurred vision, seizure
- Re-sedation can occur due to short half-life, may repeat dose at 20 minutes intervals with maximum of 1 mg/dose and 3mg/hr

Other anxiolytic & hypnotic

- Zolpidem
  - act on GABA, No anticonvulsant, No withdrawal effect
  - more selective for alpha-1 subunit of benzodiazepine receptor complex
  - like the BZs, the actions of zolpidem are antagonised by flumazenil
  - the risk of development of tolerance and dependence

with extended use is less than with the use of hypnotic BZs

  - orally rapid absorbed, hepatic oxidation by Cyt-P450
  - SE: nausea, dizziness, headache, insomnia, agitation, GI-upset
  - Dosage reduction in hepatic dysfuction, elderly.

Other anxiolytic & hypnotic

- Zaleplon
  - Affect psychomotor & cognitive function
  - Rapid onset and short duration of action are favorable properties for those patients who have difficulty falling asleep.
  - Short half life 1h
  - Metabolized by Cyp 3A4

Serotonin Agonist-Buspirone

- MOA: unknown, does not interact with GABA-BZ receptor complex, has partial agonist of serotonin type 1A receptor
- Act on dopamine receptors
- No anticonvulsant or muscle relaxant
- No potential for abuse, physical dependence or withdrawal symptoms
- Delayed onset of action (2-3 weeks)

Serotonin Agonist-Buspirone

- metabolized by CYP3A4
- Increase prolactin secretion and growth hormones, cause hypothermia
- SE: nausea, dizziness, headache, insomnia, agitation
- Increased risk of serotonin syndrome when co-administered with SSRI

Antihistamines

- Tx of anxiety & insomnia, Non-addicting
- Some anticholinergic effects
- Diphenhydramine [Benadryl]
  - 25-100 mg hs sleep OR 10-25 mgr prn anxiety
- Hydroxyzine [Atarax]
  - 25-100 mg hs sleep
  - 10-25 mg 1-4 times/day

Beta-blockers

- Physiologic component of anxiety:
  - tachycardia, palpitations, tremor, sweating
- No CNS depression
  - non-addicting, no drowsiness
- Do not use in asthma, diabetes, CHF
  - monitor BP, pulse
- Helpful for performance anxiety:
  - propranolol

BARBITURATES

Barbiturates depress the CNS at all level in a dose-dependent fashion. Now it mainly used in anaesthesia and treatment of epilepsy; use as sedative-hypnotic agents is no longer recommended.

BARBITURATES

Reasons:

(1) have a narrow therapeutic-to-toxic dosage range.

(2) suppress REM sleep.

(3) Tolerance develops relatively quickly.

(4) have a high potential for physical dependence and abuse.

(5) potent inducers of hepatic drug-metabolising enzymes.

BARBITURATES

Classification

(1)Ultra-short-acting barbiturates: act within seconds, and their duration of action is 30min. Therapeutic use of Thiopental: anesthesia

(2)Short-acting barbiturates: have a duration of action of about 2h. The principal use of Secobarbital : sleep-inducing hypnotics.

II . BARBITURATES

Classification

(3)Intermediate-acting barbiturates: have and effect lasting 3-5h. The principal use of Amobarbital is as hypnotics.

(4)Long-acting barbiturates: have a duration of action greater than 6h. Such as Barbital and Phenobarbital. Therapeutic uses: hypnotics and sedative, and antiepileptic agents at low doses.

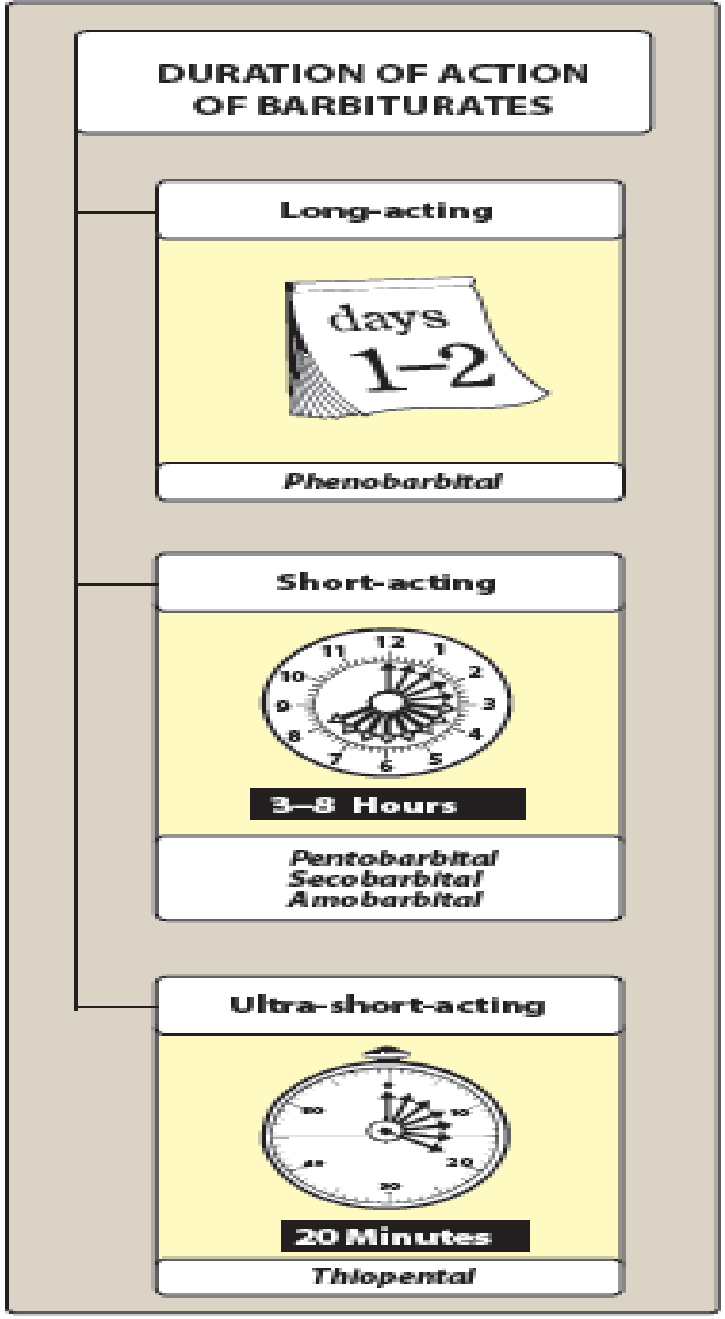


Figure 9.8
Barbiturates classified according to their durations of action.

MECHANISM OF ACTION

(1) Barbiturates share with benzodiazepines the ability to enhance the action of GABA, but they bind a different site on the GABA-receptor/chloride channel, and their action seems to prolong the duration of the opening of GABA-activated chloride channels.

MECHANISM OF ACTION

(2) At high doses, barbiturates can inhibit the release of the Ca^{2+}-dependent neurotransmitter.

Pharmacokinetics

- High lipid solubility allows rapid transport across the blood-brain barrier and results in a short onset.
- Removal from the brain occurs via redistribution to the other tissues results in short duration of action.
- Barbiturates and their metabolites the excretion via the renal route. Alkalinization of the urine expedites the excretion of barbiturates. Treatment of acute overdosage: Sodium bicarbonate.

Therapeutic uses

- Sedative-hypnotic agents
- Be used in the emergency treatment of convulsions as in status epilepticus.
- Anesthetic (or be given before anesthetic)
- Combination with antipyretic-analgesic
- Treatment of hyperbilirubinemia and kernicterus in the neonate.

TABLE 34–3 • Characteristics of Barbiturate Subgroups

Barbiturate Subgroup	Representative Drug	Lipid Solubility	Time Course: Onset (min)	Time Course: Duration (hr)	Applications
Ultrashort-acting	Thiopental	High	0.5	0.2	Induction of anesthesia; treatment of seizures
Short- to intermediate-acting	Secobarbital	Moderate	10–15	3–4	Treatment of insomnia
Long-acting	Phenobarbital	Low	60 or less	10–12	Treatment of seizures

Figure 9.9
Adverse effect of barbiturates.

Adverse effects

- After effect: hangover---dizzy, drowsiness, amnesia, impaired judgment, disorientation.

- Tolerance: decreased responsiveness to a drug following repeated exposure because of down-regulation of receptors and induction of hepatic drug-metabolising enzymes.

Adverse effects

- Dependence: including psychologic and physiologic dependence. Withdrawal symptoms: excitation, insomnia, tremor, anxiety, hallucinations and sometimes convulsions.
- Depressant effect on respiration: can cross the placental barrier during pregnancy and secrete to breast milk.

Treatment of acute overdosage

- An overdose can result in coma, diminished reflexes, severe respiratory depression, hypotension leading to cardiovascular collapse, and renal failure.
- Treatment (A.B.C):

  (1) supporting respiration and circulation.

  (2) alkalinizing the urine and promoting diuresis.

  (3) Hemodialysis or peritoneal dialysis.

Nonbarbiturate sedative-hypnotics

Chloral hydrate

(1) relatively safe hypnotic, inducing sleep in a half hour and lasting about 6h.

(2) used mainly in children and the elder, and the patients when failed to other drug.

TABLE 34–5 • Some Drugs Used for Insomnia

Drug	Time Course		Use in Insomnia*		Bedtime Dosage (mg)	
	Onset (min)	Duration	DFA	DMS	Nonelderly	Elderly
Benzodiazepines						
Triazolam [Halcion]	15–30	Short	✓		0.125–0.25	0.13
Flurazepam† [Dalmane]	30–60	Long	✓	✓	30	7.5
Quazepam† [Doral]	20–45	Long	✓	✓	15	7.5
Estazolam [ProSom]	15–60	Intermediate		✓	1–2	0.5–1
Temazepam [Restoril]	45–60	Intermediate		✓	15–30	7.5–15
Benzodiazepine-like Drugs						
Eszopiclone [Lunesta]	60	Intermediate	✓	✓	2–3	1–2
Zolpidem [Ambien]	30	Short‡	✓	✓	10	5
Zaleplon [Sonata]	15–30	Ultrashort	✓		10–20	5
Melatonin Receptor Agonist						
Ramelteon [Rozerem]	30	Short	✓		8	
Antidepressant						
Trazodone [Desyrel]	60–120	Long		✓	25–75	
Antihistamines						
Doxylamine [Unisom]	60–120	Long		✓	25	
Diphenhydramine [Nytol, Sominex]	60–180	Long		✓	25–50	

*DFA = difficulty falling asleep, DMS = difficulty maintaining sleep.
†Because of its long duration, this drug is not generally recommended.
‡The controlled-release formulation [Ambien CR] has an 8-hour duration.

Teaching

- Don’t use alcohol
- Do not operate equipment
- Do not drive
- **DO NOT RAPIDLY DISCONTINUE**
- **SHORT-TERM USE ONLY**

Sedative/Hypnotics

All of the anxiolytics/sedative/hypnotics should be used only for symptomatic relief.

****

All the drugs used alter the normal sleep cycle and should be administered only for days or weeks, never for months.

****

USE FOR

SHORT-TERM TREATMENT

ONLY!!