Chapter 22

Sedative-Hypnotic Drugs
1. Introduction

- Sedative = quiets patient, gives a feeling of relaxation and rest
  Not necessarily accompanied by sleep

- Hypnotic = produces sleep
1. Introduction

- An effective **sedative** 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.
2. Basic Pharmacology of Sedative-Hypnotics

The linear slope for drug A is typical of many of the older sedative-hypnotics, including the barbiturates and alcohols. With such drugs, an increase in dose higher than that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, these sedative-hypnotics may depress respiratory and vasomotor centers in the medulla, leading to coma and death. Deviations from a linear dose-response relationship, as shown for drug B, require proportionately greater dosage increments to achieve central nervous system depression more profound than hypnosis. This appears to be the case for benzodiazepines and for certain newer hypnotics that have a similar mechanism of action.
Benzodiazepines: wildly used, not to lead general anesthesia, or death.

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, leading to coma and death.

Newer Hypnotics: Several drugs with novel chemical structures have been introduced more recently for use in sleep disorders.
2-1. Chemical Classification

- Benzodiazepines

The benzodiazepines are widely used sedative-hypnotics. All of the structures are 1,4-benzodiazepines, and most contain a carboxamide group in the 7-membered heterocyclic ring structure. A substituent in the 7 position, such as a halogen or a nitro group, is required for sedative-hypnotic activity. The structures of triazolam and alprazolam include the addition of a triazole ring at the 1,2-position.
2-1. Chemical Classification

- Barbiturates

The chemical structures of some older and less commonly used sedative-hypnotics, including several barbiturates, are shown in Figure 22-3. Glutethimide and meprobamate are of distinctive chemical structure but are practically equivalent to barbiturates in their pharmacologic effects. They are rarely used. The sedative-hypnotic class also includes compounds of simpler chemical structure, including ethanol and chloral hydrate.
2-1. Chemical Classification

- Newer Hypnotics

Several drugs with novel chemical structures have been introduced more recently for use in sleep disorders. Zolpidem, an imidazopyridine, zaleplon, a pyrazolopyrimidine, and eszopiclone, a cyclopyrrolone although structurally unrelated to benzodiazepines, share a similar mechanism of action, as described below. Eszopiclone is the (S) enantiomer of zopiclone, a hypnotic drug that has been available outside the United States since 1989. Ramelteon, a melatonin receptor agonist, is a new hypnotic drug (see Ramelteon). Buspirone is a slow-onset anxiolytic agent whose actions are quite different from those of conventional sedative-hypnotics (see Buspirone).
Newer Hypnotics

Ramelteon

Ramelteon, a novel hypnotic drug prescribed specifically for patients who have difficulty in falling asleep, is an agonist at MT1 and MT2 melatonin receptors located in the suprachiasmatic nuclei of the brain. Ramelteon reduced the latency of persistent sleep with no effects on sleep architecture and no rebound insomnia or significant withdrawal symptoms.

The CYP1A2 isoform of cytochrome P450 is mainly responsible for the metabolism of ramelteon, but the CYP2C9 isoform is also involved.

The drug should not be used in combination with inhibitors of CYP1A2 (eg, ciprofloxacin, fluvoxamine, tacrine, zileuton) or CYP2C9 (eg, fluconazole) and should be used with caution in patients with liver dysfunction. The CYP inducer rifampin markedly reduces the plasma levels of both ramelteon and its active metabolite.

Adverse effects of ramelteon include dizziness, somnolence, fatigue, and endocrine changes as well as decreases in testosterone and increases in prolactin.
2-1. Chemical Classification

- Newer Hypnotics

**Buspirone**

Buspirone has selective anxiolytic effects, and relieves anxiety without causing marked sedative, hypnotic, or euphoric effects. Unlike benzodiazepines, the drug has no anticonvulsant or muscle relaxant properties. Buspirone does not interact directly with GABAergic systems. It may exert its anxiolytic effects by acting as a partial agonist at brain 5-HT1A receptors, but it also has affinity for brain dopamine D2 receptors.

Buspirone is rapidly absorbed orally. The major metabolite is 1-(2-pyrimidyl)-piperazine (1-PP), which has 2-adrenoceptor-blocking actions and which enters the central nervous system to reach higher levels than the parent drug.

The elimination half-life of buspirone is 2–4 hours, and liver dysfunction may slow its clearance. Rifampin, an inducer of cytochrome P450, decreases the half-life of buspirone; inhibitors of CYP3A4 (eg, erythromycin, ketoconazole, grapefruit juice, nefazodone) can markedly increase its plasma levels.

Buspirone is an FDA category B drug in terms of its use in pregnancy.
2-2. Pharmacokinetics

1. The rates of oral absorption of sedative-hypnotics differ depending on a number of factors, including lipophilicity. For example, the absorption of triazolam is extremely rapid, and that of diazepam and the active metabolite of clorazepate is more rapid than other commonly used benzodiazepines. Clorazepate, a prodrug, is converted to its active form, desmethyldiazepam (nordiazepam), by acid hydrolysis in the stomach. Most of the barbiturates and other older sedative-hypnotics, as well as the newer hypnotics (eszopiclone, zaleplon, zolpidem), are absorbed rapidly into the blood following oral administration.

2. Lipid solubility plays a major role in determining the rate at which a particular sedative-hypnotic enters the central nervous system.

3. All sedative-hypnotics cross the placental barrier during pregnancy. If sedative-hypnotics are given during the predelivery period, they may contribute to the depression of neonatal vital functions. Sedative-hypnotics are also detectable in breast milk and may exert depressant effects in the nursing infant.
2-2. Pharmacokinetics

- Biotransformation

Metabolic transformation to more water-soluble metabolites is necessary for clearance of sedative-hypnotics from the body. The microsomal drug-metabolizing enzyme systems of the liver are most important in this regard, so elimination half-life of these drugs depends mainly on the rate of their metabolic transformation.
Most benzodiazepines undergo microsomal oxidation (phase I reactions), including $N$-dealkylation and aliphatic hydroxylation catalyzed by cytochrome P450 isozymes, especially CYP3A4. The metabolites are subsequently conjugated (phase II reactions) to form glucuronides that are excreted in the urine.
2-2. Pharmacokinetics

- **Biotransformation**
  
  (1) Benzodiazepines

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_{max}$</th>
<th>$t_{1/2}$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>1–2</td>
<td>12–15</td>
<td>Rapid oral absorption</td>
</tr>
<tr>
<td>Chlorzepoxide</td>
<td>2–4</td>
<td>15–40</td>
<td>Active metabolites; erratic bioavailability from IM injection</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>1–2 (nordiazepam)</td>
<td>50–100</td>
<td>Prodrug; hydrolyzed to active form in stomach</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1–2</td>
<td>20–80</td>
<td>Active metabolites; erratic bioavailability from IM injection</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>1</td>
<td>6</td>
<td>Minor active metabolites</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>1–2</td>
<td>40–100</td>
<td>Active metabolites with long half-lives</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1–6</td>
<td>10–20</td>
<td>No active metabolites</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>2–4</td>
<td>10–20</td>
<td>No active metabolites</td>
</tr>
<tr>
<td>Temazepam</td>
<td>2–3</td>
<td>10–40</td>
<td>Slow oral absorption</td>
</tr>
<tr>
<td>Triazolam</td>
<td>1</td>
<td>2–3</td>
<td>Rapid onset; short duration of action</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>&lt; 1</td>
<td>1–2</td>
<td>Metabolized via aldehyde dehydrogenase</td>
</tr>
<tr>
<td>Zoledem</td>
<td>1–3</td>
<td>1.5–3.5</td>
<td>No active metabolites</td>
</tr>
</tbody>
</table>

$^1$Time to peak blood level.

$^2$Includes half-lives of major metabolites.
2-2. Pharmacokinetics

- Biotransformation

(1) Benzodiazepines

They vary greatly in duration of action, and can be roughly divided into:

- **Short-acting compounds**: triazolam (Tmax 1h, t1/2 2-3 h) (favors its use as a hypnotic rather than as a sedative drug)
- **Medium-acting compounds**: estazolam (Tmax 1h, t1/2 6 h)
- **Long-acting compounds**: diazepam, flurazepam (50h)
2-2. Pharmacokinetics

- Biotransformation

(2) Barbiturates

With the exception of phenobarbital, only insignificant quantities of the barbiturates are excreted unchanged. The major metabolic pathways involve oxidation by hepatic enzymes to form alcohols, acids, and ketones, which appear in the urine as glucuronide conjugates. The overall rate of hepatic metabolism in humans depends on the individual drug but (with the exception of the thiobarbiturates) is usually slow. The elimination half-lives of secobarbital and pentobarbital range from 18 to 48 hours in different individuals. The elimination half-life of phenobarbital in humans is 4–5 days. Multiple dosing with these agents can lead to cumulative effects.
2-2. Pharmacokinetics

- Biotransformation

(3) Newer Hypnotics

Most of them are metabolized to inactive metabolites via oxidation and hydroxylation by hepatic cytochromes P450 including the CYP3A4 isozyme. Dosage should be reduced in patients with hepatic impairment and in the elderly.
2-2. Pharmacokinetics

- Excretion

The water-soluble metabolites of sedative-hypnotics, mostly formed via the conjugation of phase I metabolites, are excreted mainly via the kidney.
2-3. Pharmacodynamics

- GABA receptor
2-3. Pharmacodynamics

○ Neuropharmacology

1. **Benzodiazepines** appear to increase the efficiency of GABAergic synaptic inhibition. The benzodiazepines do not substitute for GABA but appear to enhance GABA's effects allosterically without directly activating GABA$_A$ receptors or opening the associated chloride channels. The enhancement in chloride ion conductance induced by the interaction of benzodiazepines with GABA takes the form of an increase in the frequency of channel-opening events.

2. **Barbiturates** also facilitate the actions of GABA at multiple sites in the central nervous system, but—in contrast to benzodiazepines—they appear to increase the duration of the GABA-gated chloride channel openings. At high concentrations, the barbiturates may also be GABA-mimetic, directly activating chloride channels. Barbiturates are less selective, because they also depress the actions of the excitatory neurotransmitter glutamic acid via binding to the AMPA receptor. Barbiturates also exert nonsynaptic membrane effects in parallel with their effects on GABA and glutamate neurotransmission. This multiplicity of sites of action of barbiturates may be the basis for their ability to induce full surgical anesthesia and for their more pronounced central depressant effects (which result in their low margin of safety) compared with benzodiazepines and the newer hypnotics.
2-3. Pharmacodynamics

Organ Level Effects

Sedation

Hypnosis
The use of sedative-hypnotics for more than 1-2 weeks leads to some tolerance to their effects on sleep patterns.

Anesthesia
High doses of certain sedative-hypnotics depress the central nervous system to the point known as stage III of general anesthesia.

Anticonvulsant effects
Many sedative-hypnotics are capable of inhibiting the development and spread of epileptiform electrical activity in the central nervous system in association with their selectivity.

Muscle Relaxation
Drugs at high doses may also depress transmission at the skeletal neuromuscular junction.

Effects on Respiration and Cardiovascular
To produce significant respiratory depression in patients with pulmonary disease. Effects on respiration are dose-related, and depression of the medullary respiratory center is the usual cause of death due to overdose of sedative-hypnotics.
In hypovolemic states, heart failure, and other diseases that impair cardiovascular function, normal doses of sedative-hypnotics may cause cardiovascular depression. At toxic doses, myocardial contractility and vascular tone may both be depressed by central and peripheral effects, leading to circulatory collapse.
Tolerance—decreased responsiveness to a drug following repeated exposure—is a common feature of sedative-hypnotic use. It may result in the need for an increase in the dose required to maintain symptomatic improvement or to promote sleep. It is important to recognize that partial cross-tolerance occurs between the sedative-hypnotics described here and also with ethanol—a feature of some clinical importance.

The consequences of abuse of these agents can be defined in both psychologic and physiologic terms. The psychologic component may initially parallel simple neurotic behavior patterns difficult to differentiate from those of the inveterate coffee drinker or cigarette smoker. When the pattern of sedative-hypnotic use becomes compulsive, more serious complications develop, including physiologic dependence and tolerance.

Physiologic dependence can be described as an altered physiologic state that requires continuous drug administration to prevent an abstinence or withdrawal syndrome. In the case of sedative-hypnotics, this syndrome is characterized by states of increased anxiety, insomnia, and central nervous system excitability that may progress to convulsions.
3. Benzodiazepine Antagonists: Flumazenil

Flumazenil is one of several 1,4-benzodiazepine derivatives with high affinity for the benzodiazepine binding site on the GABA-A receptor that act as competitive antagonists. It blocks many of the actions of benzodiazepines, zolpidem, zaleplon, and eszopiclone, but does not antagonize the central nervous system effects of other sedative-hypnotics, ethanol, opioids, or general anesthetics. Flumazenil is approved for use in reversing the central nervous system depressant effects of benzodiazepine overdose and to hasten recovery following use of these drugs in anesthetic and diagnostic procedures.
# 4. Clinical Pharmacology of Sedative-Hypnotics

**Table 22-2 Clinical Uses of Sedative-Hypnotics.**

<table>
<thead>
<tr>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>For relief of anxiety</td>
</tr>
<tr>
<td>For insomnia</td>
</tr>
<tr>
<td>For sedation and amnesia before and during medical and surgical procedures</td>
</tr>
<tr>
<td>For treatment of epilepsy and seizure states</td>
</tr>
<tr>
<td>As a component of balanced anesthesia (intravenous administration)</td>
</tr>
<tr>
<td>For control of ethanol or other sedative-hypnotic withdrawal states</td>
</tr>
<tr>
<td>For muscle relaxation in specific neuromuscular disorders</td>
</tr>
<tr>
<td>As diagnostic aids or for treatment in psychiatry</td>
</tr>
</tbody>
</table>
Advantages of benzodiazepines for anxiety

- a rapid onset of action
- a relatively high therapeutic index, plus availability of flumazenil for treatment of overdose
- a low risk of drug interactions based on liver enzyme induction
- minimal effects on cardiovascular or autonomic functions.
4. Clinical Pharmacology of Sedative-Hypnotics

Disadvantages of benzodiazepines

- Dependence
- Depression of central nervous system functions
- Amnestic effects
- To cause depression when administered with other drugs, including ethanol.
Nonpharmacologic therapies that are useful for sleep problems include proper diet and exercise, avoiding stimulants before retiring, ensuring a comfortable sleeping environment, and retiring at a regular time each night.

Benzodiazepines can cause a dose-dependent decrease in both REM and slow-wave sleep, though to a lesser extent than the barbiturates. The newer hypnotics zolpidem, zaleplon, and eszopiclone are less likely than the benzodiazepines to change sleep patterns. The drug selected should be one that provides sleep of fairly rapid onset (decreased sleep latency) and sufficient duration, with minimal "hangover" effects such as drowsiness, dysphoria, and mental or motor depression the following day. If benzodiazepines are used nightly, tolerance can occur, which may lead to dose increases by the patient to produce the desired effect.

Eszopiclone, zaleplon, and zolpidem have efficacies similar to those of the hypnotic benzodiazepines in the management of sleep disorders. Favorable clinical features of zolpidem and the other newer hypnotics include rapid onset of activity and modest day-after psychomotor depression with few amnestic effects.
# 4. Clinical Pharmacology of Sedative-Hypnotics

## Treatment of Sleep Problems

<table>
<thead>
<tr>
<th>Sedation</th>
<th>Dosage</th>
<th>Hypnosis</th>
<th>Dosage (at Bedtime)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.25–0.5 mg 2–3 times daily</td>
<td>Chlortal hydrate</td>
<td>500–1000 mg</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5–10 mg 2–3 times daily</td>
<td>Estazolam</td>
<td>0.5–2 mg</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>10–20 mg 2–3 times daily</td>
<td>Eszopiclone</td>
<td>1–3 mg</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>5–7.5 mg twice daily</td>
<td>Lorazepam</td>
<td>2–4 mg</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5 mg twice daily</td>
<td>Quazepam</td>
<td>7.5–15 mg</td>
</tr>
<tr>
<td>Halazepam</td>
<td>20–40 mg 3–4 times daily</td>
<td>Secobarbital</td>
<td>100–200 mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1–2 mg once or twice daily</td>
<td>Temazepam</td>
<td>7.5–30 mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>15–30 mg 3–4 times daily</td>
<td>Triazolam</td>
<td>0.125–0.5 mg</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>15–30 mg 2–3 times daily</td>
<td>Zaleplon</td>
<td>5–20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zolpidem</td>
<td>5–10 mg</td>
</tr>
</tbody>
</table>
5. Clinical Toxicology of Sedative-Hypnotics

1. Depression of the central nervous system: drowsiness, impaired judgment, and diminished motor skills
2. Dose-related anterograde amnesia: they can significantly impair ability to learn new information.
3. Dependence: may occur at usual doses taken beyond several weeks.
4. Withdrawal: may occur even when discontinuation is not abrupt (e.g., by 10% every 3 days). Symptoms include: tachycardia, increased blood pressure, muscle cramps, anxiety, insomnia, panic attacks, impairment of memory and concentration, perceptual disturbances, derealization, hallucinations, hyperpyrexia, seizures. May continue for months.
5. Rebound anxiety: return of target symptoms, with increased intensity.
6. Respiratory or Cardiovascular depression