Chapter 22

SEDATIVE-HYPNOTIC DRUGS
Introduction

• The sedative-hypnotics belong to:
  – a chemically heterogeneous class of drugs
  – almost all of which produce dose-dependent CNS depressant effects.

• A major subgroup is the benzodiazepines,
  – but representatives of other subgroups, including barbiturates, and miscellaneous agents (carbamates, alcohols, and cyclic ethers) are still in use.

• Newer drugs with distinctive characteristics include:
  – the anxiolytic buspirone,
  – several widely used hypnotics (zolpidem, zaleplon, eszopiclone),
  – and ramelteon, a novel drug used in sleep disorders.
Figure 22-1. Subgroups of drugs reviewed in this chapter.

Other classes: antihistamine....
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Reduction of anxiety</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>A drug that reduces anxiety, a sedative</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>Induction of sleep</td>
</tr>
<tr>
<td>REM sleep</td>
<td>Phase of sleep associated with rapid eye movements; most dreaming takes place during REM sleep</td>
</tr>
<tr>
<td>Tolerance</td>
<td>Reduction in drug effect requiring an increase in dosage to maintain the same response</td>
</tr>
<tr>
<td>Physiologic dependence</td>
<td>The state of response to a drug whereby removal of the drug evokes unpleasant symptoms, usually the opposite of the drug's effects</td>
</tr>
<tr>
<td>Psychologic dependence</td>
<td>The state of response to a drug whereby the drug taker feels compelled to use the drug and suffers anxiety when separated from the drug</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>Loss of consciousness associated with absence of response to pain</td>
</tr>
<tr>
<td>Coma</td>
<td>Extremely deep anesthesia or depression of brain activity; precursor to respiratory and circulatory failure</td>
</tr>
</tbody>
</table>
Pharmacokinetics
Absorption and Distribution

• Most sedative-hypnotic drugs are lipid-soluble
  – and are absorbed well from the gastrointestinal tract,
  – with good distribution to the brain.

• Drugs with the highest lipid solubility (eg, thiopental)
  – enter the CNS rapidly
  – and can be used as induction agents in anesthesia.
  – The CNS effects of thiopental are terminated by rapid redistribution of the drug from brain to other highly perfused tissues, including skeletal muscle.

• Other drugs with a rapid onset of CNS action include eszopiclone, zaleplon, and zolpidem.
Metabolism and Excretion

- Sedative-hypnotics are metabolized before elimination from the body,
  - mainly by hepatic enzymes.
  - Metabolic rates and pathways vary among different drugs.

- Many benzodiazepines are converted initially to active metabolites with long half-lives.
  - After several days of therapy with some drugs (e.g., diazepam, flurazepam), accumulation of active metabolites can lead to excessive sedation.

- Lorazepam and oxazepam
  - undergo extrahepatic conjugation and do not form active metabolites.

- The barbiturates are extensively metabolized,
  - with the exception of phenobarbital, which is excreted partly unchanged in the urine,
3. **Metabolism:** Most BZDs are metabolized by hepatic microsomal enzyme systems.
   - They are excreted in the urine as glucuronides or oxidized metabolites.
Metabolism and Excretion

- **Chloral hydrate** is oxidized to **trichloroethanol**, an active metabolite.

- **Rapid metabolism** by liver enzymes is **responsible** for the **short duration** of action of **zolpidem**.
  - A biphasic release form of zolpidem extends its plasma half-life.

- **Zaleplon** undergoes even more rapid hepatic metabolism by aldehyde oxidase and **cytochrome P450**.

- **Eszopiclone** is also metabolized by **cytochrome P450** with a half-life of 6 h.

- The **duration of CNS actions** of sedative-hypnotic drugs ranges from
  - just a few hours (eg, zaleplon < zolpidem = triazolam = eszopiclone < chloral hydrate)
  - to more than 30 h (eg, chlordiazepoxide, clorazepate, diazepam, phenobarbital).
Mechanisms of Action

• No single mechanism of action for sedative-hypnotics has been identified,
  – and the different chemical subgroups may have different actions.

• Certain drugs (eg, benzodiazepines) facilitate neuronal membrane inhibition by actions at specific receptors.
Benzodiazepines

• Receptors for benzodiazepines (BZ receptors) are present in many brain regions, including:
  – the thalamus, limbic structures, and the cerebral cortex.

• The BZ receptors form part of a GABA \(_{A}\) receptor-chloride ion channel macromolecular complex,
  – a pentameric structure assembled from 5 subunits each with 4 transmembrane domains.

• Binding of benzodiazepines facilitates the inhibitory actions of GABA (\(\gamma\)-aminobutyric acid, inhibitory neurotransmitter),
  – which are exerted through increased chloride ion conductance.

• Benzodiazepines increase the frequency of GABA-mediated chloride ion channel opening.
Benzodiazepines

- **Flumazenil** reverses the **CNS effects** of benzodiazepines
  - and is classified as an **antagonist** at **BZ receptors**.

- Certain **beta-carbolines** have a **high affinity for BZ receptors**
  - and can **elicit anxiogenic** and **convulsant** effects.
  - These drugs are classified as **inverse agonists**.
Barbiturates

• Barbiturates depress neuronal activity in the midbrain reticular formation,
  – facilitating and prolonging the inhibitory effects of GABA and glycine.

• Barbiturates also bind to multiple isoforms of the GABA$_A$ receptor but at different sites from those with which benzodiazepines interact.
  – Their actions are not antagonized by flumazenil.

• Barbiturates increase the duration of GABA-mediated chloride ion channel opening.

• They may also block the excitatory transmitter glutamic acid, and, at high concentration, sodium channels.
Other Drugs

• The newer hypnotics zolpidem, zaleplon, and eszopiclone are
  – not benzodiazepines
  – but appear to exert their CNS effects via interaction with certain benzodiazepine receptors, classified as BZ subtypes.

• In contrast to benzodiazepines, these drugs bind more selectively, interacting only with GABA$_A$ receptor isoforms that contain $\alpha_1$ subunits.

• Their CNS depressant effects can be antagonized by flumazenil.
Pharmacodynamics

- The **CNS effects** of most sedative-hypnotics depend on dose.
- These effects range from:
  - **sedation** and relief of anxiety (*anxiolysis*), through **hypnosis** (facilitation of sleep), to **anesthesia** and **coma**.

- Depressant effects are **additive** when 2 or more drugs are given together.

- The **steepness** of the dose–response curve varies among drug groups;
  - those with **flatter curves**, such as **benzodiazepines** and the newer hypnotics (eg, zolpidem), are safer for clinical use.
FIGURE 22-1 Dose-response curves for two hypothetical sedative-hypnotics.
Relationships between dose of benzodiazepines and barbiturates and their CNS effects.
Organ level effects
1. Sedation

- Sedative actions, with relief of anxiety,
  - occur with all drugs in this class.

- Anxiolysis is usually accompanied by some impairment of psychomotor functions, and behavioral disinhibition may also occur.

- In animals, most conventional sedative-hypnotics release punishment-suppressed behavior.
2. Hypnosis

- Sedative-hypnotics can:
  - promote sleep onset
  - and increase the duration of the sleep state.

- Rapid eye movement (REM) sleep duration is usually decreased at high doses;
  - a rebound increase in REM sleep may occur on withdrawal from chronic drug use.

- Effects on sleep patterns occur infrequently with newer hypnotics such as zaleplon and zolpidem.
3. Anesthesia

- At **high doses** of most older sedative-hypnotics,
  - loss of consciousness may occur,
  - with amnesia
  - and suppression of reflexes (like pain).

- **Anterograde amnesia** is more likely with benzodiazepines than with other sedative-hypnotics.

- **Anesthesia** can be produced by:
  - most barbiturates (eg, thiopental)
  - and certain benzodiazepines (eg, midazolam).
4. Anticonvulsant Actions

- **Suppression of seizure** activity occurs with:
  - high doses of most of the barbiturates and some of the benzodiazepines,
  - but this is usually at the cost of marked sedation.

- **Selective anticonvulsant** action (ie, suppression of convulsions at doses that do not cause severe sedation)
  - occurs with only a few of these drugs (eg, phenobarbital, clonazepam).

- **High doses of i.v. diazepam, lorazepam, or phenobarbital** are used in status epilepticus.
  - In this condition, heavy sedation is desirable.
5. Muscle Relaxation

• Relaxation of skeletal muscle occurs
  – only with high doses of most sedative-hypnotics.

• However, diazepam is effective at sedative dose levels
  – for specific spasticity states, including cerebral palsy.

• Meprobamate also has some selectivity as a muscle relaxant.
6. Medullary Depression

• **High doses** of conventional sedative-hypnotics, especially alcohols and barbiturates, can cause **depression of medullary neurons**, leading to:
  – respiratory arrest,
  – hypotension,
  – and cardiovascular collapse.

• These effects are the cause of **death** in suicidal overdose.
Tolerance and Dependence

- **Tolerance**—a *decrease in responsiveness*—occurs when sedative-hypnotics are used *chronically* or *in high dosage*.

- **Cross-tolerance** may occur among *different chemical subgroups*.

- **Psychological dependence** occurs frequently with *most sedative-hypnotics* and is manifested by:
  - the *compulsive use* of these drugs to *reduce anxiety*.

- **Physiologic dependence** constitutes an altered state that leads to an *abstinence syndrome (withdrawal state)* when the drug is discontinued.

- **Withdrawal signs**, which may include:
  - anxiety,
  - tremors,
  - hyperreflexia,
  - and seizures,
  - occur *more commonly* with *shorter-acting drugs*. 
Tolerance and Dependence

• The dependence liability of zolpidem, zaleplon, and eszopiclone may be less than that of the benzodiazepines—since withdrawal symptoms are minimal after their abrupt discontinuance.
Clinical Uses

• Most of these uses can be predicted from the pharmacodynamic effects outlined previously.
Anxiety States

• Benzodiazepines are favoured in the drug treatment of:
  – acute anxiety states
  – and for rapid control of panic attacks.

• Although it is difficult to demonstrate the superiority of one drug over another, alprazolam and clonazepam have greater efficacy than other benzodiazepines in the longer term treatment of panic and phobic disorders.

• Note the increasing use of newer antidepressants in the treatment of chronic anxiety states.
Sleep Disorders

• Benzodiazepines, including estazolam, flurazepam, and triazolam, have been widely used in primary insomnia and for the management of certain other sleep disorders.

• Lower doses should be used in elderly patients
  – who are more sensitive to their CNS depressant effects.

• More recently there has been increasing use of zolpidem, zaleplon, and eszopiclone in insomnia, since:
  • they have rapid onset
  • with minimal effects on sleep patterns
  • and cause less daytime cognitive impairment than benzodiazepines.

• Note that sedative-hypnotic drugs are not recommended for breathing-related sleep disorders.
Other Uses

• **Thiopental** is commonly used for the **induction of anesthesia**, and certain **benzodiazepines** (eg, **diazepam**, **midazolam**) are used as **components of anesthesia** protocols including those used in day surgery.

• **Special uses include:**
  • the management of **seizure disorders** (eg, **clonazepam**, **phenobarbital**)
  • and **bipolar disorder** (eg, **clonazepam**)
  • and treatment of **muscle spasticity** (eg, **diazepam**).

• **Longer acting** benzodiazepines (eg, **chlordiazepoxide**, **diazepam**) are used in the management of **withdrawal states** in persons **physiologically dependent** on **ethanol** and other sedative-hypnotics.
Toxicity

Psychomotor Dysfunction

• This includes:
  – cognitive impairment,
  – decreased psychomotor skills,
  – and unwanted daytime sedation.

• These adverse effects are more common with benzodiazepines that have active metabolites with long half-lives (eg, diazepam, flurazepam),
  – but can also occur after a single dose of a short-acting benzodiazepine such as triazolam.
Toxicity

• The dosage of a sedative-hypnotic should be reduced in elderly patients, who are more susceptible to drugs that cause psychomotor dysfunction.
  – In such patients excessive daytime sedation has been shown to increase the risk of falls and fractures.

• Anterograde amnesia may also occur with benzodiazepines, especially when used at high dosage,
  – an action that forms the basis for their criminal use in cases of "date rape."

• Zolpidem and the newer hypnotics
  – cause modest day-after psychomotor depression with few amnestic effects.

• However, all prescription drugs used as sleep aids may cause functional impairment, including "sleep driving," defined as
  – "driving while not fully awake after ingestion of a sedative-hypnotic product, with no memory of the event."
Additive CNS Depression

• This occurs when *sedative-hypnotics* are used *with other drugs*
  1. *in the class*
  2. as well as with *alcoholic* beverages,
  3. *antihistamines*,
  4. *antipsychotic* drugs,
  5. *opioid* analgesics,
  6. and *tricyclic antidepressants*.

• This is the *most common type of drug interaction involving sedative-hypnotics* (additive effect).
Overdosage

• Overdosage of sedative-hypnotic drugs causes severe respiratory and cardiovascular depression; these potentially lethal effects
  – are more likely to occur with alcohols, barbiturates, and carbamates than with benzodiazepines or the newer hypnotics such as zolpidem.

• Management of intoxication requires:
  – maintenance of a patent airway and ventilatory support.

• Flumazenil may reverse CNS depressant effects of:
  – benzodiazepines, eszopiclone, zolpidem, and zaleplon
  – but has no beneficial actions in overdosage with other sedative-hypnotics.
Other Adverse Effects

- **Barbiturates and carbamates** (but not benzodiazepines, eszopiclone, zolpidem, or zaleplon)
  - induce the **formation** of the liver microsomal enzymes that metabolize drugs.

- This enzyme induction may lead to **multiple drug interactions**.

- **Barbiturates** may also precipitate **acute intermittent porphyria** in susceptible patients.

- **Chloral hydrate** may **displace coumarins** from plasma protein binding sites and **increase anticoagulant effects**.
Atypical Sedative-Hypnotics
Buspirone

- **Buspirone** is a *selective anxiolytic*,
  - with *minimal CNS depressant* effects (it does *not affect driving skills*)
  - and has *no anticonvulsant or muscle relaxant* properties.

- The drug *interacts* with the 5-HT$_{1A}$ subclass of *brain serotonin receptors* as a *partial agonist*,
  - but the *precise mechanism* of its *anxiolytic effect* is *unknown*.

- Buspirone has a *slow onset of action (>1 week)* and is used in *generalized anxiety* disorder(s), but *is less effective* in *panic disorders*. 
Atypical Sedative-Hypnotics

Buspirone

- **Tolerance** development is *minimal* with chronic use,

- and there is *little rebound anxiety* or withdrawal symptoms on discontinuance.

- **Buspirone** is metabolized by CYP3A4,
  - and its plasma levels are markedly *increased* by drugs such as erythromycin and ketconazole.

- **Side effects of buspirone** include:
  - tachycardia, paresthesias, pupillary constriction, and gastrointestinal distress.

- Buspirone has **minimal abuse liability** and is not a schedule-controlled drug. The drug appears to be *safe in pregnancy*. 
Ramelteon

• This **novel hypnotic drug** that activates **melatonin receptors** in the suprachiasmatic nuclei of the **CNS**:  
  • **decreases** the **latency of sleep onset** with **minimal rebound insomnia** or **withdrawal symptoms**.

• Ramelteon has **no direct effects** on **GABA-ergic neurotransmission** in the CNS.

• Unlike conventional hypnotics ramelteon appears to have **minimal abuse liability**, and it is **not a controlled substance**.
Ramelteon

- The drug is **metabolized** by hepatic **cytochrome P450** forming an active metabolite.
  - The **CYP inducer** rifampin **markedly reduces** plasma levels of ramelteon and its metabolite.

- Conversely, **inhibitors of CYP1A2** (eg, fluvoxamine) or **CYP2C9** (eg, fluconazole) increase **plasma levels of ramelteon**.

- The **adverse effects** of the drug include:
  - dizziness,
  - fatigue,
  - and **endocrine changes** including **decreased testosterone** and **increased prolactin**.
Thank you