

## Anxiolytic and Hypnotic Drugs

- ❑ Disorders involving anxiety are among the most common mental disorders.
- ❑ Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source).
- ❑ The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation.
- ❑ Episodes of mild anxiety are common life experiences and do not warrant treatment. However, severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytics) and/or some form of psychotherapy.
- ❑ Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep-inducing) agents.
- ❑ [Figure 9.1](#) summarizes the anxiolytic and hypnotic agents.
- ❑ Some antidepressants are also indicated for certain anxiety disorders; however, they are discussed with the antidepressants.

### Benzodiazepines

- ✿ Benzodiazepines are widely used anxiolytic drugs.
- ✿ They have largely replaced barbiturates and *meprobamate* in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective ([Figure 9.2](#)).
- ✿ Though benzodiazepines are commonly used, they are not necessarily the best choice for anxiety or insomnia. Certain antidepressants with anxiolytic action, such as the selective serotonin reuptake inhibitors (SSRIs), are preferred in many cases, and nonbenzodiazepine hypnotics and antihistamines may be preferable for insomnia.

#### A. Mechanism of action

- The targets for benzodiazepine actions are the  $\gamma$ -aminobutyric acid (GABA<sub>A</sub>) receptors.
- [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).]
- The GABA<sub>A</sub> receptors are composed of a combination of five  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits that span the postsynaptic membrane ([Figure 9.3](#)).
- For each subunit, many subtypes exist (for example, there are six subtypes of the  $\alpha$  subunit).
- Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore.
- The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials.
- Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the  $\alpha$  subunit and the  $\gamma$  subunit on the GABA<sub>A</sub> receptor ([Figure 9.3](#)).

- Benzodiazepines increase the frequency of channel openings produced by GABA.
- The clinical effects of individual benzodiazepines correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

**B. Actions:** All benzodiazepines exhibit the following actions:

**1. Reduction of anxiety**

- ✓ At low doses, benzodiazepines are anxiolytic.
- ✓ They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having the  $\alpha_2$  subunit in their GABA<sub>A</sub> receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.

**2. Sedative/hypnotic**

- ✓ All benzodiazepines have sedative and calming properties, and some can produce hypnosis (artificially produced sleep) at higher doses.
- ✓ The hypnotic effects are mediated by the  $\alpha_1$ -GABA<sub>A</sub> receptors.

**3. Anterograde amnesia**

- ✓ Temporary impairment of memory with the use of the benzodiazepines is also mediated by the  $\alpha_1$ -GABA<sub>A</sub> receptors
- ✓ The ability to learn and form new memories is also impaired.

**4. Anticonvulsant**

- ✓ This effect is partially, although not completely, mediated by  $\alpha_1$ -GABA<sub>A</sub> receptors.

**5. Muscle relaxant**

- ✓ At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the  $\alpha_2$ -GABA<sub>A</sub> receptors are largely located.
- ✓ [Note: *Baclofen* [BAK-loe-fen] is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.]

**C. Therapeutic uses**

The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

**1. Anxiety disorders**

- ✓ Benzodiazepines are effective for the treatment of anxiety associated with panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, and extreme phobias, such as fear of flying.
- ✓ The benzodiazepines are also useful in treating anxiety related to depression and schizophrenia.
- ✓ These drugs should be reserved for severe anxiety and should not be used to manage the stress of everyday life.
- ✓ Because of their addictive potential, they should only be used for short periods of time.

- ✓ The longer-acting agents, such as *clonazepam* [kloe- NAZ-e-pam], *lorazepam* [lor-AZ-e-pam], and *diazepam* [dye-AZ-e-pam], are often preferred in patients with anxiety that require prolonged treatment.
- ✓ The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects.
- ✓ [Note: Tolerance is decreased responsiveness to repeated doses of the drug that occurs when used for more than 1 to 2 weeks.]
- ✓ For panic disorders, *alprazolam* [al-PRAY-zoe-lam] is effective for short- and long-term treatment, although it may cause withdrawal reactions in approximately 30% of patients.

## 2. Sleep disorders

- ✓ Benzodiazepine hypnotics decrease the latency to sleep onset .
- ✓ In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation (“hangover”) upon awakening.
- ✓ Short-acting ***triazolam*** [try-AY-zoe-lam] is effective in treating individuals who have problems falling asleep.
- ✓ The risk of withdrawal and rebound insomnia is higher with *triazolam* than with other agents.
- ✓ Intermediate-acting ***temazepam*** [te-MAZ-e-pam] is useful for patients who experience frequent awakenings and have difficulty staying asleep.
- ✓ ***Temazepam*** should be administered 1 to 2 hours before the desired bedtime.
- ✓ Long-acting *flurazepam* [flure-AZ-e- pam] is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly.
- ✓ *Estazolam* [eh-STAY-zoe-lam] and *quazepam* [QUAY-ze-pam] are considered intermediate- and long-acting agents, respectively. In general, hypnotics should be used for only a limited time, usually 1 to 3 weeks.

## 3. Amnesia

- ✓ The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopy, dental procedures, and angioplasty.
- ✓ They cause a form of conscious sedation, allowing the patient to be receptive to instructions during these procedures.
- ✓ *Midazolam* [mi-DAY-zoe-lam] is a benzodiazepine used to facilitate anterograde amnesia while providing sedation prior to anesthesia.

## 4. Seizures

- ✓ ***Clonazepam*** is used as an adjunctive therapy for certain types of seizures, whereas *lorazepam* and *diazepam* are the drugs of choice in terminating status epilepticus.

- ✓ Due to cross-tolerance, *chlordiazepoxide* [klor-di-az-e-POX-ide], *clorazepate* [klor-AZ-e-pate], *diazepam*, *lorazepam*, and *oxazepam* [ox- AZ-e-pam] are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.

## 5. Muscular disorders

- ✓ *Diazepam* is useful in the treatment of skeletal muscle spasms and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

## D. Pharmacokinetics

### 1. Absorption and distribution

- ✿ The benzodiazepines are lipophilic.
- ✿ They are rapidly and completely absorbed after oral administration, distribute throughout the body, and penetrate into the CNS.

### 2. Duration of action

- ✿ The half-lives of the benzodiazepines are important clinically, because the duration of action may determine the therapeutic usefulness.
- ✿ The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups (Figure 9.4).
- ✿ The longer-acting agents form active metabolites with long half-lives. However, ***with some benzodiazepines, the clinical duration of action does not correlate with the actual half-life*** (otherwise, a dose of *diazepam* could conceivably be given only every other day, given its long half-life and active metabolites).
- ✿ This may be due to receptor dissociation rates in the CNS and subsequent redistribution to fatty tissues and other areas.

### 3. Fate

- ✿ Most benzodiazepines, including *chlordiazepoxide* and *diazepam*, are metabolized by the hepatic microsomal system to compounds that are also active.
- ✿ For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites.
- ✿ The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites.
- ✿ All benzodiazepines cross the placenta and may depress the CNS of the newborn if given before birth.
- ✿ The benzodiazepines are not recommended for use during pregnancy. Nursing infants may also be exposed to the drugs in breast milk.

## E. Dependence

- ✿ Psychological and physical dependence can develop if high doses of benzodiazepines are given for a prolonged period.
- ✿ All benzodiazepines are controlled substances.

- ✿ Abrupt discontinuation of these agents results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures.
- ✿ Benzodiazepines with a short elimination half-life, such as *triazolam*, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as *flurazepam* (Figure 9.5).

#### F. Adverse effects

- ✿ Drowsiness and confusion are the most common adverse effects of the benzodiazepines.
- ✿ Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile.
- ✿ Cognitive impairment (decreased recall and retention of new knowledge) can occur with use of benzodiazepines.
- ✿ Benzodiazepines should be used cautiously in patients with liver disease
- ✿ Alcohol and other CNS depressants enhance the sedative–hypnotic effects of the benzodiazepines.
- ✿ Benzodiazepines are, however, considerably less dangerous than the older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol or opioids, are taken concurrently.

### **Benzodiazepine Antagonist**

- ❑ **Flumazenil** [floo-MAZ-eh-nill] is a GABA receptor antagonist that rapidly reverses the effects of benzodiazepines.
- ❑ The drug is available for intravenous (IV) administration only.
- ❑ Onset is rapid, but the duration is short, with a half- life of about 1 hour.
- ❑ Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.
- ❑ Administration of *flumazenil* may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity.
- ❑ Seizures may also result if the patient has a mixed ingestion with tricyclic antidepressants or antipsychotics.
- ❑ Dizziness, nausea, vomiting, and agitation are the most common adverse effects.

### **Other Anxiolytic Agents**

#### A. Antidepressants

- Many antidepressants are effective in the treatment of chronic anxiety disorders and should be considered as first- line agents, especially in patients with concerns for addiction or dependence.
- SSRIs (such as *escitalopram* or *paroxetine*) or serotonin/norepinephrine reuptake inhibitors (SNRIs, such as *venlafaxine* or *duloxetine*) may be used alone or prescribed in combination with a benzodiazepine during the first week of treatment (Figure 9.6).
- After 4 to 6 weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered.

- While only certain SSRIs or SNRIs have been approved for the treatment of anxiety disorders such as GAD, the efficacy of these drugs is most likely a class effect. Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse.

## B. *Buspirone*

*Buspirone* [byoo-SPYE-rone] is useful for the chronic treatment of GAD and has an efficacy comparable to that of benzodiazepines. It has a slow onset of action and is not effective for short-term or “as-needed” treatment of acute anxiety. The actions of *buspirone* appear to be mediated by serotonin (5-HT<sub>1A</sub>) receptors, although it also displays some affinity for D<sub>2</sub> dopamine receptors and 5-HT<sub>2A</sub> serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. In addition, *buspirone* lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines. The frequency of adverse effects is low, with the most common effects being headache, dizziness, nervousness, nausea, and lightheadedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. *Buspirone* does not potentiate the CNS depression of alcohol. [Figure 9.7](#) compares common adverse effects of *buspirone* and the benzodiazepine *alprazolam*.

# Barbiturates

- ❖ The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep.
- ❖ They have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence, are lethal in overdose, and are associated with severe withdrawal symptoms. All barbiturates are controlled substances.

## A. Mechanism of action

- ❖ The sedative–hypnotic action of the barbiturates is due to their interaction with GABA<sub>A</sub> receptors, which enhances GABAergic transmission.
- ❖ The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines.
- ❖ Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors.
- ❖ These molecular actions lead to decreased neuronal activity.

## B. Actions

- ❑ Barbiturates are classified according to their duration of action ([Figure 9.8](#)).
- ❑ Long-acting *phenobarbital* [fee-noe- BAR-bi-tal] has a duration of action greater than a day.
- ❑ *Pentobarbital* [pen-toe-BAR-bi-tal], *secobarbital* [see-koe- BAR-bi-tal], *amobarbital* [am-oh-BAR-bi-tal], and *butalbital* [bu-TAL-bi-tal] are short-acting barbiturates.

### 1. Depression of CNS

- ❑ At low doses, the barbiturates produce sedation (have a calming effect and reduce excitement).

- ❑ At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose.
- ❑ Barbiturates do not raise the pain threshold and have no analgesic properties.
- ❑ They may even exacerbate pain.
- ❑ Chronic use leads to tolerance.

## 2. Respiratory depression

Barbiturates suppress the hypoxic and chemoreceptor response to CO<sub>2</sub>, and overdose is followed by respiratory depression and death.

### C. Therapeutic uses

#### 1. Anesthesia

- ❑ The ultra–short-acting barbiturates have been historically used intravenously to induce anesthesia but have been replaced by other agents.

#### 2. Anticonvulsant

- ❑ *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.
- ❑ However, *phenobarbital* can depress cognitive development in children and decrease cognitive performance in adults, and it should be used for seizures only if other therapies have failed.
- ❑ Similarly, *phenobarbital* may be used for the treatment of refractory status epilepticus.

#### 3. Sedative/hypnotic

- ❑ Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia.
- ❑ When used as hypnotics, they suppress REM sleep more than other stages.
- ❑ However, the use of barbiturates for insomnia is no longer generally accepted, given their adverse effects and potential for tolerance.
- ❑ ***Butalbital*** is commonly used in combination products (with *acetaminophen* and *caffeine* or *aspirin* and *caffeine*) as a sedative to assist in the management of tension or migraine headaches.

### D. Pharmacokinetics

- ⊕ Barbiturates are well absorbed after oral administration and distribute throughout the body.
- ⊕ All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue.
- ⊕ Barbiturates readily cross the placenta and can depress the fetus. These agents are metabolized in the liver, and inactive metabolites are excreted in urine.

### E. Adverse effects

- ⊕ Barbiturates cause drowsiness, impaired concentration, and mental and psychomotor impairment (Figure 9.9).

- ☹️ The CNS depressant effects of barbiturates synergize with those of *ethanol*.
- ☹️ Hypnotic doses of barbiturates produce a drug “hangover” that may lead to impaired ability to function normally for many hours after waking.
- ☹️ Occasionally, nausea and dizziness occur.
- ☹️ Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system.
- ☹️ Barbiturates are contraindicated in patients with acute intermittent porphyria.
- ☹️ Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest.
- ☹️ Withdrawal is much more severe than that associated with opioids and can result in death. Death may also result from overdose.
- ☹️ severe depression of respiration and central cardiovascular depression results in a shock-like condition with shallow, infrequent breathing.
- ☹️ Treatment includes supportive care and gastric decontamination for recent ingestions.

## Other Hypnotic Agents

### A. Zolpidem

- ❑ The hypnotic *zolpidem* [ZOL-pi-dem] is not structurally related to benzodiazepines, but it binds to GABA<sub>A</sub> receptors with relative selectivity for those with the  $\alpha_1$  subunit.
- ❑ *Zolpidem* has no anticonvulsant or muscle-relaxing properties at hypnotic doses.
- ❑ It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use.
- ❑ *Zolpidem* is rapidly absorbed after oral administration.
- ❑ It has a rapid onset of action and short elimination half-life (about 2 to 3 hours).
- ❑ The drug provides a hypnotic effect for approximately 5 hours (Figure 9.10).
- ❑ [Note: A lingual spray and an extended-release formulation are also available. A sublingual tablet formulation may be used for middle-of-the-night awakening.]
- ❑ *Zolpidem* undergoes hepatic oxidation by the CYP450 system to inactive products. Thus, drugs such as *rifampin*, which induce this enzyme system, shorten the half-life of *zolpidem*, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life.
- ❑ Adverse effects of *zolpidem* include headache, dizziness, anterograde amnesia, and next-morning impairment (especially with extended-release formulations).
- ❑ Sleep-walking, sleep-driving, and performing other activities while not fully awake have been reported.



- ❑ Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs, *zolpidem*, *zaleplon*, and *eszopiclone*, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics.
- ❑ All three agents are controlled substances.

## B. Zaleplon

- ❑ *Zaleplon* [ZAL-e-plon] is an oral nonbenzodiazepine hypnotic similar to *zolpidem*; however, *zaleplon* causes fewer residual effects on psychomotor and cognitive function compared to *zolpidem* or the benzodiazepines.
- ❑ This may be due to its rapid elimination, with a half-life of approximately 1 hour. The drug is metabolized by CYP3A4.

## C. Eszopiclone

- ❑ *Eszopiclone* [es-ZOE-pi-clone] is an oral nonbenzodiazepine hypnotic that has been shown to be effective for insomnia for up to 6 months.
- ❑ *Eszopiclone* is rapidly absorbed (time to peak, 1 hour), extensively metabolized by oxidation and demethylation via the CYP450 system, and mainly excreted in urine.
- ❑ Elimination half-life is approximately 6 hours.
- ❑ Adverse events with *eszopiclone* include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.

## D. Melatonin receptor agonists

- ❑ ***Ramelteon*** [ram-EL-tee-on] and ***tasimelteon*** [tas-i-MEL-tee-on] are selective agonists at the MT<sub>1</sub> and MT<sub>2</sub> subtypes of melatonin receptors.
- ❑ Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep–wake cycle.
- ❑ Stimulation of MT<sub>1</sub> and MT<sub>2</sub> receptors by *ramelteon* and *tasimelteon* is thought to induce and promote sleep.
- ❑ They have minimal potential for abuse, and no evidence of dependence or withdrawal has been observed. Therefore, *ramelteon* and *tasimelteon* can be administered long-term.
- ❑ *Ramelteon* is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency).
- ❑ Common adverse effects of *ramelteon* include dizziness, fatigue, and somnolence. *Ramelteon* may also increase prolactin levels.
- ❑ *Tasimelteon* is indicated for non–24-hour sleep–wake disorder, often experienced by patients who are blind.
- ❑ The most common adverse effects of *tasimelteon* are headache, abnormal dreams, increase in liver function tests, and possible upper respiratory tract infections.

- ❑ CYP450 1A2 and 3A4 are the principle isoenzymes required for metabolism of *ramelteon* and *tasimelteon*, and, thus, drug–drug interactions are possible with inducers or inhibitors of these enzymes.

#### E. Antihistamines

Antihistamines with sedating properties, such as diphenhydramine, *hydroxyzine*, and *doxylamine*, are effective in treating mild situational insomnia. However, they have undesirable adverse effects (such as anticholinergic effects) that make them less useful than the benzodiazepines and the nonbenzodiazepines. Sedative antihistamines are marketed in numerous over-the-counter products.

#### F. Antidepressants

The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades. *Doxepin* [DOX-e-pin], an older tricyclic agent with SNRI mechanisms of antidepressant and anxiolytic action, is approved at low doses for the management of insomnia. Other antidepressants, such as *trazodone* [TRAZ-oh-done], *mirtazapine* [mir-TAZ-a-pine], and other older tricyclic antidepressants with strong antihistamine properties are used off-label for the treatment of insomnia (see Chapter 10).

#### G. Suvorexant

- ❑ *Suvorexant* [soo-voe-REX-ant] is an antagonist of the orexin receptor.
- ❑ Orexin is a neuropeptide that promotes wakefulness.
- ❑ Antagonism of the effects of orexin suppresses the wake drive from this neuropeptide.
- ❑ This antagonism may also explain the adverse events that are similar to signs of narcolepsy and cataplexy.
- ❑ The loss of orexin-producing neurons is believed to be an underlying pathology for narcolepsy.
- ❑ Daytime somnolence and increased suicidal ideation are other reported adverse effects.
- ❑ *Suvorexant* is mainly metabolized by CYP450 3A4, and, thus, it may have drug interactions with CYP3A4 inducers or inhibitors.

Figure 9.11 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs.

With best regards,

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