Anxiolytic and Hypnotic Drugs

9

Jose A. Rey

I. OVERVIEW

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 other antidepressants (see Chapter 10).

II. 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, 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 γ-aminobutyric acid ($GABA_A$) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] The $GABA_A$ receptors are composed of a combination of five α, β, and γ subunits that span the postsynaptic membrane (Figure 9.3). For each subunit, many subtypes exist (for example, there are six subtypes of the α subunit). Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore (Figure 9.3). The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials.

BENZODIAZEPINES
Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam
Flurazepam DALMANE
Lorazepam ATIVAN
Midazolam VERSED
Oxazepam
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION

BENZODIAZEPINE ANTAGONIST
Flumazenil ROMAZICON

OTHER ANXIOLYTIC DRUGS
Antidepressants VARIOUS (SEE CHAPTER 10)
Buspirone BUSPAR

BARBITURATES
Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

OTHER HYPNOTIC AGENTS
Antihistamines VARIOUS (SEE CHAPTER 30)
Doxepin SILENOR
Eszopiclone LUNESTA
Ramelteon ROZEREM
Zaleplon SONATA
Zolpidem AMBIEN, INTERMEZZO, ZOLPIMIST

Figure 9.1
Summary of anxiolytic and hypnotic drugs.

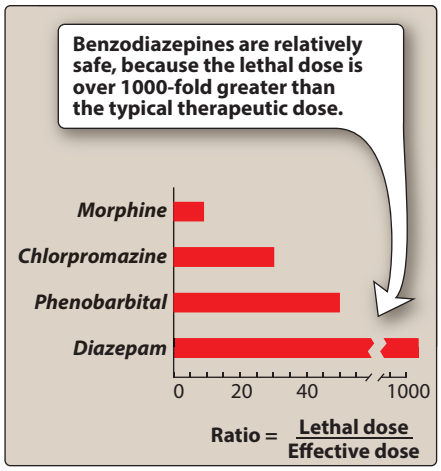

Figure 9.2
Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 14), *chlorpromazine* (an antipsychotic, see Chapter 11), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam.*

Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the α subunit and the γ subunit on the $GABA_A$ receptor (Figure 9.3). [Note: These binding sites are sometimes labeled "benzodiazepine (BZ) receptors." Common BZ receptor subtypes in the CNS are designated as BZ_1 or BZ_2 depending on whether the binding site includes an α_1 or α_2 subunit, respectively.] Benzodiazepines increase the frequency of channel openings produced by GABA. [Note: Binding of a benzodiazepine to its receptor site increases the affinity of GABA for the GABA-binding site (and vice versa).] The clinical effects of the various 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 to some extent:

1. **Reduction of anxiety:** At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having the α_2 subunit in their $GABA_A$ receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.

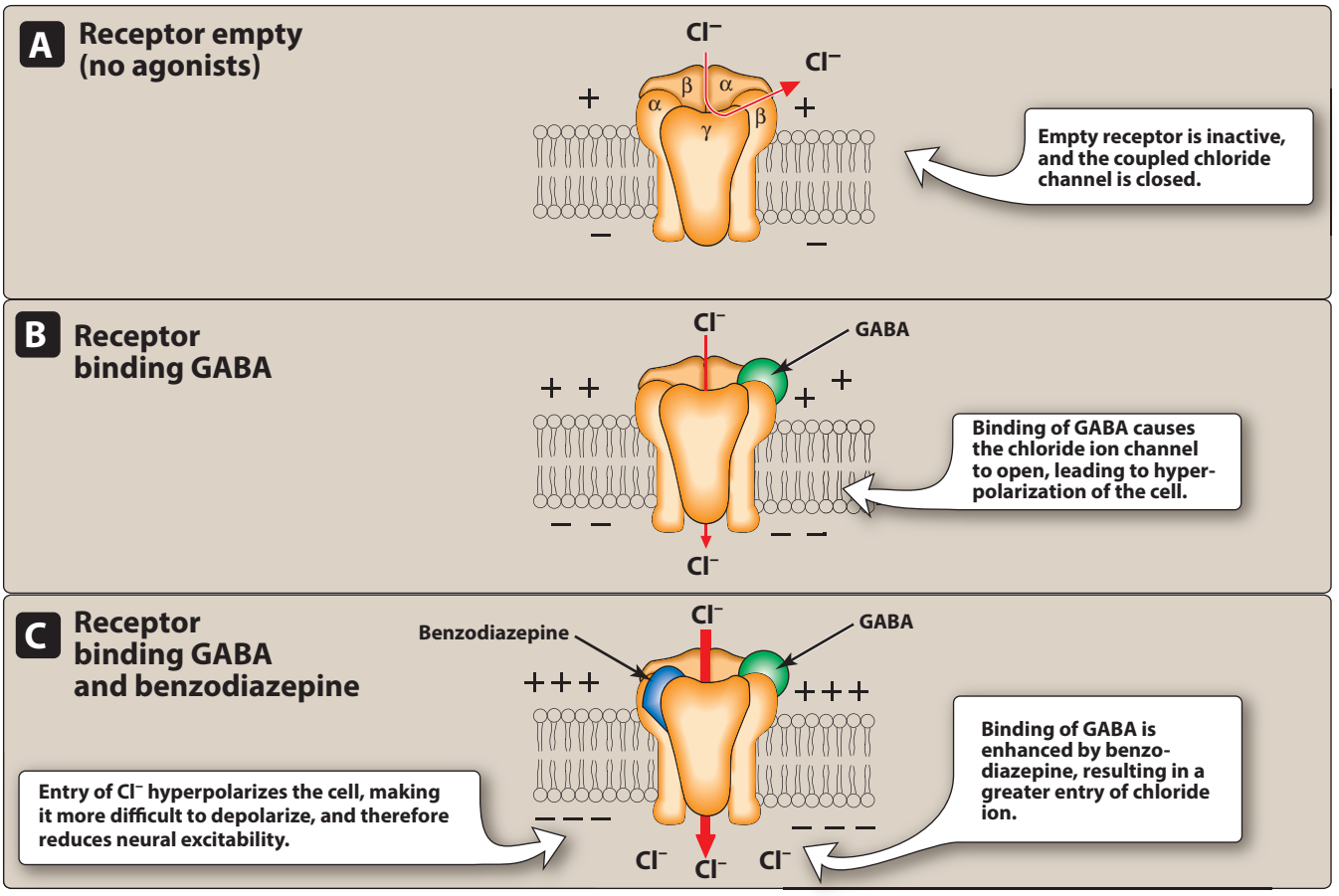

Figure 9.3
Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid.

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 α_1-$GABA_A$ receptors.

3. **Anterograde amnesia:** Temporary impairment of memory with use of the benzodiazepines is also mediated by the α_1-$GABA_A$ receptors. The ability to learn and form new memories is also impaired.

4. **Anticonvulsant:** Several benzodiazepines have anticonvulsant activity. This effect is partially, although not completely, mediated by α_1-$GABA_A$ 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 α_2-$GABA_A$ receptors are largely located. *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, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

1. **Anxiety disorders:** Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive–compulsive disorder, and extreme anxiety associated with 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 only and not used to manage the stress of everyday life. Because of their addiction 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 those patients with anxiety that may require prolonged treatment. The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. [Note: Tolerance (that is, decreased responsiveness to repeated doses of the drug) occurs when used for more than 1 to 2 weeks. Tolerance is associated with a decrease in GABA receptor density. Cross-tolerance exists between the benzodiazepines and *ethanol*.] For panic disorders, *alprazolam* [al-PRAY-zoe-lam] is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30% of patients.

2. **Sleep disorders:** A few of the benzodiazepines are useful as hypnotic agents. These agents decrease the latency to sleep onset and increase stage II of non–rapid eye movement (REM) sleep. Both REM sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation (“hangover”) upon

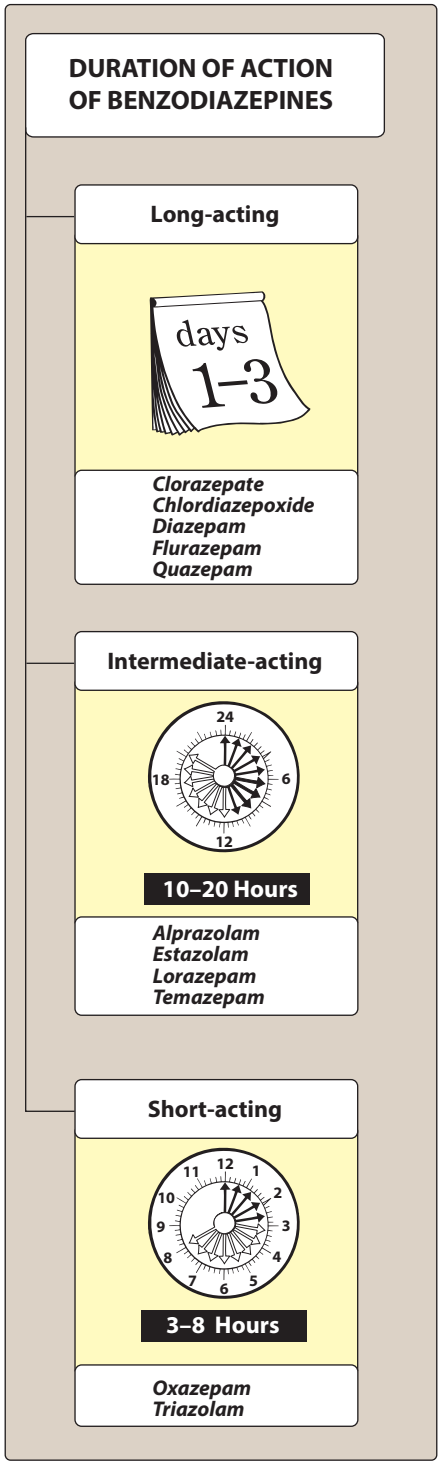

Figure 9.4
Comparison of the durations of action of the benzodiazepines.

awakening. Commonly prescribed benzodiazepines for sleep disorders include intermediate-acting *temazepam* [te-MAZ-e-pam] and short-acting *triazolam* [try-AY-zoe-lam]. 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.

   a. **Temazepam:** This drug is useful in patients who experience frequent wakening. However, because the peak sedative effect occurs 1 to 3 hours after an oral dose, it should be given 1 to 2 hours before bedtime.

   b. **Triazolam:** Whereas *temazepam* is useful for insomnia caused by the inability to stay asleep, short-acting *triazolam* is effective in treating individuals who have difficulty in going to sleep. Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia. Therefore, this drug is not a preferred agent, and it is best used intermittently. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 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 person to be receptive to instructions during these procedures. *Midazolam* [mi-DAY-zoe-lam] is a benzodiazepine used to facilitate amnesia while causing sedation prior to anesthesia.

4. **Seizures:** *Clonazepam* is occasionally used as an adjunctive therapy for certain types of seizures, whereas *lorazepam* and *diazepam* are the drugs of choice in terminating status epilepticus (see Chapter 12). 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, such as occur in muscle strain, 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 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. Drug effects are terminated not only by excretion but also by redistribution. 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 on benzodiazepines can develop if high doses of the drugs are given for a prolonged period. All benzodiazepines are controlled substances. Abrupt discontinuation of the benzodiazepines 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 side 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 long-term recall and retention of new knowledge) can occur with use of benzodiazepines. *Triazolam* often shows a rapid development of tolerance, early morning insomnia, and daytime anxiety, as well as amnesia and confusion.

Benzodiazepines should be used cautiously in patients with liver disease. These drugs should be avoided in patients with acute angle-closure glaucoma. 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, are taken concurrently.

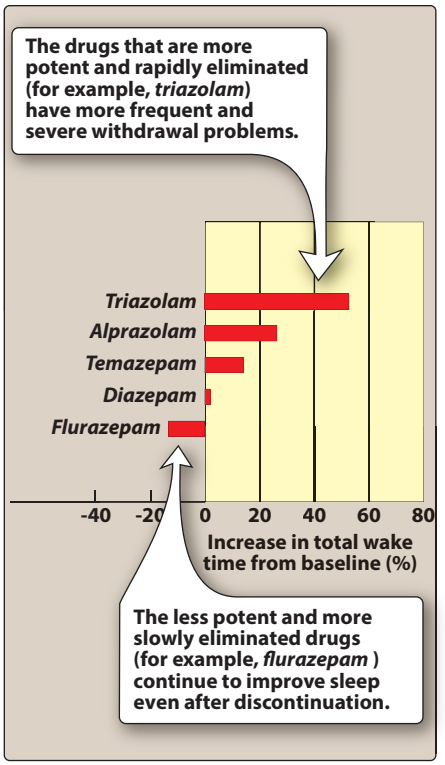

Figure 9.5
Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.

III. BENZODIAZEPINE ANTAGONIST

Flumazenil [floo-MAZ-eh-nill] is a GABA receptor antagonist that can rapidly reverse 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

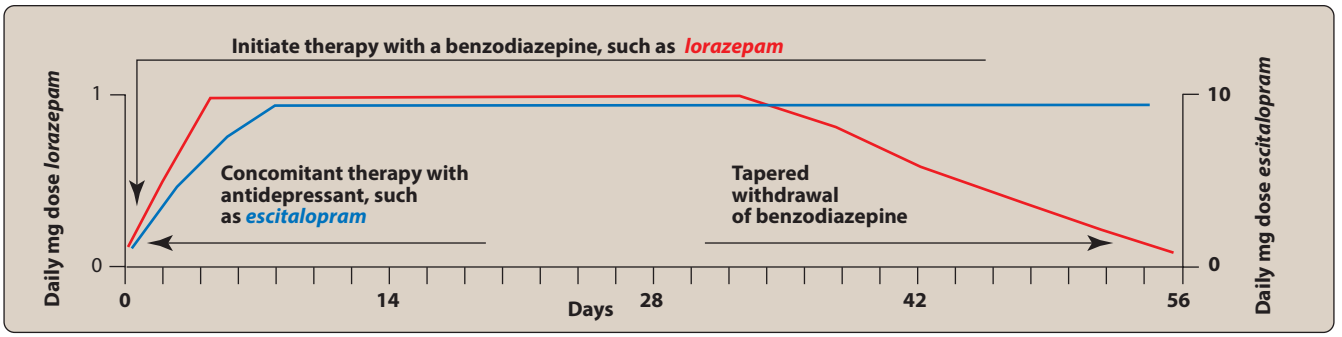

Figure 9.6
Treatment guideline for persistent anxiety.

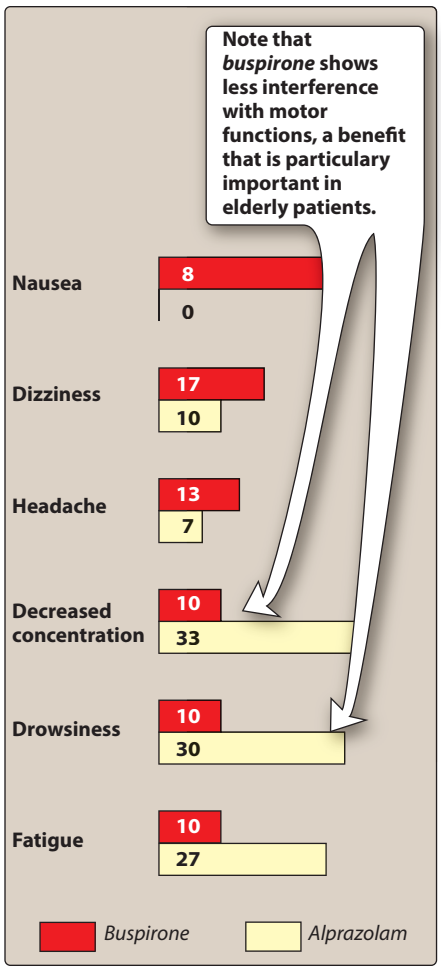

Figure 9.7
Comparison of common adverse effects of *buspirone* and *alprazolam*. Results are expressed as the percentage of patients showing each symptom.

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 side effects.

IV. 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. Selective serotonin reuptake inhibitors (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 low dose of a benzodiazepine during the first weeks 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. SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines and have become first-line treatment for GAD. While only certain SSRIs or SNRIs have been approved for the treatment of GAD, the efficacy of these drugs for GAD is most likely a class effect. Thus, the choice among these antidepressants should be based upon side effects and cost. 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 the benzodiazepines. It has a slow onset of action and is not effective for short-term or "as-needed" treatment of acute anxiety states. The actions of *buspirone* appear to be mediated by serotonin (5-HT_{1A}) receptors, although it also displays some affinity for D_2 dopamine receptors and 5-HT_{2A}

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 headaches, dizziness, nervousness, nausea, and light-headedness. 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 some common adverse effects of *buspirone* and the benzodiazepine *alprazolam.*

V. BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence and are associated with very severe withdrawal symptoms. All barbiturates are controlled substances. Certain barbiturates, such as the very short-acting *thiopental,* have been used to induce anesthesia but are infrequently used today due to the advent of newer agents with fewer adverse effects.

A. Mechanism of action

The sedative–hypnotic action of the barbiturates is due to their interaction with $GABA_A$ 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. Anesthetic concentrations of *pentobarbital* also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.

B. Actions

Barbiturates are classified according to their duration of action (Figure 9.8). For example, ultra–short-acting *thiopental* [thye-oh-PEN-tal] acts within seconds and has a duration of action of about 30 minutes. In contrast, 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.

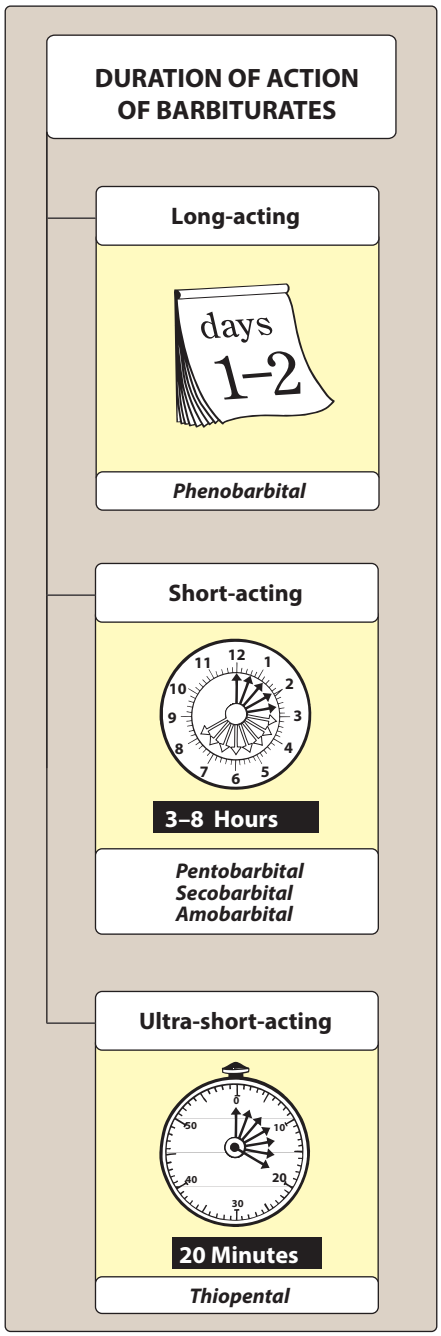

Figure 9.8
Barbiturates classified according to their durations of action.

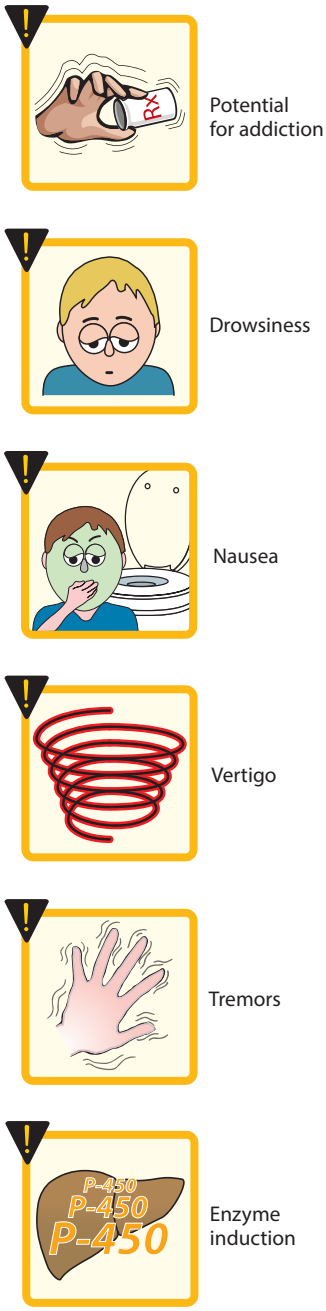

Figure 9.9
Adverse effects of barbiturates.

2. **Respiratory depression:** Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdosage is followed by respiratory depression and death.

C. Therapeutic uses

1. **Anesthesia:** The ultra–short-acting barbiturates, such as *thiopental,* have been used intravenously to induce anesthesia but have largely been replaced by other agents.

2. **Anticonvulsant:** *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression. It is used in long-term management of tonic–clonic seizures. However, *phenobarbital* can depress cognitive development in children and decrease cognitive performance in adults, and it should be used 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-type 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. This movement is important in causing the short duration of action of *thiopental* and similar short-acting derivatives. 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 physical sluggishness (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 opiates and can result in death. Death may also result from overdose. Severe depression of respiration is coupled with central cardiovascular depression and results in a shock-like condition with shallow, infrequent breathing. Treatment includes supportive care and gastric decontamination for recent ingestions.

VI. OTHER HYPNOTIC AGENTS

A. Zolpidem

The hypnotic *zolpidem* [ZOL-pi-dem] is not structurally related to benzodiazepines, but it selectively binds to the benzodiazepine receptor subtype BZ_1. *Zolpidem* has no anticonvulsant or muscle-relaxing properties. It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use. *Zolpidem* is rapidly absorbed from the gastrointestinal (GI) tract, and it has a rapid onset of action and short elimination half-life (about 2 to 3 hours). It 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 nightmares, agitation, anterograde amnesia, headache, GI upset, dizziness, and daytime drowsiness. 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. This may be due to their relative selectivity for the BZ_1 receptor. All three agents are controlled substances.

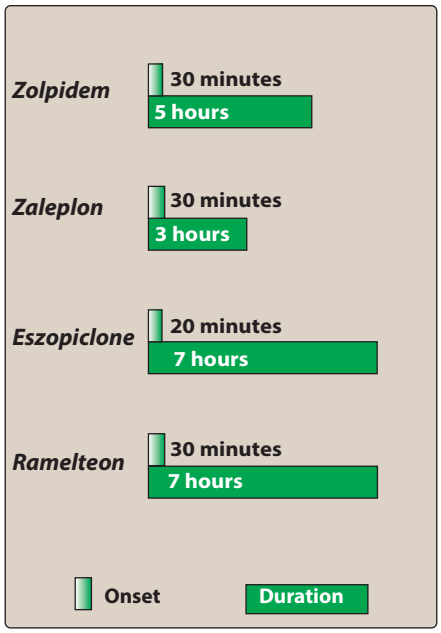

Figure 9.10
Onset and duration of action of the commonly used nonbenzodiazepine hypnotic agents.

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 also acts on the BZ_1 receptor. It 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. Ramelteon

Ramelteon [ram-EL-tee-on] is a selective agonist at the MT_1 and MT_2 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_1 and MT_2 receptors by *ramelteon* is thought to induce and promote sleep. *Ramelteon* is indicated for the treatment of insomnia characterized by difficulty falling asleep (increased sleep latency). It has minimal potential for abuse, and no evidence of dependence or withdrawal effects has been observed. Therefore, *ramelteon* can be administered long term. Common adverse effects of *ramelteon* include dizziness, fatigue, and somnolence. *Ramelteon* may also increase prolactin levels.

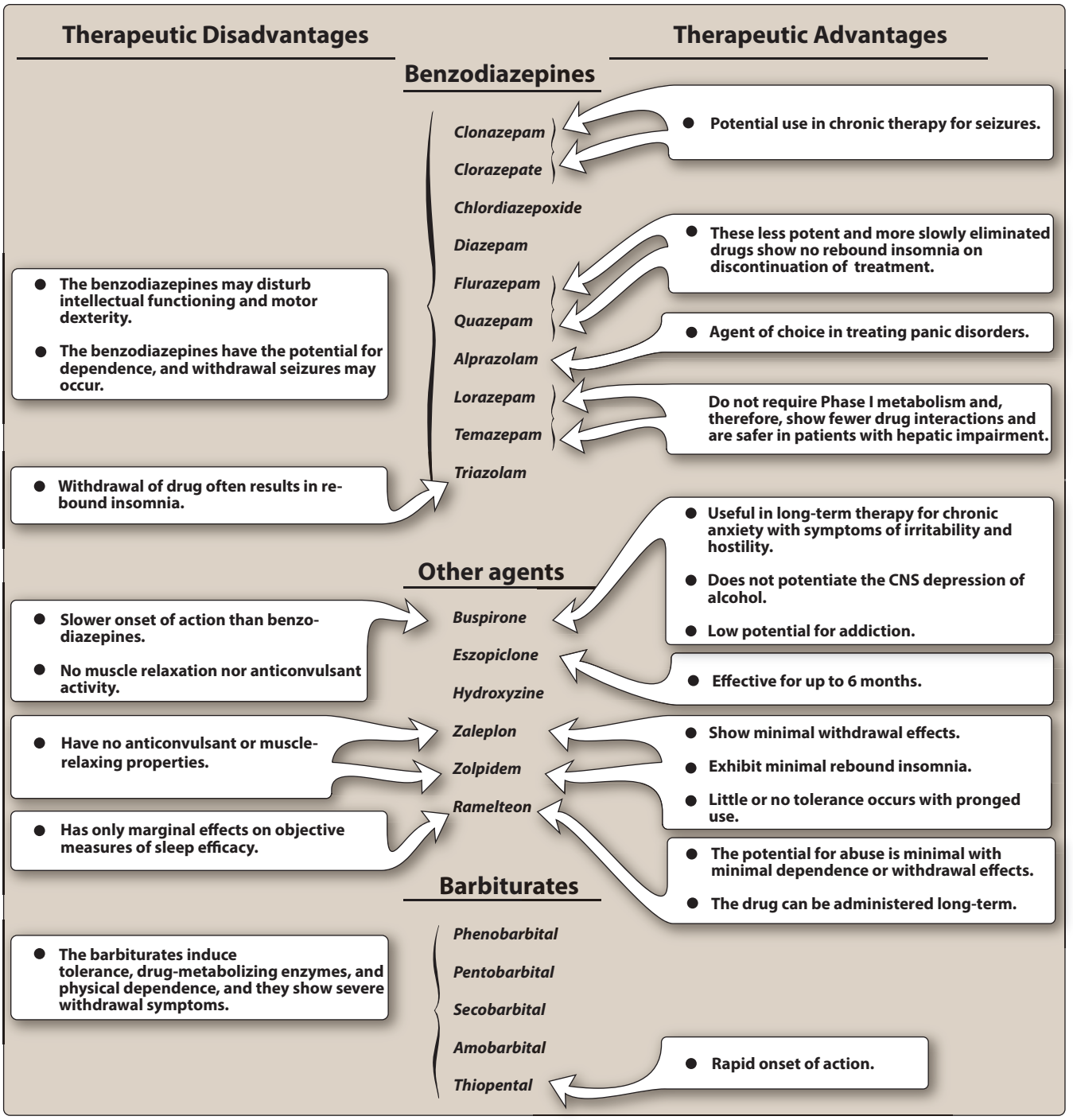

Figure 9.11
Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.

E. Antihistamines

Some antihistamines with sedating properties, such as *diphenhydramine, hydroxyzine,* and *doxylamine,* are effective in treating mild types of situational insomnia. However, they have undesirable side effects (such as anticholinergic effects) that make them less useful than the

benzodiazepines and the nonbenzodiazepines. Some 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, was recently 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).

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

Study Questions

Choose the ONE best answer.

9.1 Which one of the following statements is correct regarding benzodiazepines?

A. Benzodiazepines directly open chloride channels.
B. Benzodiazepines show analgesic actions.
C. Clinical improvement of anxiety requires 2 to 4 weeks of treatment with benzodiazepines.
D. All benzodiazepines have some sedative effects.
E. Benzodiazepines, like other CNS depressants, readily produce general anesthesia.

Correct answer = D. Although all benzodiazepines can cause sedation, the drugs labeled "benzodiazepines" in Figure 9.1 are promoted for the treatment of sleep disorder. Benzodiazepines enhance the binding of $GABA_A$ to its receptor, which increases the permeability of chloride. The benzodiazepines do not relieve pain but may reduce the anxiety associated with pain. Unlike the tricyclic antidepressants and the monoamine oxidase inhibitors, the benzodiazepines are effective within hours of administration. Benzodiazepines do not produce general anesthesia and, therefore, are relatively safe drugs with a high therapeutic index.

9.2 Which one of the following is a short-acting hypnotic?

A. Phenobarbital.
B. Diazepam.
C. Chlordiazepoxide.
D. Triazolam.
E. Flurazepam.

Correct answer = D. Triazolam is a short-acting drug. It has little daytime sedation. The other drugs listed are longer acting.

9.3 Which one of the following statements is correct regarding the anxiolytic and hypnotic agents?

A. Phenobarbital shows analgesic properties.
B. Diazepam and phenobarbital induce the cytochrome P450 enzyme system.
C. Phenobarbital is useful in the treatment of acute intermittent porphyria.
D. Phenobarbital induces respiratory depression, which is enhanced by the consumption of ethanol.
E. Buspirone has actions similar to those of the benzodiazepines.

Correct answer = D. Barbiturates and ethanol are a potentially lethal combination. Phenobarbital is unable to alter the pain threshold. Only phenobarbital strongly induces the synthesis of the hepatic cytochrome P450 drug-metabolizing system. Phenobarbital is contraindicated in the treatment of acute intermittent porphyria. Buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation.

9.4 A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

A. None.
B. Lorazepam.
C. Pentobarbital.
D. Phenytoin.
E. Buspirone.

Correct answer = B. It is important to treat the seizures associated with alcohol withdrawal. Benzodiazepines, such as chlordiazepoxide, diazepam, or the shorter-acting lorazepam, are effective in controlling this problem. They are less sedating than pentobarbital or phenytoin.

9.5 Which one of the following is a short-acting hypnotic and better for sleep induction compared to sleep maintenance?

A. Temazepam.
B. Flurazepam.
C. Zaleplon.
D. Buspirone.
E. Escitalopram.

Correct answer = C. Zaleplon has the shortest half-life and duration of action. Buspirone and escitalopram are not effective hypnotic agents. Temazepam and flurazepam have longer durations of action and will reduce nighttime awakenings but will have a greater risk of daytime sedation or hangover effect compared to zaleplon.

9.6 Which of the following agents has a rapid anxiolytic effect and would be best for the acute management of anxiety?

A. Buspirone.
B. Venlafaxine.
C. Lorazepam.
D. Escitalopram.
E. Duloxetine.

Correct answer = C. The benzodiazepines have same-dose, first-dose efficacy for anxiety, whereas the other agents require 2 to 8 weeks for clinically significant improvement in anxiety.

9.7 Which of the following sedative–hypnotic agents utilizes melatonin receptor agonism as the mechanism of action to induce sleep?

A. Zolpidem.
B. Eszopiclone.
C. Estazolam.
D. Ramelteon.
E. Diphenhydramine.

Correct answer = D. Ramelteon is the only melatonin receptor agonist to promote sleep, especially in sleep-phase disrupted sleep. Zolpidem, eszopiclone, and estazolam all utilize the benzodiazepine receptor, and diphenhydramine is a histamine receptor antagonist.

9.8 All of the following agents for the management of insomnia are controlled substances and may have a risk for addiction or dependence except:

A. Zaleplon.
B. Flurazepam.
C. Doxepin.
D. Zolpidem.
E. Triazolam.

Correct answer = C. Only doxepin, a tricyclic agent with significant antihistaminergic properties, is considered to have no risk of addiction or dependence, whereas the other agents listed all have DEA schedule IV designations with some risk for addiction or dependence, especially when used for extended periods.

9.9 All of the following agents may cause cognitive impairment, including memory problems when used at recommended doses except:

A. Diphenhydramine.
B. Zolpidem.
C. Alprazolam.
D. Phenobarbital.
E. Ramelteon.

Correct answer = E. All of the above listed agents, except ramelteon, have been associated with cognitive impairments, including memory impairment. Diphenhydramine likely causes its cognitive problems from its anticholinergic and antihistaminergic effects. Zolpidem, alprazolam, and phenobarbital are well-known causes of cognitive impairment, including anterograde amnesia. Ramelteon has safety data extending to 6 months and is a noncontrolled hypnotic agent acting as a melatonin receptor agonist. It is not considered to have a risk for cognitive impairment as compared to the other agents listed.

9.10 Which agent is best used in the Emergency Room setting for patients who are believed to have received too much of a benzodiazepine drug or taken an overdose of benzodiazepines?

A. Diazepam.
B. Ramelteon.
C. Flumazenil.
D. Doxepin.
E. Naloxone.

Correct answer = C. Flumazenil is only indicated to reverse the effects of benzodiazepines via antagonizing the benzodiazepine receptor. It should be used with caution due to a risk of seizures if the patient has been a long time recipient of benzodiazepines or if the overdose attempt was with mixed drugs. Naloxone is an opioid receptor antagonist. The other agents are not efficacious in reversing effects of benzodiazepines.