IV. **OTHER ANXIOLYTIC AGENTS**

1. **Antidepressants**

Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders and should be seriously consid- ered as fi rst-line agents, especially in patients with concerns for addic- tion or dependence or a history of addiction or dependence to other substances. Selective serotonin reuptake inhibitors (SSRIs, such a escit- alopram), or selective serotonin and norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine) may be used alone, or prescribed in com- bination with a low dose of a benzodiazepine during the fi rst weeks of treatment (Figure 9.6). After four to six weeks, when the antidepressant begins to produce an anxiolytic eff ect, the benzodiazepine dose can be tapered. SSRIs and SNRIs have a lower potential for physical depen- dence than the benzodiazepines, and have become fi rst-line treatment for GAD. While only certain SSRIs or SNRIs have been approved by the FDA for the treatment of GAD, the effi cacy of these drugs for GAD is most likely a class eff ect. Thus, the choice among these antidepressants can be based upon side eff ects and cost. Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefi t and prevent relapse. Please refer to Chapter 12 for a discussion of the antidepressant agents.

1. **Buspirone**

Buspirone [byoo-SPYE-rone] is useful for the chronic treatment of GAD and has an effi cacy comparable to that of the benzodiazepines. This agent is not eff ective for short-term or “as-needed” treatment of acute anxiety states. The actions of buspirone appear to be mediated by sero- tonin (5-HT1A) receptors, although other receptors could be involved, because buspirone displays some affinity for DA2 dopamine receptors and 5-HT2A serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. In addition, buspirone lacks the anticon- vulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation. However, it does cause hypothermia and can increase prolactin and growth hormone. The frequency of adverse effects is low, with the most common effects being headaches, dizzi- ness, nervousness, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. It does not potentiate the CNS depression of alcohol. Buspirone has the disadvantage of a slow onset of action. Figure 9.7 compares some of the common adverse effects of buspirone and the benzodiazepine alprazo- lam.

**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, drug-metabolizing enzymes, and physical dependence and are associated with very severe withdrawal symptoms. Foremost is their ability to cause coma in toxic doses. Certain barbiturates, such as the very short-acting thiopental, are still used to induce anesthesia (see p. 145).

1. **Mechanism of action**

The sedative-hypnotic action of the barbiturates is due to their interac- tion with GABAA receptors, which enhances GABAergic transmission. The binding site is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolong- ing the duration of the chloride-channel openings. In addition, barbitu- rates can block excitatory glutamate receptors. Anesthetic concentra- tions of pentobarbital also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.

1. **Actions**

Barbiturates are classified according to their duration of action (Figure 9.8). For example, thiopental [thye-oh-PEN-tal], which acts within sec- onds and has a duration of action of about 30 minutes, is used in the IV induction of anesthesia. By contrast, phenobarbital [fee-noe-BAR-bi- tal], which has a duration of action greater than a day, is useful in the treatment of seizures (see p. 187). Pentobarbital [pen-toe-BAR-bi-tal], secobarbital [see-koe-BAR-bi-tal], and amobarbital [am-oh-BAR-bi-tal] are short-acting barbiturates, which are effective as sedative and hyp- notic (but not anti-anxiety) agents.

1. **Depression of CNS**: At low doses, the barbiturates produce seda- tion (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 depres- sion 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 CO2, and overdosage is followed by respiratory depression and death.

3. **Enzyme induction**: Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are depen- dent on CYP450 metabolism to reduce their concentration.

C. **Therapeutic uses**

**1. Anesthesia**: Selection of a barbiturate is strongly infl uenced by the desired duration of action. The ultrashort-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.

2. **Anticonvulsant**: Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. Phenobarbital has been regarded as the drug of choice for treatment of young chil- dren with recurrent febrile seizures. However, phenobarbital can depress cognitive performance in children, and the drug should be used cautiously. Phenobarbital has specifi c anticonvulsant activity that is distinguished from the nonspecifi c CNS depression.

**3. Anxiety:** 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, most have been replaced by the benzodiazepines.

D. **Pharmacokinetics**

Barbiturates are absorbed orally and distributed widely throughout the body. All barbiturates redistribute in the body, from the brain to the splanchnic areas, to skeletal muscle, and, fi nally, to adipose tissue. This movement is important in causing the short duration of action of thio- pental 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 eff ects**

1. **CNS**: Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness (Figure 9.9). The CNS depressant eff ects of barbiturates synergize with those of ethanol.

2. **Drug hangover**: Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes. This drug hangover may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.

3. **Precautions**: As noted previously, barbiturates induce the CYP450 system and, therefore, may decrease the duration of action of drugs that are metabolized by these hepatic enzymes. Barbiturates increase porphyrin synthesis and are contraindicated in patients with acute intermittent porphyria.

4. **Physical dependence**: Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomit- ing, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death.

5. **Poisoning**: Barbiturate poisoning has been a leading cause of death resulting from drug overdoses for many decades. Severe depression of respiration is coupled with central cardiovascular depression and results in a shock-like condition with shallow, infrequent breathing. Treatment includes artificial respiration and purging the stomach of its contents if the drug has been recently taken. [Note: No specific barbiturate antagonist is available.] Hemodialysis may be necessary if large quantities have been taken. Alkalinization of the urine often aids in the elimination of phenobarbital.

VI. **OTHER HYPNOTIC AGENTS**

1. **Zolpidem**

The hypnotic zolpidem [ZOL-pi-dem] is not a benzodiazepine in struc- ture, but it acts on a subset of the benzodiazepine receptor family, BZ1. Zolpidem has no anticonvulsant or muscle-relaxing properties. It shows few withdrawal effects and exhibits minimal rebound insomnia and little or no 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) and provides a hyp- notic effect for approximately 5 hours (Figure 9.10). [Note: An extend- ed-release formulation is now available.] 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 this drug. Adverse effects of zolpidem include nightmares, agitation, 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 BZ1 receptor. B. Zaleplon Zaleplon (ZAL-e-plon) is very similar to zolpidem in its hypnotic actions, but zaleplon causes fewer residual effects on psychomotor and cogni- tive functions 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 (see p. 14).

1. **Eszopiclone**

Eszopiclone [es-ZOE-pi-clone] is an oral nonbenzodiazepine hypnotic (also using the BZ1 receptor similar to zolpidem and zaleplon) and is also used for treating insomnia. Eszopiclone been shown to be effec- tive for up to 6 months compared to a placebo. 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 reported with eszopiclone include anxiety, dry mouth, headache, peripheral ede- ma, somnolence, and unpleasant taste.

1. **Ramelteon**

Ramelteon [ram-EL-tee-on] is a selective agonist at the MT1 and MT2 subtypes of melatonin receptors. Normally, light stimulating the retina transmits a signal to the suprachiasmatic nucleus (SCN) of the hypo- thalamus that, in turn, relays a signal via a lengthy nerve pathway to the pineal gland that inhibits the release of melatonin from the gland. As darkness falls and light ceases to strike the retina, melatonin release from the pineal gland is no longer inhibited, and the gland begins to secrete melatonin. Stimulation of MT1 and MT2 receptors by melatonin in the SCN is able to induce and promote sleep and is thought to main- tain the circadian rhythm underlying the normal sleep–wake cycle. Ramelteon is indicated for the treatment of insomnia in which falling asleep (increased sleep latency) is the primary complaint. The poten- tial for abuse of ramelteon is believed to be minimal, and no evidence of dependence or withdrawal eff ects has been observed. Therefore, ramelteon can be administered long term. Common adverse eff ects of ramelteon include dizziness, fatigue, and somnolence. Ramelteon may also increase prolactin levels.

1. **Antihistamines**

Some antihistamines with sedating properties, such as diphenhy- dramine, hydroxyzine and doxylamine, are eff ective in treating mild types of insomnia. However, these drugs are usually ineff ective for all but the milder forms of situational insomnia. Furthermore, they have numerous undesirable side eff ects (such as anticholinergic eff ects) that make them less useful than the benzodiazepines. Some sedative anti- histamines are marketed in numerous over-the-counter products.

1. **Ethanol**

Ethanol (ethyl alcohol) has anxiolytic and sedative eff ects, but its toxic potential outweighs its benefi ts. Ethanol [ETH-an-ol] is a CNS depres- sant, producing sedation and, ultimately, hypnosis with increasing dosage. Because ethanol has a shallow dose–response curve, sedation occurs over a wide dosage range. It is readily absorbed orally and has a volume of distribution close to that of total body water. Ethanol is metabolized primarily in the liver, fi rst to acetaldehyde by alcohol dehy- drogenase and then to acetate by aldehyde dehydrogenase (Figure 9.11). Elimination is mostly through the kidney, but a fraction is excreted through the lungs. Ethanol synergizes with many other sedative agents and can produce severe CNS depression when used in conjunction with benzodiazepines, antihistamines, or barbiturates. Chronic consumption can lead to severe liver disease, gastritis, and nutritional defi ciencies. Cardiomyopathy is also a consequence of heavy drinking. The treatment of choice for alcohol withdrawal is the benzodiazepines. Carbamazepine is eff ective in treating convulsive episodes during withdrawal.

G**. Drugs to treat alcohol dependence**

1. **Disulfiram**: Disulfi ram [dye-SUL-fi -ram] blocks the oxidation of acet- aldehyde to acetic acid by inhibiting aldehyde dehydrogenase (see Figure 9.11). This results in the accumulation of acetaldehyde in the blood, causing fl ushing, tachycardia, hyperventilation, and nausea. Disulfi ram has found some use in the patient seriously desiring to stop alcohol ingestion. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant eff ects of disulfi ram-induced acetaldehyde accumulation.

2. **Naltrexone**: Naltrexone [nal-TREX-own] is a long-acting opiate antagonist that should be used in conjunction with supportive psy- chotherapy. Naltrexone is better tolerated than disulfi ram and does not produce the aversive reaction that disulfi ram does.

3. **Acamprosate**: Acamprosate [AK-om-PRO-sate] is an agent used in alcohol dependence treatment programs with an as yet poorly understood mechanism of action. This agent should also be used in conjunction with supportive psychotherapy.

Figure 9.12 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs.