

30

Sedative–hypnotic and Anxiolytic
Drugs

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DRUG LIST

GENERIC NAME	PAGE	GENERIC NAME	PAGE
Alprazolam	357	Lorazepam	357
Bupirone	356	Midazolam	359
Chloral hydrate	361	Oxazepam	357
Chlordiazepoxide	359	Prazepam	357
Clonazepam	359	Propranolol	361
Clorazepate	357	Temazepam	357
Diazepam	359	Triazolam	357
Flurazepam	357	Zephalon	360
Hydroxyzine	361	Zolpidem	360

The primary use of sedative–hypnotic and anxiolytic drugs is to encourage calmness (*anxiolytics* or *sedatives*) or to produce sleep (*sedative–hypnotics*). All people are subject to states of emotional tension and uneasiness. For otherwise healthy individuals, these occasions are usually sufficiently mild and short that pharmacological intervention is unnecessary. However, at times the symptoms of anxiety become quite discomforting and can interfere with a person's ability to function effectively. Anxiety almost invariably accompanies many medical and surgical conditions, and it is often a symptom of psychiatric illness. When the symptoms become intolerable or interfere with the treatment of the underlying disease and if counseling is not sufficient, drug treatment can be considered as a means of helping patients cope with their anxiety.

All central nervous system depressants have some ability to relieve anxiety. However, most of these drugs

relieve symptoms of anxiety only at doses that produce noticeable sedation. Drugs used to produce sedation and relieve anxiety are consistently among the most commonly prescribed drugs. Whether they are prescribed too frequently remains a matter of controversy.

Insomnia includes a wide variety of sleep disturbances, such as difficulty in falling asleep, early or frequent awakenings, and remaining unrefreshed after sleep. Use of sedative–hypnotic drugs is one approach to the therapy of insomnia. Other measures include advice to avoid stimulants before retiring, maintenance of a proper diet, initiation of an exercise program, and avoidance of stressful or anxiety-provoking situations.

Most anxiolytic and sedative–hypnotic drugs produce dose-dependent depression of central nervous system function. The ideal anxiolytic drug should calm the patient without causing too much daytime sedation and drowsiness and without producing physical or psycho-

logical dependence. Similarly, the ideal hypnotic drug should allow the patient to fall asleep quickly and should maintain sleep of sufficient quality and duration so that the patient awakes refreshed without a drug hangover. Also, both types of drugs should have very low toxicity and should not interact with other medications in such a way as to produce unwanted or dangerous effects.

AZAPIRONES

Buspirone (*BuSpar*) is the first example of a class of anxiolytic agents that can relieve some symptoms of anxiety in doses that do not cause sedation. Buspirone is structurally unrelated to existing psychotropic drugs.

Mechanism of Action

Although buspirone has been shown to interact with a number of neurotransmitter systems in the brain, it appears that its clinically relevant effects are mediated through interactions at the serotonin (5-hydroxytryptamine, 5-HT) 5-HT_{1A} receptor, where it acts as a partial agonist.

Pharmacokinetics

Buspirone is well absorbed from the gastrointestinal tract, and peak blood levels are achieved in 1 to 1.5 hours; the drug is more than 95% bound to plasma proteins. Buspirone is extensively metabolized, with less than 1% of the parent drug excreted into the urine unchanged. At least one of the metabolic products of buspirone is biologically active. The parent drug has an elimination half-life of 4 to 6 hours.

Pharmacological Actions

Buspirone is as effective as the benzodiazepines in the treatment of general anxiety. However, the full anxiolytic effect of buspirone takes several weeks to develop, whereas the anxiolytic effect of the benzodiazepines is maximal after a few days of therapy. In therapeutic doses, buspirone has little or no sedative effect and lacks the muscle relaxant and anticonvulsant properties of the benzodiazepines. In addition, buspirone does not potentiate the central nervous system depression caused by sedative-hypnotic drugs or by alcohol, and it does not prevent the symptoms associated with benzodiazepine withdrawal.

Clinical Uses

Buspirone is effective in general anxiety and in anxiety with depression.

Adverse Effects

Like the benzodiazepines, buspirone appears to be safe even when given in very high doses. The most common side effects are dizziness, light-headedness, and headache. Abuse, dependence, and withdrawal have not been reported, and buspirone administration does not produce any cross-tolerance to the benzodiazepines. Buspirone has been reported to increase blood pressure in patients taking monoamine oxidase inhibitors, and it may increase plasma levels of haloperidol if coadministered with that agent.

BENZODIAZEPINES

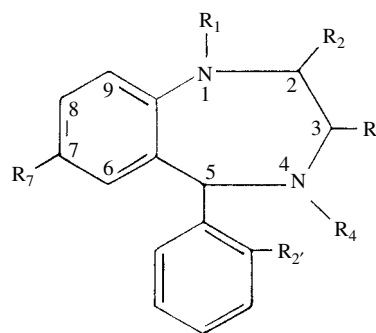
The benzodiazepines constitute the most commonly used group of anxiolytics and sedative-hypnotics. Since the first member of this group, *chlordiazepoxide*, was introduced, many congeners have been marketed. Most of these drugs possess anxiolytic, sedative-hypnotic, and anticonvulsant properties. Thus, the clinical indications for specific benzodiazepines are not absolute, and their uses overlaps considerably.

Chemistry

The basic chemical structure of the benzodiazepines consists of a benzene ring coupled to a seven-member heterocyclic structure containing two nitrogens (diazepine) at positions 1 and 4 (Fig. 30.1). Of the 2,000 benzodiazepines that have been synthesized, approximately 15 clinically useful compounds are on the market in the United States (Table 30.1).

Mechanism of Action

The benzodiazepines bind with high affinity to specific macromolecules within the central nervous system. *These benzodiazepine-binding sites (receptors) are closely associated with the receptors for γ -aminobutyric*



1,4-Benzodiazepine nucleus

FIGURE 30.1

General structure of 1,4 benzodiazepines.

TABLE 30.1 Clinical Uses of the Sedative–Hypnotic and Anxiolytic Drugs

Drugs	Therapeutic Uses
Alprazolam (<i>Xanax</i>)	Anxiety
Buspirone (<i>BuSpar</i>)	Anxiety
Chloral hydrate (<i>Noctec, Somnos</i>)	Insomnia
Chlordiazepoxide (<i>Librium</i>)	Anxiety, alcohol withdrawal
Chlorazepate (<i>Tranxene</i>)	Anxiety
Diazepam (<i>Valium</i>)	Anxiety, muscle relaxation, status epilepticus
Flurazepam (<i>Dalmane</i>)	Insomnia
Flumazenil (<i>Romazicon</i>)	Reverse benzodiazepine-induced sedation
Hydroxyzine (<i>Atarax, Vistaril</i>)	Anxiety
Lorazepam (<i>Ativan</i>)	Anxiety
Midazolam (<i>Versed</i>)	Anesthesia
Oxazepam (<i>Serax</i>)	Anxiety
Prazepam (<i>Centrax</i>)	Anxiety
Propranolol (<i>Inderal</i>)	Anxiety
Temazepam (<i>Restoril</i>)	Insomnia
Triazolam (<i>Halcion</i>)	Insomnia
Zolpidem (<i>Ambien</i>)	Insomnia
Zaleplon (<i>Sonata</i>)	Insomnia

acid (GABA), which is the major inhibitory neurotransmitter in the mammalian brain. Benzodiazepines potentiate GABAergic neurotransmission in essentially all areas of the central nervous system. This enhancement is thought to occur indirectly at the postsynaptic GABA_A receptor complex.

The functional significance of this drug–receptor interaction is that the *receptor complex regulates the entrance of chloride into the postsynaptic cells*. The increase in chloride conductance mediated by GABA is intensified by the benzodiazepines. This facilitation of GABA-induced chloride conductance results in greater hyperpolarization of these cells and therefore leads to diminished synaptic transmission.

Another chemical class of sedative–hypnotic drugs, the *barbiturates*, also binds to receptors associated with the GABA–chloride ionophore, but these drugs appear to prolong rather than intensify GABA's effects. Fig. 24.4 shows the presumed drug receptor–GABA–chloride ionophore relationship.

In addition to the clinically useful benzodiazepines, which act as agonists at the benzodiazepine receptor, at least two other types of ligands also interact with this binding site. These are the benzodiazepine receptor *antagonists* and the *inverse agonists*. For example, flumazenil (*Romazicon*) is a receptor antagonist that selectively blocks the effects of other benzodiazepines at their binding sites; it has clinical application in the treat-

ment of benzodiazepine overdose and in the reversal of benzodiazepine-induced sedation. The inverse agonists are compounds that interact with benzodiazepine receptors and decrease, rather than increase, GABA-mediated changes. They also can antagonize the effects of benzodiazepine agonists and when administered alone, can be anxiogenic and proconvulsant.

Pharmacokinetics

Benzodiazepines are usually given orally and are well absorbed by this route. Since the benzodiazepines are weak bases, they are less ionized in the relatively alkaline environment of the small intestine, and therefore, most of their absorption takes place at this site. For emergency treatment of seizures or when used in anesthesia, the benzodiazepines also can be given parenterally. Diazepam and lorazepam are available for intravenous administration.

The distribution of the benzodiazepines from blood to tissues and back again is a dynamic process with considerable influence on the onset and duration of the therapeutic effects produced by these compounds. Those having greater lipid solubility tend to enter the central nervous system more rapidly and thus tend to produce their effects more quickly. Several of the benzodiazepines have therapeutic effects that are much shorter in duration than would be predicted based on their rates of metabolism and excretion; redistribution away from the central nervous system is of primary importance in terminating their therapeutic effects.

Although tissue redistribution of benzodiazepines may be an important means of terminating the actions of selected members of this class of drugs, many benzodiazepines do undergo extensive biotransformation. Metabolism takes place both by dealkylation (phase 1) and conjugation (phase 2) reactions. In many instances, dealkylation can result in the formation of pharmacologically active compounds. Indeed, *most clinically available benzodiazepines are converted in the liver to one or more active metabolites*. In several cases the active metabolites have a much longer half-life than the parent compound. In one case, acid hydrolysis in the stomach converts an inactive compound (clorazepate) to an active drug (nordazepam). Figure 30.2 shows the biotransformations involved in the metabolism of representative benzodiazepines. The water-soluble metabolites of the benzodiazepines are excreted primarily in the urine.

Since most of the benzodiazepines do undergo biotransformation, it is possible that changes in liver function may alter the duration of the therapeutic effect produced by these drugs. Despite the fact that few clinical studies have demonstrated serious toxicities associated with benzodiazepine administration in individuals with compromised liver function, prudence in the use of

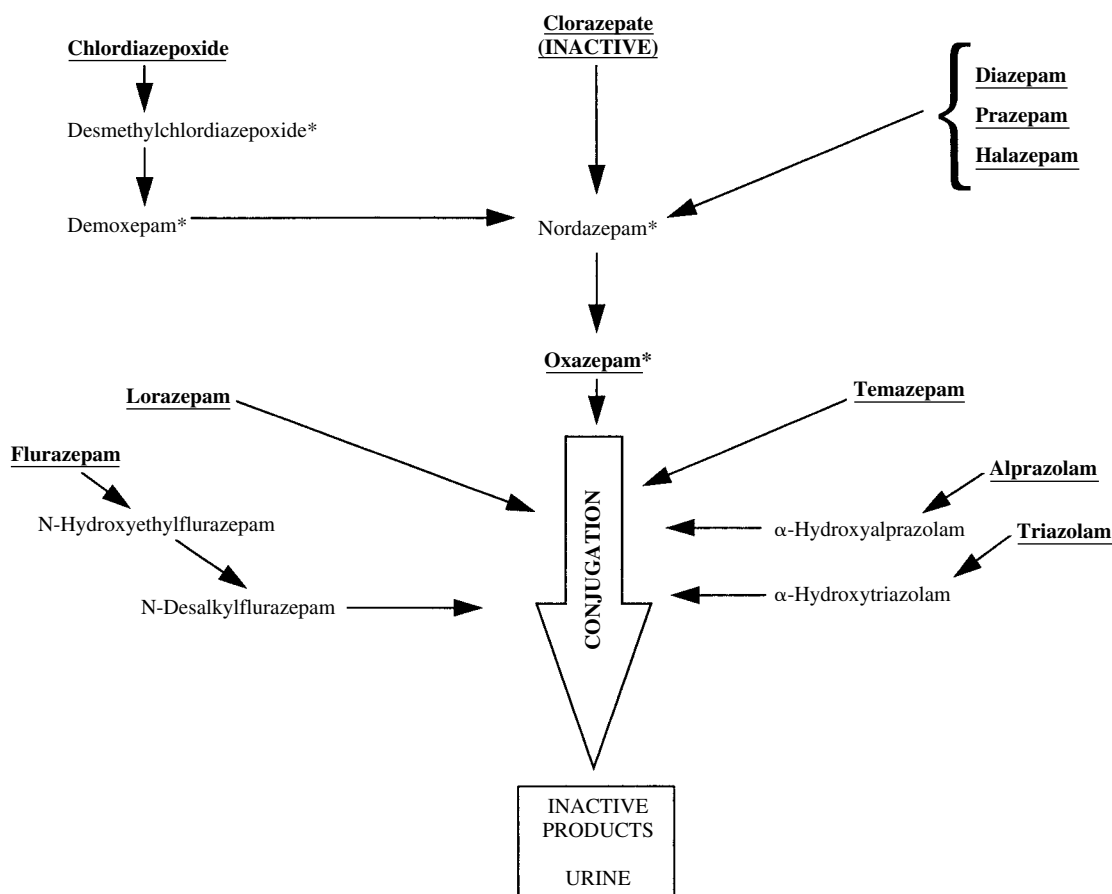


FIGURE 30.2

The metabolism of some benzodiazepines. In some cases, several active metabolites are formed. A result is very long apparent half-lives. In many cases, the ultimate product is oxazepam. *Active metabolic product.

these compounds in the elderly and in individuals with liver disease seems advisable.

One of the great disadvantages associated with many of the sedative and hypnotic drugs (e.g., barbiturates, propanediol carbamates), which have now largely been replaced by the benzodiazepines, is the fact that those drugs are very effective inducers of hepatic drug-metabolizing enzymes. Since the benzodiazepines are only weak inducers of hepatic microsomal enzymes, they cause relatively few clinically significant drug interactions related to metabolism of other drugs.

Pharmacological Actions

Although it is widely claimed that the benzodiazepine drugs have a specific calming or anxiolytic effect, their most prominent and easily quantifiable action is central nervous system depression. In very low therapeutic doses, this depression manifests as relief of anxiety that is often accompanied by a feeling of sluggishness or drowsiness. As the dose is increased, the degree of depression is intensified such that muscle relaxation, hyp-

nosis, and a more intense central nervous system depression occur. This depression is related to the ability of these drugs to facilitate the inhibitory actions of GABA.

A significant advantage of the benzodiazepines over other central nervous system depressants (e.g., the barbiturates) is that they possess a much greater separation between the dose that produces sleep and the dose that produces death. *This increased margin of safety has been one of the major reasons benzodiazepines have largely replaced the barbiturates and other types of sedative-hypnotics in the treatment of anxiety and insomnia.* In addition, benzodiazepine administration is associated with few side effects.

Clinical Uses Anxiety

Anxiety disorders are among the most common forms of psychiatric illness. Anxiety often accompanies other psychiatric disease and such medical illnesses as angina pectoris, gastrointestinal disorders, and hypertension.

Anxiety that results from fear caused by an acute illness or a stressful event, such as a divorce or the loss of a loved one, is usually self-limiting and can be of relatively short duration. Other disorders that have anxiety as a component are not necessarily associated with a life event, and may persist for considerable periods, even throughout the individual's life.

Both acute and chronic anxiety can be treated with benzodiazepines, although it is anticipated that for most anxiety disorders counseling will also play an important role. Benzodiazepines employed in the treatment of anxiety should be used in the lowest effective dose for the shortest duration so that they will provide maximum benefit to the patient while minimizing the potential for adverse reactions. For most types of anxiety, none of the benzodiazepines is therapeutically superior to any other. Choice of a particular agent is usually made on the basis of pharmacokinetic (Table 30.2) considerations. A benzodiazepine with a long half-life should be considered if the anxiety is intense and sustained. A drug with a short half-life may have advantages when the anxiety is provoked by clearly defined circumstances and is likely to be of short duration.

Insomnia

All of the benzodiazepines will produce sedative–hypnotic effects of sufficient magnitude to induce sleep, provided that the dose is high enough. However, the aim in the treatment of sleep disorders is to induce sleep that is as close as possible to natural sleep so that the patient falls asleep quickly, sleeps through the night, and has sleep of sufficient quality to awake refreshed.

Extensive sleep studies have been conducted with a variety of sedative–hypnotic drugs, and all of these drugs appear to alter the normal distribution of rapid eye movement (REM) and non-REM sleep. Most of the older sedative–hypnotic agents markedly depress REM sleep. In contrast, when the benzodiazepines are used in appropriate doses, they depress REM sleep to a much smaller extent. As with treatment of anxiety, the choice

of a particular benzodiazepine to treat a sleep disturbance is again generally based on pharmacokinetic criteria. While longer-acting compounds may ensure that a patient will sleep through the night, they also may cause cumulative effects resulting in daytime sluggishness or drug hangover. Shorter-acting compounds avoid the hangover problem, but their use may be associated with early awakening and an increase in daytime anxiety.

Epilepsy and Seizures

Nearly all central nervous system depressants have some capacity to suppress seizures by virtue of their depressant activity on the brain and spinal cord. Clonazepam and diazepam are two benzodiazepines that depress epileptiform activity and are used in the treatment of epilepsy and seizure disorders (see Chapter 32).

Sedation, Amnesia, and Anesthesia

Benzodiazepines have the capacity to produce a calming effect and to cause *anterograde amnesia*, in which the patient cannot recall events that took place for some time after the drug was administered. Benzodiazepine-induced sedation and amnesia are deemed useful in the preparation of patients for anesthesia, surgery, and other frightening or unpleasant medical and dental procedures and diagnostic tests. Midazolam is a frequently used anesthetic benzodiazepine (see Chapter 25).

Muscle Relaxation

Benzodiazepines have the capacity to depress polysynaptic reflexes and have been shown to decrease decerebrate rigidity in cats and spasticity in patients with cerebral palsy. What is not clear is whether they can, in humans, relax voluntary muscles in doses that do not cause considerable central nervous system depression. Nevertheless, benzodiazepines, such as diazepam, are often prescribed for patients who have muscle spasms and pain as a result of injury. In these circumstances, the sedative and anxiolytic properties of the drug also may promote relaxation and relieve tension associated with the condition.

Alcohol and Sedative–Hypnotic Withdrawal

Withdrawal from long-term high-dose use of alcohol or sedative–hypnotic drugs can be life threatening if physical dependence is present. Benzodiazepines, such as chlordiazepoxide (*Librium*) and diazepam (*Valium*), are sometimes used to lessen the intensity of the withdrawal symptoms when alcohol or sedative–hypnotic drug use is discontinued. Benzodiazepines are also employed to help relieve the anxiety and other behavioral symptoms that may occur during rehabilitation.

TABLE 30.2 Pharmacokinetic Properties of Selected Benzodiazepines

Drug	Time to peak (hr)	Elimination half-life (hr)*
Chlordiazepoxide	0.5–2.0	8–20
Diazepam	0.5–1.5	20–60
Flurazepam	0.5–1.0	24–120
Alprazolam	1.0–2.0	12–15
Oxazepam	2.0–4.0	4–12
Triazolam	1.5–2.0	3–5

*Includes parent compounds and active metabolites.

Adverse Effects and Toxicities

Most adverse effects associated with use of the benzodiazepines are related to their ability to produce central nervous system depression. These include drowsiness, excessive sedation, impaired motor coordination, confusion, and memory loss. These effects are most troublesome during the initial week or two of treatment. Subsequently, the patient becomes tolerant and these effects produce less difficulty. Although for most individuals these symptoms are mild, patients should be cautioned against engaging in potentially dangerous tasks such as operating machinery or driving a car during the initial treatment period.

Less common adverse effects include blurred vision, hallucinations, and paradoxical reactions consisting of excitement, stimulation, and hyperactivity. Also, a variety of gastrointestinal complaints occur, and blood dyscrasias have been reported, but these are rare. Benzodiazepine administration during pregnancy, delivery, or lactation has the potential to have adverse effects on the fetus or newborn.

As with other central nervous system depressants, the effects of benzodiazepines are additive with those of ethanol. Patients should be warned that *ethanol-containing beverages may produce a more profound depression when taken simultaneously with a benzodiazepine.*

One of the major reasons for the popularity of the benzodiazepines is their relative safety. Overdoses with the benzodiazepines occur commonly, but fatal toxic occurrences are rare. Fatal intoxications are more likely in children, in individuals with respiratory difficulties, and in individuals who have consumed another central nervous system depressant, such as alcohol. After an overdose, the patient begins a deep sleep that may last for 24 to 48 hours, depending on the dose. However, even with large overdoses, the patient can usually still be aroused.

Tolerance and dependence do occur with the use of benzodiazepines. Discontinuation of drug administration, particularly abrupt withdrawal, can be associated with a variety of symptoms, including rebound insomnia and rebound anxiety. The level of insomnia or anxiety may even exceed that which preceded the treatment. Usually, *a gradual tapering of the dose until it is eventually discontinued lessens the likelihood of a withdrawal reaction*, although in some individuals even this method of drug removal can result in anxiety, apprehension, tension, insomnia, and loss of appetite. More severe symptoms may occur when an individual withdraws from a supratherapeutic dose, particularly if the drug has been taken for months or years. These symptoms can include, in addition to those already mentioned, muscle weakness, tremor, hyperalgesia, nausea, vomiting, weight loss, and possibly convulsions.

Drug Interactions

When used with other sedative-hypnotics or alcohol, the benzodiazepines will produce additive central nervous system depression.

Many benzodiazepines are metabolized by the cytochrome P450 (CYP) enzyme designated CYP3A4. CYP3A4 is inhibited by grapefruit juice and by drugs such as ketoconazole, itraconazole, nefazodone, erythromycin, and ritonavir. Coadministration of these substances along with a benzodiazepine may result in intensification and prolongation of the benzodiazepine effect. Conversely, rifampin, carbamazepine, and phenytoin can induce the CYP3A4 enzyme, and therefore their coadministration can reduce the therapeutic effect of the benzodiazepines.

OTHER BENZODIAZEPINE RECEPTOR AGONISTS

Zolpidem (*Ambien*) and zaleplon (*Sonata*) are structurally unrelated to the benzodiazepines, but both drugs share pharmacological properties with the benzodiazepines. They bind to benzodiazepine receptors and facilitate GABA-mediated inhibition.

In usual sedative doses, zolpidem preserves deep sleep (stages 3 and 4) and has only minor and inconsistent effects on REM sleep. Compared with the benzodiazepines, zolpidem has relatively weak anxiolytic, anticonvulsant, and skeletal muscle relaxant properties at therapeutic doses. Zolpidem has a rapid onset and a relatively short duration of action. It is well absorbed after oral administration, with approximately 70% bioavailability. It undergoes hydroxylation and oxidation to inactive metabolites in the liver. Its elimination half-life is approximately 2.5 hours, which is usually sufficient to provide for a normal 8 hours of sleep without daytime grogginess.

Principal side effects are gastrointestinal and central nervous system symptoms, including drowsiness, dizziness, and diarrhea. Zolpidem may increase the depressant effects of other sedative drugs, such as the antipsychotics, tricyclic antidepressants, and antihistamines.

There is less therapeutic experience with the newer zaleplon than with zolpidem. Zaleplon has a rapid onset and a half-life of approximately 1 hour. It is extensively metabolized by aldehyde dehydrogenase, so that less than 1% of a dose is excreted unchanged. Because of its rapid onset of action and short biological half-life, zaleplon is well suited for treatment of sleep onset insomnia. Its short half-life often does not ensure a full 8 hours of sleep.

SEDATIVES AND ANXIOLYTICS WITH OTHER MAJOR USES

Antihistamines

Several H₁ histamine antagonists (e.g., diphenhydramine, promethazine, and hydroxyzine) have been used as sedative–hypnotics, since they produce some degree of sedation. While this sedation is usually considered a side effect of their antihistaminic activity, in some cases the sedation is sufficient to allow the drugs to be used in the treatment of anxiety and sleep disturbances. For these drugs, *the anxiolytic properties are thought to be a direct consequence of their ability to produce sedation.*

Hydroxyzine hydrochloride (*Atarax, Vistaril*) is the antihistamine with the greatest use in the treatment of anxiety. It is often used to reduce the anxiety that is associated with anesthesia and surgery. It also produces sedation, dries mucous membranes (via an anticholinergic mechanism), and has antiemetic activity. A more extensive discussion of the pharmacology of the H₁-receptor antagonists is found in Chapter 38.

β -Adrenoceptor Blocking Agents

β -Adrenoceptor antagonists, such as propranolol (*Inderal*), have been widely used in the treatment of cardiovascular diseases (see Chapters 16 and 20). These β -blockers also are useful in some forms of anxiety, particularly those that are characterized by somatic symptoms or by performance anxiety (stage fright). There is general agreement that β -blockers can lessen the severity and perhaps prevent the appearance of many of the autonomic responses associated with anxiety. These symptoms include tremors, sweating, tachycardia, and palpitations.

Antidepressants

Antidepressant drugs, such as the *tricyclic antidepressants* and the *selective serotonin reuptake inhibitors (SSRIs)*, are very important for the treatment of psychotic depression (see Chapter 34). They have been shown to be effective when used in the treatment of several anxiety disorders, including general anxiety, obsessive-compulsive disorder, and several phobias, including agoraphobia. Because the SSRIs are less toxic than the tricyclic antidepressants, their use in the treatment of anxiety is safer and less likely to produce serious side effects.

OLDER SEDATIVE–HYPNOTIC AND ANXIOLYTIC AGENTS

Before the introduction of the benzodiazepines, a number of drugs from different chemical and pharmacological classes were used in the treatment of anxiety and insomnia. However, these drugs are more toxic and produce more serious side effects than do the benzodiazepines. Many also have significant abuse potential. Consequently, most of these compounds are no longer widely used. These drugs include the barbiturates (e.g., pentobarbital, amobarbital), carbamates (e.g., meprobamate), piperidinediones (e.g., glutethimide), and alcohols (e.g., ethchlorvynol).

Chloral hydrate (*Noctec, Somnos*) was developed in the late 1800s and is still used as a sedative–hypnotic agent. It is a hydrated aldehyde with a disagreeable smell and taste that is rapidly reduced in vivo to trichloroethanol, which is considered to be the active metabolite. It produces a high incidence of gastric irritation and allergic responses, occasionally causes cardiac arrhythmias, and is unreliable in patients with liver damage.

NONPRESCRIPTION DRUGS

A wide variety of sedative–hypnotic products that do not require a prescription are available. Most of these over-the-counter products have antihistamines, such as pyrilamine, diphenhydramine, or promethazine, as the active ingredient. In most cases, the dose of the active ingredient is low and the preparations are safe.

Ethanol (ethyl alcohol) has central nervous system depressant properties and is widely used to relieve anxiety and produce sedation. Although some medical practitioners occasionally prescribe an alcoholic beverage for relieving minor anxiety and inducing sleep, individuals frequently self-medicate with ethanol. Many individuals who abuse alcohol may have started using it to relieve symptoms of central nervous system disorders, such as anxiety and depression.

Ethanol produces central nervous system depression over a wide range of doses. Its effects are additive or sometimes more than additive with other central nervous system depressants. Symptoms often associated with acute alcohol intoxication include increase in self-confidence, loss of inhibitions, euphoria, and loss of judgment. With increasing doses motor and intellectual impairment become prominent. Chronic abuse of ethanol leads to severe liver impairment (see Chapter 35).

Study QUESTIONS

- A 21-year-old man is a full-time college student who also works 25 hours per week. Over the past 3 months he has become increasingly anxious. He says he is tired most of the time and has trouble concentrating on his studies. Which of the following drugs would be the most appropriate initial pharmacologic treatment for his anxiety?

 - Phenobarbital
 - Alprazolam
 - Zolpidem
 - Hydroxyzine
 - Propranolol
- A 33-year-old woman has recently undergone a divorce. She reports that although she is exhausted, it usually takes her 2 or more hours to fall asleep at night. Which of the following drugs would help relieve her sleep disturbance while being least disruptive to REM sleep?

 - Triazolam
 - Chloral hydrate
 - Zolpidem
 - Amobarbital
 - Hydroxyzine
- A 54-year-old man is scheduled for an elective colonoscopy that will take approximately 20 minutes. Which of the following drugs would be most likely to produce the desired anesthesia and anterograde amnesia?

 - Buspirone
 - Zephalon
 - Midazolam
 - Chlordiazepoxide
 - Hydroxyzine
- A 33-year-old woman has a 15-year history of alcohol abuse. She comes to the emergency department for treatment of injuries received in a fall. She says she has been drinking heavily and almost continuously for 2 weeks, and she wants to stop. Which of the following drugs would most effectively and safely lessen the intensity of her withdrawal syndrome?

 - Buspirone
 - Chlordiazepoxide
 - Chloral hydrate
 - Midazolam
 - Zolpidem
- A 23-year-old medical student has to make a presentation before his classmates. He is very anxious about this presentation and reports that on one previous occasion the sweating and palpitations that accompany his stage fright were so intense that he was unable to complete his presentation. Pretreatment with which of the following drugs

would relieve his symptoms without making him drowsy?

- Alprazolam
- Zephalon
- Chloral hydrate
- Propranolol
- Diazepam

ANSWERS

- B.** The young man's anxiety is probably caused by the stress induced by a full college curriculum along with working 25 hours per week. A benzodiazepine antianxiety agent would help relieve his symptoms.
- C.** Zolpidem is effective at relieving sleep-onset insomnia. The other agents listed could also induce sleep, although each would be expected to produce more disruption of sleep rhythm than would zolpidem.
- C.** Midazolam, like all benzodiazepines given in sufficient dose, has the capacity to produce anterograde amnesia. It is also available in an injectable form and frequently is used as an anesthetic agent during short procedures.
- B.** Chlordiazepoxide, through its metabolites, has a relatively long biological half-life. It will prevent many of the severe symptoms of acute alcohol withdrawal. Buspirone is not a sedative and will not suppress alcohol withdrawal. The other agents have sedative properties and could potentially suppress alcohol withdrawal but each has a much shorter biological half-life than chlordiazepoxide.
- D.** As a β -adrenoceptor blocker, propranolol can relieve many of the symptoms of stage fright. For this use it can be taken once a few hours before the performance. Chronic dosing is usually not necessary. The other agents produce sedation.

SUPPLEMENTAL READING

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CASE Study Nighttime Anxiety

M. W. is a 22-year-old woman who visits her doctor because she is extremely tired. She reports that although she is exhausted at bedtime, she typically cannot fall asleep for at least an hour or two. She moved to town 2 months ago and has her first full-time job. She likes her job but fears that her supervisors think she is “dumb” because she has made some careless mistakes. After falling to sleep, she sometimes wakes an hour or more before her alarm goes off, usually thinking about her dumb mistakes. Her problems with sleeping began approximately 5 months ago, when she was studying for final examinations in her senior year of college. Aside from a minor dermatological condition, she is in excellent health. What treatment would you recommend for her insomnia and fatigue?

ANSWER: Zolpidem is the best choice. M. W.’s inability to sleep well is probably the result of anxiety caused by several stresses in her life. She is a recent college graduate, has a new job, and has moved to a new town. These events constitute three stressors, which can induce anxiety and sleep loss. The sleep loss and anxiety are usually of relatively short duration. Zolpidem has a quick onset and a half-life of approximately 2.5 hours. If taken at bedtime, it should allow her to fall asleep quickly and sleep through most or all of the night. Its elimination is fast enough that it should not produce residual drowsiness during the day. A week-long trial of zolpidem should help M. W. overcome her sleep disturbance.