CHAPTER

7

Anxiolytics and Sedative-Hypnotics

THE NATURE AND NEUROPHYSIOLOGY OF ANXIETY

Anxiety is a normal part of life. The sense of apprehension or nervousness we feel when getting ready for a first date, sitting in a job interview, preparing to write an exam, or calculating whether there is enough money in the bank account to cover the month's rent—these anxieties are common and normal. But when anxiety is unrelenting, unreasonably exaggerated given the circumstances, and interrupts one's ability to meet the everyday demands of life, that degree of anxiety is not normal.

Anxiety disorders are the most common of all psychiatric conditions, with a lifetime prevalence estimated to be as high as 28.8% (Kessler, Berglund, et al., 2005). Women are up to twice as likely as men to suffer from anxiety, and there appears to be a genetic component, as anxiety disorders tend to run in families. The *DSM-IV-TR* includes five classes of anxiety disorders, and research links them with abnormal brain physiology, especially in the limbic system and in regions communicating with it.

Generalized anxiety disorder is characterized by excessive and relentless worry whereby an individual feels irritable, keyed up or on edge, tense, easily fatigued, and has trouble concentrating attention on daily tasks. The source of the anxiety is often vague or unrealized, so the person cannot easily confront it directly, and the anxiety persists. Functional MRI (fMRI) studies show hyperactivity of the amygdala, whereas the ventromedial prefrontal cortex, which suppresses amygdalar activity, tends to be underactive (Damsa, Kosel, & Moussally, 2009).

Social phobia or *social anxiety disorder* is the most frequently experienced anxiety disorder. It is the fear of being scrutinized, rejected, or embarrassed in public. Oftentimes, sufferers will avoid social interactions to prevent distress. Like those with generalized anxiety disorder, social phobia is marked by hyperactivity of the amygdala and also of the orbitofrontal cortex (Damsa et al., 2009).

The category *specific phobia* refers to the extreme anxiety that results when confronting or even thinking about certain objects or situations. Some common phobias include fear of specific animals (spiders, dogs), natural environments (heights, storms), blood–injection–injury (needles, medical procedures), and situations (elevators, flying). fMRI studies of people presented with or even anticipating a feared stimulus (such as a spider) show heightened activity of many brain regions: visual areas, supplementary motor regions, thalamus, amygdala, anterior cingulate cortex, and insular cortex (Damsa et al., 2009).

Panic disorder is associated with panic attacks—seemingly unprovoked, quickly mounting, full-blown alarm reactions marked by heightened sympathetic nervous system activity. Racing heartbeat, sweating, trembling, chest pain, difficulty breathing, nausea, and a sense of losing control or detachment from reality are all features of panic attack. Sufferers may fear they are having a heart attack or a stroke, or are dying. A specific phobia, called *agoraphobia*, often coincides with panic disorder. This is the fear of being in a place or situation from which it would be difficult to escape or get help if a panic attack were to occur, such as on an airplane or in an empty parking garage. Although agoraphobia is not one of the five major classes of anxiety disorders according to the *DSM-IV-TR*, it is proposed to become its own diagnosable disorder in the *DSM-5*. MRI studies of individuals with panic disorder show structural brain abnormalities, specifically a reduction in the volume of the anterior cingulate cortex and an increase in gray matter within the insula, superior temporal gyrus, midbrain, and pons (Damsa et al., 2009).

Other considerations for the *DSM-5* include the reclassification of the two final anxiety disorders—obsessive compulsive disorder and posttraumatic stress disorder—into separate diagnostic categories. *Obsessive compulsive disorder* is characterized by persistently nagging, uncontrollable, anxiety-provoking thoughts that often involve checking, counting, avoiding, or cleaning (obsessions) that a person attempts to relieve or dispel by engaging in some repetitious behavior (compulsion). One common obsession is the fear of contamination, which an individual may try to relieve with compulsive, excessive washing and scrubbing of the skin. Individuals with obsessive compulsive disorder exhibit a reduction in the volume of the hippocampus and amygdala and increased volume in the anterior cingulate cortex; deformities of the thalamus; decreased activation of the orbitofrontal cortex, thalamus, and basal ganglia; and increased activation of the caudate and frontal and parietal cortices (Damsa et al., 2009).

Posttraumatic stress disorder can develop after experiencing a traumatic event, such as a natural disaster, abuse, or military combat, where one's safety or life was threatened. The sufferer may reexperience the event in dreams or illusions and lose his or her sense of safety, pleasure in life, and connectedness to loved ones and friends. Structural brain abnormalities associated with posttraumatic stress disorder include a reduction in the volume of the hippocampus, anterior cingulate cortex, and insula and dysfunctional activation of other regions including the amygdala and prefrontal cortex (Damsa et al., 2009).

The anxiety disorders are highly comorbid (co-occurring) with depression and are often treated with medications more commonly thought of as antidepressants (see Chapter 13). An interesting genetic similarity between individuals with anxiety and those with depression is an increased likelihood of possessing one or two short alleles (gene forms) of the promoter region of the serotonin (5-HT) transporter gene, which regulates the number of 5-HT transporter proteins. As is the case with depression, possessing the short form of this portion of gene is associated with heightened risk of developing an anxiety disorder (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010).

Insomnia, which includes difficulty falling asleep or getting a full night of restful sleep, is considered a risk factor for both anxiety and depression, and up to 80% of individuals with insomnia experience other psychiatric symptoms (Jansson-Fröjmark & Lindblom, 2008; Stewart et al., 2006). Some of the drugs discussed in this chapter are also used in the treatment of insomnia.

INTRODUCTION TO ANXIOLYTICS AND SEDATIVE-HYPNOTICS

The term *anxiolytic* (or, more historically, *tranquilizer*) is applied to drugs that are used therapeutically to treat agitation and anxiety disorders. The term *sedative-hypnotic* refers to drugs that are used to sedate and aid sleep (i.e., sleeping pills). There are several categories of drugs that have anxiolytic and sedating effects. The most common in use today is the *benzodiazepines*. Before that, the *barbiturates* were widely used. A number of other substances that are neither barbiturates nor benzodiazepines have also been used as sedative-hypnotics or anxiolytics. They include older drugs like *meprobamate* (Miltown) and *methaqualone* (Quaalude), which were widely used in the 1960s but are no longer used today. More newly developed classes of drugs include the *nonbenzodiazepines* such as *abecarnil* and *alpidem* (these have similar therapeutic and side effects as the benzodiazepines, but have significantly different chemical structures) and a class of drugs introduced since the late 1990s called the

Z drugs, which include *zolpidem*, *zopiclone*, *zaleplon*, and *eszopiclone* (these have increasingly become the accepted treatment for insomnia, as they have a shorter duration of action and are associated with less risk of tolerance and abuse [Richey & Krystal, 2011]).

The hypnotic, sedating, and tranquilizing properties of all these drugs arise from similar neural mechanisms; that is, their principal mechanism of action is the modulation of $GABA_A$ receptor activity—but they have different binding affinities, potencies, and efficacies at specific receptor subunits, which may result in discrete and specific pharmacological effects, depending on the drug (more about this in the section on neurophysiology). For the most part, the medical use of the drug (i.e., whether a drug is prescribed as an anxiolytic or as a sedative-hypnotic) is determined mainly by other factors, such as the speed of action and the duration of effect. Fast-acting drugs with short duration of action are useful as sedative-hypnotics, and longer-acting drugs are used as anxiolytics. Before the introduction of benzodiazepines, one problem with using long-acting barbiturates as anxiolytics was the impairment caused by their sedating actions. The newer drugs and the Z drugs, however, are now able to target specific symptoms, diminishing some of the unpleasant side effects associated with older drugs.

Anxiolytics and sedative-hypnotics share some properties with alcohol (see Chapter 6), with inhaled solvents, and with other substances generally called depressants or general anesthetics. *GHB* (gamma-hydroxybutyrate) is a peculiar substance that occurs naturally in the body and shares many properties with the sedative-hypnotics. It could well have been included in this chapter, but it also has many unique properties that have caused some to suggest that it is a unique pharmacological entity. For this reason it will be discussed in Chapter 15.

HISTORY OF ANXIOLYTIC AND SEDATIVE-HYPNOTIC DRUG DEVELOPMENT

Before the development of the barbiturates, physicians of the nineteenth century had only a few substances that they could use to calm people or aid sleep. These were alcohol (usually in the form of brandy), bromides, chloral hydrate (otherwise known as chloral), and opium. For the most part, these were marginally effective and had unwanted side effects. Barbiturates were first synthesized in 1864, and, for over 100 years, they were one of the most useful drugs in the physician's black bag for the treatment of anxiety and insomnia, replacing brandy, bromides, and opium as tranquillizers. Barbiturates were essentially the only drugs used as sedatives and tranquillizers from the 1920s to mid-1950s (López-Muñoz, Ucha-Udabe, & Alamo, 2005).

During the twentieth century, more than 2,500 different barbiturates were synthesized, and about 50 have been marketed and used clinically (examples of these can be found in Table 7-1; some drugs may no longer be used or may not be approved for use in parts of Europe or North America). Compounds containing barbiturates have been recommended in the treatment of nearly 80 different disorders ranging from arthritis to bed-wetting (Reinisch & Sanders, 1982). In 1936 in the United States alone, 70 tons of barbiturate pills were sold, and dependence became widespread. By the 1990s, however, benzodiazepines had largely replaced barbiturates in almost all medical uses, mainly because of their improved therapeutic index. But barbiturate use has not disappeared completely. The long-acting drug phenobarbital is still prescribed to prevent epileptic seizures and to antagonize adverse stimulating effects of some drugs such as ephedrine, d-amphetamine, and theophylline. Butalbital is an intermediate-acting barbiturate combined with drugs such as aspirin, caffeine, acetaminophen, and codeine in analgesic preparations such as Fioronal and Fioricet for the treatment of headaches. Some ultrashort-acting barbiturates, such as thiopental, are given intravenously prior to surgery as anesthetic inducers. Since the 1970s, barbiturates have been used to reduce intracranial pressure following traumatic brain injury. Although not as commonly as before, amobarbital, aprobarbital, butabarbital, pentobarbital, and secobarbital are all still prescribed for the treatment of insomnia (López-Muñoz et al., 2005).

In the 1960s, barbiturates were sold illicitly on the streets as *downers*. Almost all illicit barbiturates were diverted from medical use, and as the medical use of barbiturates has declined, so has their availability and, consequently, their illicit use.

TABLE 7-1 Anxiolytic and Sedative-Hypnotic Drugs

Generic Name	Trade Name
Barbiturates	
amobarbital	Amytal
aprobarbital	Oramon
butabarbital	Butisol
butalbital	Axotal, Fioricet, Fioronal
mephobarbital	Mebaral
pentobarbital	Nembutal
phenobarbital	Luminal
secobarbital	Seconal, Quinalbarbitone
thiopental	Pentothal
Benzodiazepines	
alprazolam	Xanax
centrax	Prazepam
chlordiazepoxide	Librium
clonazepam	Rivotril, Klonopin
clorazepate	Tranxene, Novo-Clopate
diazepam	Valium
flunitrazepam	Rohypnol
flurazepam	Dalmane
lorazepam	Ativan, Temesta
nitrazepam	Mogadon
oxazepam	Serax
temazepam	Restoril
triazolam	Halcion
Z drugs and others	
abecarnil	ZK-112,119
alpidem	Ananxyl
buspirone	Buspar
eszopiclone	Lunesta
zaleplon	Sonata, Starnoc
zolpidem	Ambien, Stilnox
zopiclone	Imovane, Zimovane

The first synthesis of the benzodiazepines was a combination of good science and good luck. In the 1930s, Leo Sternback synthesized several substances known as *heptoxdiazines* while working on the chemistry of dyes in Krakow, Poland. But not until the 1950s, when he was working at the Hoffman–La Roche laboratories in the United States, did Sternback and his colleagues do further work with these compounds. Their research was stimulated by an attempt to find a new, safe drug that could be used as an anxiolytic. Their approach was simple; they would pick a class of biologically active chemicals that was simple to make and easy to change and that no one else had studied. They would then make and test as many derivatives as they could, hoping to discover a useful drug by chance. The heptoxdiazines fitted this description perfectly, so the researchers started to synthesize all sorts of new variations and had them tested for their biological properties.

None of the derivatives they tested had any biological effect. However, one of these derivatives, identified as Ro 5-0690, was not tested at that time; it was assumed to be inactive and was set aside. Not until 1957, after it had been taking up needed space on the worktable for 2 years, was it finally sent for testing. In fact, one story has it that the reason it was sent for testing rather than being thrown out was that it had "such pretty crystals." To everyone's surprise, the pretty crystals were found to have sedative properties (Sternback, 1973). The researchers finally decided to call Ro 5-0690 *chlordiazepoxide*. After further testing, it was marketed as Librium (Greenblatt & Shader, 1974).

In the years that followed, many more drugs of this type, known as the benzodiazepines, were synthesized and tested, and a number were eventually marketed as anxiolytics, sedative-hypnotics, muscle relaxants, and seizure suppressants (examples of these can also be found in Table 7-1). One of the benzodiazepines was *diazepam* (Valium), which was also developed by Sternback and marketed in 1963. Although all the benzodiazepines have very similar effects in humans, they differ in their relative potency. Some are more potent as sedative-hypnotics, and some are more potent as anxiolytics; they also differ in their speed of action. Apart from diazepam and chlordiazepoxide, common anxiolytic benzodiazepines are *lorazepam* (Ativan), *clorazepate* (Tranxene), *alprazolam* (Xanax), and *oxazepam* (Serax). Sedative-hypnotic benzodiazepines are *nitrazepam* (Mogadon), *flurazepam* (Dalmane), *triazolam* (Halcion), and *temazepam* (Restoril). *Clonazepam* (Rivotril) is used as an anticonvulsant.

Although recreational use of the benzodiazepines is not as extensive as that of the barbiturates, benzodiazepines do have addictive qualities and are liable to be

abused. One benzodiazepine piqued public interest in the mid-1990s since it was reported to be widely used on the street—*flunitrazepam* (Rohypnol). The World Health Organization reported in 1995 that illicit use of flunitrazepam was higher than for any other benzodiazepine. As a result, the UN Commission on Narcotic Drugs increased restrictions on flunitrazepam (Mintzer & Griffiths, 1998).

Rohypnol is sold in parts of Europe, Mexico, and South America, but it has never been marketed in the United States. It is smuggled from Mexico to the southern states, and, by 1995, it was being used quite extensively by young people, especially in conjunction with alcohol. It is known as *Mexican Valium, roaches,* or *roofies*. Flunitrazepam now has the status of a club drug—a drug used at dance clubs, bars, and all-night dance parties, or *raves*. Because of its powerful amnesic effects, Rohypnol also gained the reputation of being a *date rape drug* that is slipped into the drinks of young women who are then sexually assaulted. Laboratory blood tests of date rape victims throughout the United States suggest, however, that the use of Rohypnol for this purpose is not as common as publically believed. Other classes of drugs, such as alcohol and cannabis, and other benzodiazepines, such as diazepam, oxazepan, and lorazepam, are more commonly associated with date rape (ElSohly & Salamone, 1999).

The barbiturates, benzodiazepines, and nonbenzodiazepines (e.g., methaqualone, meprobamate, Z drugs) combat anxiety and insomnia principally through their actions at $GABA_A$ receptors. A variety of other drugs, used for similar purposes but with different mechanisms of action, deserve brief mention. Over-the-counter sleep aids, such as Nytol, Sominex, Sleepinal, Compoz, Unisom, and Nighttime Sleep Aid, contain the antihistamines doxylamine or diphenhydramine, which are also found in allergy and cold medications such as Benadryl or NyQuil. Antihistamines cause drowsiness by antagonizing histamine H_1 receptors in the brain and blocking the action of acetylcholine. In an attempt to regulate circadian (day/night) rhythm, some people take capsules containing melatonin, a hormone released by the pineal gland. Although not a lot of data support its effectiveness as a sedative-hypnotic, there are some indications that it may help speed the onset of sleep (Richey & Krystal, 2011). The hypocretin/orexin system has also become a target of pharmacological research; dysfunction of this system occurs in the sleep disorder *narcolepsy*.

Prescription medications most commonly considered antipsychotics (see Chapter 12) and antidepressants (see Chapter 13) offer promise as anxiolytics. In a recent study, the atypical antipsychotics quetiapine and risperidone fared better than a placebo in the treatment of generalized anxiety disorder and obsessive compulsive personality disorder (Maher et al., 2011). However, the same adverse side effects associated with these medications in the treatment of schizophrenia also occurred in their use as anxiolytics. A number of antidepressant medications of various classes, including the selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and reversible inhibitors of monoamine oxidase A (RIMAs), have also proven useful in the treatment of anxiety disorders (Reinhold, Mandos, Rickels, & Lohoff, 2011; Schneier, 2011). You will notice in Table 7-1 that a drug called buspirone (Buspar) is listed under Z drugs and Others. This medication is widely used in the treatment of anxiety disorders, but is not a benzodiazepine and does not modulate GABA activity. Instead, buspirone is a serotonin agonist, acting specifically at the $5\text{-}HT_{1A}$ receptor subtype. Its major benefit over the benzodiazepines is that it reduces anxiety without producing sedation or muscle relaxation, common effects of the benzodiazepines. Drugs such as clonidine and propanolol, which decrease sympathetic nervous system activity but antagonize noradrenergic activity, are helpful in the treatment of posttraumatic stress and panic disorder.

According to a study by the U.S. Drug Testing Advisory Board that compared pharmacy dispensing of prescription anxiolytics and sedative-hypnotics in the decade spanning 1997–2008, barbiturate prescriptions have decreased, by 22% (representing 820,000 fewer prescriptions) for phenobarbital and 61% (381,000 prescriptions) for butalbital. During the same time period, the dispensing of prescription benzodiazepines increased, by 114% for clonazepam (representing 10.9 million additional prescriptions), 71% for alprazolam (17.6 million prescriptions), 30% for temazepam (1.9 million prescriptions), 24% for lorazepam (4.2 million prescriptions), and 17% for diazepam (2.1 million prescriptions). Since their

introduction in the late 1990s, prescriptions for the Z drugs have also been increasing as these drugs are slowly replacing the benzodiazepines in the treatment of insomnia, especially in North America.

NEUROPHYSIOLOGY

The neurophysiology of the barbiturates and benzodiazepines is fairly well understood. Their effects are mediated primarily by their ability to modify transmission of the inhibitory transmitter GABA, specifically at the $GABA_A$ receptor (it might be helpful, at this point, to review the information related to GABA and its receptor subtypes found in Chapters 4 and 6).

A prototypical $GABA_A$ receptor complex is illustrated in Figure 7-1. Although $GABA_A$ receptors exist in a variety of forms, the most common type of subunit combination is $\alpha_1\beta_2\gamma_2$, which comprise approximately 60% of all $GABA_A$ receptors in the brain. GABA receptors are found all throughout the central nervous system (CNS), both at synapses and elsewhere, and seem to maintain a general level of activity that creates an *inhibitory tone* in the brain, preventing excessive excitation that could result in seizures.

The barbiturates, benzodiazepines, and nonbenzodiazepines do not modify $GABA_A$ receptor activity by altering levels of GABA or by interacting directly with GABA's receptor binding site. Instead, these drugs are positive allosteric modulators—they have their own binding sites on the $GABA_A$ receptor complex that, when occupied, enhances the effects of GABA binding. Some drugs, like abecarnil and alpidem, have a low affinity for the benzodiazepine receptor binding site and have a weak effect. Others, like diazepam, flunitrazepam, midazolam, and triazolam, have a high affinity and a correspondingly greater effect. Some compounds that act as

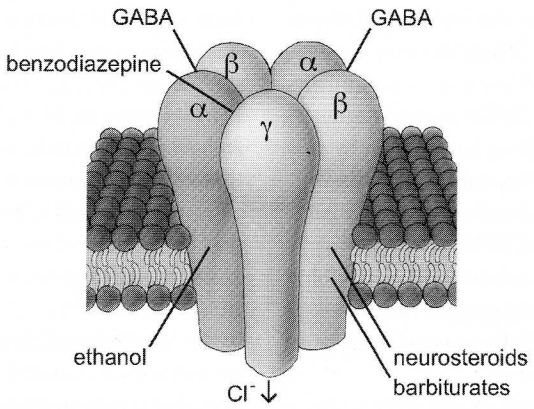

FIGURE 7-1 A schematic drawing of the $GABA_A$ receptor complex indicating the location of some of its ligand binding sites. The receptor complex is composed of five subunits: most typically two alpha (α) subunits, two beta (β) subunits, and a gamma (γ) subunit. The location of receptor binding sites is illustrated: There are two GABA (orthosteric) binding sites located at the interface of alpha and beta subunits; the benzodiazepine (allosteric) binding site is located at the interface of an alpha and a gamma subunit; and other allosteric sites for ethanol, barbiturates, and neuroactive steroids (among others) are located internal to (in the membrane-spanning portion of) the receptor complex. When the ion channel (located in the central pore of the complex) is open, it permits chloride ions (Cl^-) to pass into the cell, hyperpolarizing it and making it more difficult for excitatory neurotransmitters to depolarize the membrane and create an excitatory postsynaptic potential.

allostatic modulators of the benzodiazapine binding site have been shown to alter GABA activity dramatically, by more than 700%.

The binding site for benzodiazepines (and the Z drugs) is formed at the interface of one of the alpha subunits (α_1, α_2, α_3, or α_5) and the gamma subunit (usually γ_2, which is present in about 90% of $GABA_A$ receptor complexes; Rudolph & Knoflach, 2011). However, the high affinity and activity of benzodiazepines at α_1, α_2, α_3, and α_5 $GABA_A$ receptor subtypes is not standard in the Z drugs; their affinity for these alpha subunits differs, which may be the cause of their distinct therapeutic profiles (Nutt & Stahl, 2010).

Alpha 1 receptor subunits are found throughout the CNS. The most prominent effect of their activation is sedation, although they are also responsible to a lesser degree for the amnesic and anticonvulsant effects of benzodiazepine drugs such as diazepam (Rudolph & Knoflach, 2011). Among the Z drugs used short term to treat insomnia, zolpidem has the highest affinity at the $GABA_A$ α_1 subunit, lower affinities for α_2 and α_3 subunits, and essentially no affinity for α_5 subunits (Rudolph & Knoflach, 2011). Other Z drugs, such as zaleplon, zopiclone, and eszopiclone, have similar or only slightly lower affinities for the α_1 subunit but significantly higher affinities at α_2, α_3, and α_5 subunits, compared to zolpidem; Nutt & Stahl, 2010). For this reason, zolpidem is referred to as an α_1-selective drug (Rudolph & Knoflach, 2011). Importantly, the addictive properties of benzodiazepines have been linked to their effects on the α_1 subunit of $GABA_A$ receptors.

Activation of $GABA_A$ receptor complexes containing α_2 and α_3 subunit types also produces sedation, and, in addition, these subunits are thought to regulate brainwave activity during sleep and the transition between sleep and wakefulness. Muscle relaxation also results from the activation of these alpha subunits. However, the primary effect of α_2 and α_3 subunit activation is anxiolysis (anxiety reduction) and alteration of mood. Large numbers of α_2 and α_3 subunits are located in the cortex, dorsal raphe nucleus, limbic system, and interrelated structures that are known to regulate emotion.

Alpha 5 subunits play some role in muscle relaxation and sedation, but appear to be more highly involved in learning and memory; concentrations of $GABA_A$ receptor complexes containing α_5 subunits are found in the hippocampus (Nutt & Stahl, 2010). Activation of α_5 subunits is likely related to the amnesic effects of anxiolytic drugs. Tolerance to the sedative actions of benzodiazepines has also been linked to the α_5 subunit.

With different alpha subunits playing varying roles, it is possible that the therapeutic and side effects of GABAergic drugs are related to their distinctive selectivity for particular subunits. A major problem with using GABAergic drugs as anxiolytics is the co-occurring, unwanted sedation. A major goal of anxiety research is to create drugs that will selectively and preferentially activate alpha subunits responsible for producing anxiolysis rather than those primarily involved in sedation and sleep.

The benzodiazepines show lower affinity and activity at α_4 and α_6 $GABA_A$ receptor subunits, and this pattern is also seen with the Z drugs.

When benzodiazepines and Z drugs bind, their ability to modulate the function of the $GABA_A$ receptor complex is self-limiting; that is, these drugs are not, on their own, able to cause conformational changes in the receptor complex that lead to the opening of the Cl^- ion channel and hyperpolarization of the cell. GABA must also be bound to its orthosteric binding site if the benzodiazepines are to have any effect on the receptor's ion channel. The copresence of benzodiazepine increases the affinity with which GABA binds to its site and enhances the conductance of the Cl^- ion channel; the conductance is of a similar degree as if high concentrations of GABA alone were present.

At low doses, the barbiturates have similar effects to the benzodiazepines. The binding site for barbiturates is in the membrane-spanning portion of the receptor complex. At high doses, barbiturates are quite different in their effects on the $GABA_A$ receptor complex—they are able to open the Cl^- ion channel by themselves, without the co-presence of GABA binding. Therefore, there is an upper limit on the inhibitory effect of the benzodiazepines and Z drugs on the brain, but no upper limit on the inhibitory effect of the barbiturates. High doses of benzodiazepines can cause extreme sedation and grogginess but are not life threatening. High doses of barbiturates produce unconsciousness and anesthesia (Richards, 1980), and they depress breathing by inhibiting the autonomic centers in the brainstem. The respiratory depression caused by barbiturates is similar to the depression caused by alcohol. Barbiturates cause slow, shallow breathing and, at high doses, may prevent

breathing altogether. This depression of breathing and a similar depression of the cardiovascular system are the main cause of death in cases of barbiturate overdose. The difference in the potential to cause lethal overdose is the major difference between the barbiturates and the benzodiazepines and is one of the main reasons why the benzodiazepines have replaced the barbiturates as anxiolytics and long-term sedative-hypnotics.

Why would the brain have receptor sites for benzodiazepines? It is likely that the body has endogenous substances that use these receptors. A search is under way to find an endogenous benzodiazepine. It is thought that such a substance might be responsible for modulating anxiety. In fact, it has been demonstrated that there is an enhancement in the receptivity of benzodiazepine receptors immediately following periods of stress in laboratory animals. Such an increase would make an endogenous benzodiazepine more effective and would increase inhibitory tone, making the organism less sensitive to the physiological and possibly cognitive effects of stress and distress (Hommer, Skolnick, & Paul, 1987; Martin & Acre, 1996).

An endogenous benzodiazepine, however, might have exactly the opposite effect. We know that there are some benzodiazepines that work as *inverse agonists* or *negative $GABA_A$ modulators*. They act opposite to the usual benzodiazepine effect; that is, they decrease GABA's ability to open the Cl^- ion channel, and they increase feelings of tension, anxiety, and panic (Carvalho, de Greckshk, Chapouthier, & Rossier, 1983; Squires & Braestrup, 1977; Stephenson, 1987). Likewise, there are barbiturate inverse agonists that act in opposition to GABA to induce seizures (Ticku & Olsen, 1978).

Even though many of the effects of the benzodiazepines and barbiturates can be understood in terms of their ability to modulate GABA activity, their neurophysiology is complex, and other transmitters and neuromodulators may also be involved. For example, the benzodiazepines are known to enhance the effects of adenosine, another inhibitory transmitter, by blocking its reuptake and permitting its accumulation (Phillis & O'Regan, 1988), an effect directly opposite to that of caffeine (see Chapter 9).

Benzodiazepines, though considered safer and less addicting than the barbiturates, are known to have abuse potential. Dependence, defined by high-dose use over a prolonged period, is not common among individuals who are prescribed these medications, but abuse is prevalent among individuals who obtain the drugs without prescription and who are also dependent upon alcohol and other drugs (Kan, Breteler, van der Ven, Timmermans, & Zitman, 2001). Like all addictive drugs, benzodiazepines influence the transmission of dopamine in the mesolimbic dopamine pathway, which projects from the ventral tegmental area to the nucleus accumbens and prefrontal cortex. If you refer to Figure 12-1 in Chapter 12, you will notice that glutamate, dopamine, and GABA neurons all converge within the ventral tegmental area. Benzodiazepines increase dopamine activity by binding to α_1-containing $GABA_A$ receptors and inhibiting GABAergic interneurons that synapse upon dopamine cell bodies within the ventral tegmental area. The net result is a reduction in GABA neuron firing and a disinhibition (freeing) of dopamine neurons that are normally suppressed by GABA interneuron activity. This disinhibition of dopamine activity leads to neuroplastic changes within the mesocortical pathway, specifically in the firing of excitatory glutamatergic neurons that synapse upon dopamine cell bodies in the ventral tegmental area. Glutamate activity is amplified, driving dopamine cell firing even higher. In laboratory research using mice, just a single administration of diazepam or zolpidem resulted in neuroplastic changes in glutamate activity (Heikkinen, Möykkynen, & Korpi, 2009).

ROUTE OF ADMINISTRATION AND ABSORPTION

Both barbiturates and benzodiazepines are weak acids. Benzodiazepines have a pKa of about 3.5 to 5.0, and they are readily absorbed from digestive and parenteral administration. The choice of route depends on the purpose for which the drug is given. If a rapid effect is needed, an intravenous injection would be indicated, but can sometimes result in local irritation (Lader, 2011). If a long-term effect is wanted, as when diazepam is used to treat anxiety, the oral route is appropriate. Absorption from the digestive system is more rapid than absorption from an intramuscular site, probably because the drugs tend to bind to protein and do so more readily at an injection site than in the digestive system. There are reports that flunitrazepam can cause very rapid effects when the tablets are ground into a powder and administered intranasally (Woods & Winger, 1997).

There is a range of lipid solubility in the benzodiazepines and a resulting difference in the speed of absorption of different benzodiazepines. Diazepam, one of the fastest-acting benzodiazepines, reaches a peak in about 30 to 60 minutes. Other fast-acting benzodiazepines are midazolam, temazepam, flunitrazepam, and triazepam. Oxazepam is slower acting and may take several hours to peak (Busto, Bendayan, & Sellers, 1989). Among individuals, there is a great deal of variability in the rate of absorption and the peak blood levels obtained after a given dose of a benzodiazepine. A dose of diazepam given to one person may cause a blood level 20 times higher than the same dose in another person (Garattini, Mussini, Marcucci, & Guaitani, 1973).

Absorption from the digestive system may be greatly increased by the drinking of alcohol. After small amounts of alcohol are ingested, the blood levels of diazepam can be nearly doubled (Laisi, Linnoila, Seppala, & Mattila, 1979).

The Z drugs are readily absorbed from the digestive system and reach a peak in about an hour. There is considerable first-pass metabolism of zaleplon.

DISTRIBUTION AND EXCRETION

Once a barbiturate or benzodiazepine is in the blood, distribution and, consequently, duration of action are determined by the lipid solubility of the particular drug. The highly lipid-soluble drugs pass through the blood–brain barrier quickly, and their effects on the brain are seen quickly. However, the effects can disappear rapidly because their levels in the brain soon fall. This decrease occurs because highly lipid-soluble drugs become redistributed to areas of the body that contain fat. From these fat deposits, the drug is released slowly into the blood and metabolized by the liver. Thus, fast-acting drugs also tend to have a short duration of action, even though they may still circulate at low levels in the blood for a period of time (Busto et al., 1989; Mark, 1971).

The redistribution of the benzodiazepines in body fat creates a two-phase excretion curve. During the first phase, there is a rather rapid drop in blood level as the drug is redistributed. This phase has a half-life of 2 to 10 hours. In the second phase, the blood level drops more slowly because the drug remaining in the blood is being metabolized, and, as it is metabolized, it is being replaced by the drug slowly being released from body fat. The half-life during this phase varies from 27 to 48 hours, although the half-life of some benzodiazepines, such as triazolam, is much faster, about 2 to 4 hours (Lader, 2011; Wilder & Bruni, 1981). There is considerable variability in the half-lives of benzodiazepines from individual to individual.

The duration of the effect of the benzodiazepines, however, is not always determined by their half-lives because the metabolites of some of the older benzodiazepines (e.g., diazepam, chlordiazepoxide, and flurazepam) are also active. These metabolites have even longer half-lives and may have somewhat different effects. In the development of newer benzodiazepines, consideration has been given to the elimination of these active metabolites. The newer benzodiazepines—oxazepam, triazolam, alprazolam, clonazepam, and lorazepam—do not have any active metabolites (American Society of Hospital Pharmacists, 1987; Rickels, 1983).

The benzodiazepines and barbiturates also cross the placental barrier easily, and they appear in the milk of nursing mothers.

The metabolism of benzodiazepines can be slowed by the consumption of alcohol. It has been shown that the half-life of chlordiazepoxide is increased by 60% after a small drink of alcohol (Desmond, Patwardham, Schenker, & Hoyumpa, 1980). Zaleplon has an extremely short half-life of about 1 hour (Julien, 2001).

EFFECTS ON THE BODY

Apart from a depression in respiration and a slight drop in blood pressure, barbiturates have few physiological effects at low doses. Unlike the barbiturates, the benzodiazepines do not produce significant depression of respiration in healthy individuals, even at high doses. They also have little effect on heart rate or blood pressure. The benzodiazepines are also reported to increase appetite, and weight gain is sometimes a consequence of continuous use (Greenblatt & Shader, 1974; Haney, Comer, Fischman, & Foltin, 1997).

Outside the CNS, the benzodiazepines have very few effects. They have muscle-relaxant properties that are clinically useful and appear to result from the effect of the drug on the brain rather than on the muscles themselves. These properties have made benzodiazepines useful in treating increased muscle tone caused by multiple sclerosis, Parkinson's disease, and brain injury. The

benzodiazepines are also reported to be useful in the treatment of backache and muscle strain. When taken for anxiolytic or sedative-hypnotic purposes, ataxia and tremor are unwanted side effects.

The benzodiazepines are anticonvulsants, and they are useful in treating *petit mal* seizures and infantile spasms; however, for long-term control of epilepsy, the benzodiazepines are not likely to replace the barbiturate and barbiturate-like drugs now commonly in use.

Effects on Sleep

The benzodiazepines are effective in treating insomnia; flurazepam is widely used in the United States, and nitrazepam is used in Europe for this purpose. Zolpidem is also one of the most widely used hypnotics. These drugs decrease latency to fall asleep, decrease wakefulness during the night, and increase total sleeping time. Unfortunately, benzodiazepines, like the barbiturates, decrease the percentage of time spent in REM as well as in stage 3 and stage 4 sleep. This effect diminishes with continued use, and when the drug is discontinued, after as little as 2 weeks, there is a withdrawal rebound (Griffiths & Sannerud, 1987). With nitrazepam, this rebound reaches a peak about 10 days after the drug is stopped and may last for several weeks. With the increase in REM comes an increase in rebound insomnia, that is, bizarre dreaming, restlessness, and wakefulness during the night (Oswald, Lewis, Tangey, Firth, & Haider, 1973). The desire to resume taking the drug to get a good night's sleep increases accordingly.

This rebound appears to be a withdrawal symptom that can be eliminated simply by returning to the use of the sleeping pill. As a result, once people have started to use sedative-hypnotics for sleep, they find it difficult to stop. After periods as short as a week, they find that they cannot get a good night's sleep without their pill, and every time they try to stop, the same thing happens. They do not realize that they must go through a period, sometimes as long as a month, of poor sleep before they can sleep well without their pill.

Zopiclone is reported to have little, if any, rebound effect after short-term use (Hajak, 1999), and no withdrawal or rebound effects were found with zaleplon after 2 to 4 weeks of use (Elie, Ruther, Farr, Emilien, & Salinas, 1999). A number of studies have failed to demonstrate any rebound insomnia after flunitrazepam (Woods & Winger, 1997). Zaleplon, because it is relatively fast acting, reduces the time to go to sleep but does not increase total sleeping time (Elie et al., 1999).

EFFECTS ON THE BEHAVIOR AND PERFORMANCE OF HUMANS

Subjective Effects

Many (although not all) studies of the subjective effect of the benzodiazepines have shown that subjects report euphoria and liking along with sedation and fatigue (de Wit & Griffiths, 1991; Evans, Griffiths, & de Wit, 1996). In one experiment, diazepam and a placebo were given to volunteers who were asked to fill out a Profile of Mood States form at that time and at 1, 3, and 6 hours later. Compared with a placebo, doses of 5 and 10 mg of diazepam caused a decrease in feelings of arousal and vigor and an increase in fatigue and confusion. These effects were seen only at 1 hour with the low dose but were generally seen for up to 3 hours with the high dose. These feelings were considered unpleasant by the participants, few of whom voluntarily took the drug again when they were given the chance (Johanson & Uhlenhuth, 1980). Positive effects and increased liking scores for benzodiazepines are more likely to be seen in people with a history of sedative or alcohol abuse, moderate alcohol use, or opioid use, including those on methadone maintenance (Evans et al., 1996). Flunitrazepam seems more likely than other benzodiazepines to increase "liking" and "take again" scores in normal healthy volunteers and in people on methadone maintenance (Garek et al., 2001; Mintzer & Griffiths, 1998).

Effects on Performance

The benzodiazepines and barbiturates increase the critical frequency of fusion threshold, indicating a deficit in visual functioning. Some studies have also reported that the auditory flicker fusion threshold is diminished by the benzodiazepines (Vogel, 1979).

The benzodiazepines can have severe effects on memory; they cause anterograde amnesia, a loss of memory for events that occurred while under the influence of the drug (Lader, 2011). These problems occur at low doses that do not cause sedation or impair alertness or motor functioning. Memory problems are sometimes observed

in patient populations taking benzodiazepines for anxiety or insomnia. Benzodiazepine users consistently perform worse on verbal memory tasks than nonusers (Barker et al., 2004).

Memory effects do not seem to show tolerance and may persist for months after the drug is discontinued. One reason why benzodiazepines are reputedly sometimes used as date rape drugs is because the victim often has trouble remembering incidents surrounding the assault.

Psychologists who study memory sometimes use benzodiazepines as a tool to explore memory processes (Pompéia, Gorenstein, & Curran, 1996). It is often observed that, even at low doses, benzodiazepines cause deficits in *explicit memory* but not in *implicit memory*. That is, if people are asked to *use* information they acquired after taking a benzodiazepine (implicit memory), they can do that. But if they are explicitly asked to *recall* that information (explicit memory), they have trouble. There is some evidence that this distinction is a result of the fact that there are usually no retrieval cues in explicit memory tasks, but there are such cues in implicit memory tasks. In any case, it has been shown that benzodiazepine-caused memory problems can often be overcome by providing recall cues and reminders of what happened (Pompéia et al., 1966) in a manner similar to alcohol grayout (see Chapter 6).

Even though the benzodiazepines have a clear effect on the ability to acquire new information, they do not appear to alter the ability to recall information acquired prior to their administration (Taylor & Tinklenberg, 1987).

At higher blood levels, sedation occurs that can be detected by tests such as the digit symbol substitution test (which shows a decrease in working or short-term memory), by tests of attention, and by psychomotor performance tests such as reaction time. These effects can be reversed by the administration of the benzodiazepine receptor blocker flumazenil (Bareggi, Ferini-Strambi, Pirola, & Smirne, 1998).

Attention and psychomotor effects may start as soon as 1 hour after oral administration for diazepam or 3 hours for lorazepam. The duration of the impairment will vary, depending on the dose, but can last up to 24 hours. The time course of the impairment does not reflect the concentration in the blood, and shorter-acting benzodiazepines may actually cause a longer-lasting effect than long-acting benzodiazepines. The degree of impairment is not always evident to the individual, who will frequently report that he or she feels fine (Roache & Griffiths, 1987; Taylor & Tinklenberg, 1987).

It should also be remembered that the benzodiazepines can actually improve performance in some people. Improvements are usually seen in individuals who were highly anxious or were in difficult and stressful situations where anxiety might be expected to interfere with performance (Janke & DeBus, 1968).

Residual Effects

Benzodiazepines are widely used at bedtime to induce sleep. Many have such a long half-life that they are still in the body for some time the next day. Because sleeping pill users may drive to work, operate equipment, and engage in other activities that might be impaired by the drug, it is important to determine whether these residual levels of the drug can affect performance the next day. Many, but not all, studies show next-day residual effects of benzodiazepines. Not surprisingly, higher doses are more likely to have residual effects than lower doses (Woods & Winger, 1997). In an attempt to reduce these residual effects, the benzodiazepines and nonbenzodiazepines with short-elimination half-lives are now being more widely used as hypnotics.

The residual effects of benzodiazepines also greatly enhance the effect of a single drink of alcohol (Saario & Linnoila, 1976).

Among the newer sedative-hypnotics, no residual effects on reaction time, driving, or memory were seen with zopiclone, even when it was administered 4 to 6 hours before in the middle of the night (Verster et al., 2002).

Effects on Driving

Extensive research by a group at the University of Helsinki in Finland has shown that a 10-mg dose of diazepam will increase collisions in a simulated driving task. This impairment is also greatly worsened by alcohol (Linnoila & Hakkinen, 1974). A recent meta-analysis of publications examining the influence of benzodiazepines on driving supports this early research. Benzodiazepines increased the risk of traffic accident by 60 to 80%, and the likelihood of *accident responsibility* rose by 40%. Risk was greater in drivers under the age 65.

Combining alcohol with a benzodiazepine resulted in a 7.7-fold increase in accident risk (Dassanayake, Michie, Carter, & Jones, 2011). In general, evidence shows that there is a considerable risk of an automobile accident in first-time users of benzodiazepines. The risk is probably amplified by the fact that the individual is often not able to detect the impairment (Taylor & Tinklenberg, 1987). Although some tolerance may develop to this effect, driving impairments and next-day sleepiness have been seen with lorazepam after 7 days of use (van Laar, Volkerts, & Verbaten, 2001). Driving impairments in patients receiving diazepam for anxiety are still apparent 3 weeks into treatment (van Laar, Volkerts, & Willigenberg, 1992). The nonbenzodiazepine drug, zopiclone, also significantly impaired driving ability during the first 2 to 4 weeks of treatment (Dassanayake et al., 2011).

Many studies show that the benzodiazepines and Z drugs may have residual effects on driving the next morning. One study showed that flunitrazepam and, to a lesser extent, zopiclone had effects of driving at 9:00 A.M. the day after being used, but zolpidem did not. By 11:00 A.M., flunitrazepam still had effects, but neither zolpidem nor zopiclone did (Bocca et al., 1999). Similar residual effects have been reported with flurazepam but not lormetazepam, which does not have any active metabolites (Brookhuis, Volkerts, & O'Hanlon, 1990).

In spite of the foregoing evidence, the presence of benzodiazepines in the blood was not found to be a contributing factor in a large sample of road accidents after the effects of alcohol had been accounted for (Benzodiazepine/Driving Collaborative Group, 1993).

EFFECTS ON THE BEHAVIOR OF NONHUMANS

Unconditioned Behavior

One of the first effects noticed in the early screening tests of the benzodiazepines was a *taming* effect. The research animals became more placid, and fighting behavior induced by electric shocks was reduced. It has since been demonstrated that chlordiazepoxide and diazepam are effective in reducing only defensive aggression, that is, aggression induced by an attack or provoked by a painful stimulus like a shock. Unprovoked aggression or attack behavior does not seem to be altered at lower-than-toxic doses (DiMascio, 1973). It has been suggested that this change in provoked aggression is a result of the ability of the benzodiazepines to diminish anxiety. Defensive aggression is presumably a result of anxiety or fear caused by being attacked. Attack itself is not motivated by anxiety (Hoffmeister & Wuttke, 1969).

Conditioned Behavior

Benzodiazepines show the classical profile of drugs that are therapeutically useful in the treatment of anxiety. Heise and Boff (1962) showed that doses of benzodiazepine that decrease avoidance responses are one-fourth to one-sixth the size of doses that have any effect on escape responding.

The benzodiazepines also have a spectacular effect on behavior suppressed by punishment: They cause an increase in punished behavior at doses that decrease or have little effect on positively motivated behavior (Hanson, Witloslawski, & Campbell, 1967; Kleven & Koek, 1999). Animals injected with barbiturates continue to make responses that are punished by electric shock at normal, unpunished rates. The reason for their unchanged behavior does not appear to be that they no longer feel the shock; they jump and flinch when it happens, but they nevertheless continue to make the punished response.

DISCRIMINATIVE STIMULUS PROPERTIES

Laboratory animals can be readily trained to discriminate all benzodiazepines from saline. Flunitrazepam and triazolam appear to be more potent than other benzodiazepines (Woods & Winger, 1997).

Animals trained to discriminate a benzodiazepine will generalize the response to other benzodiazepines and barbiturates but not to the antipsychotics or ketamine. The discriminative stimulus effects of benzodiazepines cannot be blocked by stimulant drugs such as amphetamine, caffeine, cocaine, and the hallucinogen mescaline, but they can be blocked by drugs that block the benzodiazepine receptor (Colpaert, 1977; Lelas, Gerak, & France, 1999).

Although the benzodiazepine cue will generalize to the barbiturates, it has been shown that rats can be trained to discriminate chlordiazepoxide from barbiturates and alcohol but not from diazepam. This finding

indicates qualitative differences between the subjective effects of all these drugs, even though they are similar enough to generalize to each other (Barry, McGuire, & Krimmer, 1982). Alcohol will, however, potentiate the discriminative effects of flunitrazepam (Schechter, 1998). There is some evidence from rats that zolpidem may have slightly different discriminative effects from the benzodiazepines since there is only partial generalization to many benzodiazepines, and no generalization occurs in rats trained to discriminate alcohol (Rush, 1998).

Humans can easily learn to discriminate benzodiazepines. In one experiment, six women and seven men were able to reliably discriminate a dose of 0.375 mg of triazolam. There was no gender difference in the participants' ability to discriminate this drug, nor in their ratings of sedation or impairment of performance (Vansickel, Hays, & Rush, 2006).

TOLERANCE

Acute Tolerance

Tolerance to the effects of benzodiazepines can develop during a single administration. Such tolerance seems to be limited in humans to the effect of benzodiazepines on behavior such as digit symbol substitution and tracking and may not be seen in physiological effects. It has also been shown that the acute tolerance can develop to the motor-impairing effects of midazolam (Coldwell et al., 1998). Similarly, studies have shown that phenobarbital has a more powerful effect at a given concentration as the blood level is rising than when the blood level is descending (Ellenwood et al., 1981).

Chronic Tolerance

With repeated administration, benzodiazepines become less and less effective in their ability to modulate the effects of GABA. There is some disagreement, however, whether this is a result of a reduction in the capacity of the benzodiazepines to alter the effect of GABA or whether the sensitivity of the GABA receptor to GABA is reduced. In any case, many behavioral effects of the benzodiazepines show tolerance (Hutchison, Smith, & Darlington, 1996).

In laboratory animals, tolerance develops to many of the behavioral effects of the benzodiazepines, including their locomotor, ataxic, muscle relaxant, and anticonvulsant effects. Tolerance to the disruptive effects of chlordiazepoxide on avoidance develops in rats when the drug is administered every day for 6 weeks (Masuki & Iwamoto, 1966). Tolerance to the anxiety-reducing effects in humans is variable and appears to be related to the dosing regime and the specific benzodiazepine used (Hutchison et al., 1996).

Tolerance also develops slowly to the anticonvulsant effects of the benzodiazepines as well as to the drowsiness that is seen sometimes at therapeutic doses. Although there are some data to suggest that tolerance does not develop to the hypnotic effects of benzodiazepines and to zolpidem in particular, other work has shown that tolerance to the sleep-producing effects of these drugs develops after about 4 weeks (Rush, 1998). As mentioned earlier, there has been a tendency to prescribe short-acting benzodiazepines and nonbenzodiazepines as sleeping pills to avoid next-day residual effects, but it seems that these drugs have a tendency to develop tolerance faster than the longer-acting benzodiazepines. In addition, they also seem to cause more frequent and more intense rebound insomnia. Among the short-acting hypnotics, however, there are differences. Triazolam appears to cause more rebound insomnia than either midazolam or zolpidem (Soldatos, Dikeos, & Whitehead, 1999).

Cross-Tolerance

There is cross-tolerance between the benzodiazepines and other depressant drugs. The drowsiness sometimes produced by higher therapeutic doses of the benzodiazepines is less often seen in people who have a recent history of barbiturate and alcohol abuse (Greenblatt & Shader, 1974).

One study has shown that tolerance develops after only one exposure to the motor-impairing effect of alcohol, barbiturates, and benzodiazepines in mice. Animals that are tolerant to the barbiturates are cross-tolerant to alcohol and the benzodiazepines, and benzodiazepine-tolerant animals are tolerant to the effects of alcohol but show only weak or partial tolerance to the barbiturates. This suggests that the tolerance to barbiturates and benzodiazepines may arise from mechanisms that are similar but not identical (Khanna, Kalant, Chau, & Shah, 1998).

WITHDRAWAL

In laboratory animals, it has been shown that many benzodiazepines will cause physical dependence similar to barbiturates, and there is a cross-dependence between phenobarbital and many benzodiazepines; that is, withdrawal from phenobarbital can be blocked by benzodiazepines (Gerak et al., 2001). Nevertheless, the symptoms of barbiturate withdrawal can be much more severe than those of benzodiazepine withdrawal, as described later.

In humans, barbiturate withdrawal was first described in the medical literature in 1905, 2 years after the introduction of the first barbiturate into medical practice. In spite of this early report, the medical literature on barbiturate withdrawal was contradictory until the 1930s, when the weight of evidence could no longer be denied.

The benzodiazepines have been used widely in medical practice since the early 1960s, but, as with the barbiturates, years passed before their ability to cause physical dependence at therapeutic doses become widely acknowledged. It has been known for some time that withdrawal from relatively high doses of benzodiazepines taken for a long time will cause symptoms similar to those of withdrawal from barbiturates and alcohol: agitation, depression, abdominal pain, delirium tremens, insomnia, and seizures (Greenblatt & Shader, 1974; Hollister, Motzenbecker, & Degan, 1961). Such dependence was believed to be rare, and most physicians were confident that there was no chance of physical dependence in their patients who received low therapeutic doses. An early study estimated that physical dependence occurred in only 1% of patients receiving diazepam for various emotional disorders (Bows, 1965). In fact, physical dependence was considered so unlikely that one group of researchers concluded, "It is time to dispel the myth that the unsuspecting housewife must be protected from the careless prescribing of dangerous drugs likely to produce lifelong addiction" (Rickels, Downing, & Winokur, 1978, p. 403). It soon became apparent, however, that therapeutic doses of benzodiazepines could cause rather unpleasant withdrawal symptoms and could lead to excessive use by some individuals.

In a classic study by Cosmo Hallstrom and Malcolm Lader (1981), four patients were gradually weaned from a high daily dose (average of 135 mg) of diazepam, and six patients were weaned from a low daily dose (average of 20 mg/day). After the drug was withdrawn, patients in both groups showed symptoms that included anxiety, sleep disturbances, intolerance to bright lights and loud noises, weight loss, unsteady gait, and numbness or tingling feelings. There were also changes in brainwave activity and duplication of the increase in the electrical activity of the cortex that follows a loud noise (auditory evoked potential). These changes were similar in both the high- and low-benzodiazepine subjects. Most of the symptoms peaked in intensity after 5 days and were gone within 2 weeks. Other researchers found similar withdrawal effects with therapeutic doses (Crawford, 1981; Petursson & Lader, 1981). Therapeutic doses were clearly causing problems.

David E. Smith of the Haight-Ashbury Free Medical Clinic and Donald R. Wesson (1983) suggested, on the basis of extensive clinical experience, that there are actually two types of withdrawal from benzodiazepines:*sedative-hypnotic withdrawal* and *low-dose withdrawal*. Each has a different set of symptoms (Griffiths & Sannerud, 1987). Each type has a different time course, and the occurrence of both types of withdrawal may overlap.

Sedative-Hypnotic Withdrawal

The sedative-hypnotic type of withdrawal involves tremors, delirium, cramps, and, possibly, convulsions. These are similar to the symptoms of barbiturate and alcohol withdrawal (described in Chapter 6), and they are the symptoms described in studies of the effects of high doses of benzodiazepines. Sedative-hypnotic withdrawal can be expected in people who have taken the drug in higher-than-recommended therapeutic doses for at least a month. Generally, the withdrawal symptoms start within a few days of abstinence and are gone within about 10 days. These withdrawal symptoms are more likely to be seen with benzodiazepines that have short half-lives because blood levels of these drugs fall more rapidly than blood levels of the longer-acting drugs.

Low-Dose Withdrawal

Low-dose benzodiazepine withdrawal symptoms are seen in some individuals after low therapeutic doses have been taken for longer than 6 months. They emerge more slowly and include anxiety, panic, irregular heartbeat, increased blood pressure, impairment of memory and

concentration, feelings of unreality, muscle spasm, and a sensitivity to lights and sounds. Patients consistently report feeling as though they are walking on cotton wool, in a mist, or wearing a veil over their eyes. There are frequent reports of perceptual difficulties, such as sloping walls or floors, and distortion of reality and self-perception: "Everything feels unreal or distant"; "I feel I'm not really me"; "My head feels like a huge balloon" (Ashton, 1984, p. 1138).

Very often, these feelings come in cycles or waves; their frequency may vary with each symptom (Ashton, 1984). Smith and Wesson (1983) suggest that many symptoms cycle every 10 days. There are no consistent data on the duration of withdrawal. It has been reported to last as briefly as 2 weeks (Owen & Tyrer, 1983) and as long as a year (Ashton, 1984; Smith & Wesson, 1983).

It is not clear how many users of benzodiazepines at therapeutic doses have withdrawal symptoms; estimates range from 15 to 44% (Higgitt, Lader, & Fonagy, 1985). It is also not clear why certain people may be more susceptible than others.

As with most withdrawal symptoms, both the sedative-hypnotic type and the low-dose type of symptoms disappear quickly when the withdrawn drug is resumed. The low-dose withdrawal symptoms are especially sensitive to resumption of treatment and can be controlled with only a few milligrams of benzodiazepine.

The benzodiazepine receptor antagonist flumazenil can precipitate these low-dose symptoms in long-term users of benzodiazepines at therapeutic doses (the equivalent of 11.2 mg diazepam/day). The precipitated symptoms are similar to nonprecipitated symptoms except that they are more likely to include panic attacks. The magnitude of the withdrawal symptoms was correlated with the daily dose of benzodiazepine but was not related to the duration of use (Mintzer, Stoller, & Griffiths, 1999).

Individuals who have taken high doses of benzodiazepines for longer than 6 months may well experience both types of withdrawal (see Figure 7-2). Note that other changes may occur when the benzodiazepines are stopped. These changes are due to symptom

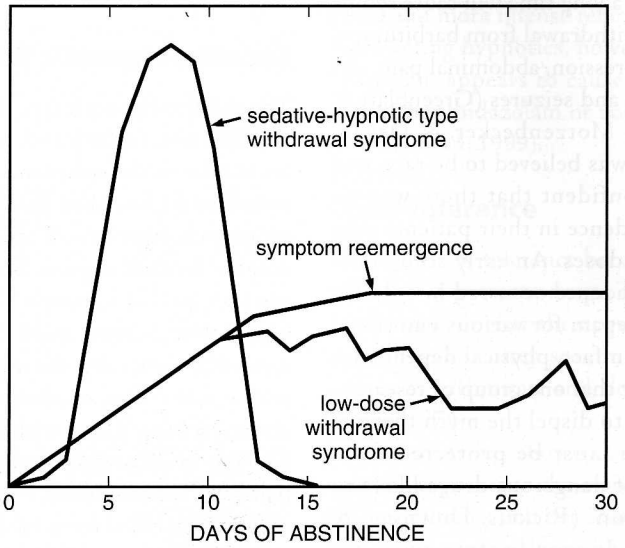

FIGURE 7-2 Two types of withdrawal symptoms that may be seen after use of the benzodiazepines. The sedative-hypnotic type of withdrawal has severe symptoms but lasts only a few days. The low-dose benzodiazepine withdrawal symptoms are less intense but last much longer and seem to come and go in cycles. Also shown is the reemergence of symptoms that were there before the benzodiazepine was started and may reappear, causing more distress. (Adapted from Smith & Wesson, 1983, p. 89)

reemergence—the expression of symptoms that were present before the drug was started and were suppressed while the drug was being used. Often these reemergent symptoms are more intense than the original symptoms experienced before taking the drug (Lader, 2011). Reemerging symptoms are not really withdrawal symptoms, but their presence contributes to and complicates benzodiazepine withdrawal.

SELF-ADMINISTRATION IN HUMANS

Laboratory Studies

CHOICE EXPERIMENTS. In a study that used normal human participants and has been replicated several times, Johanson and Uhlenhuth (1980) gave people a choice between capsules of different colors. In an earlier part of the experiment, participants had been given each of the capsules twice, so they knew what effect each colored capsule would have, even though they did not know what each capsule contained. In this experiment, the participants chose capsules containing amphetamine much more often than a placebo, but they did not choose diazepam more often than a placebo (Griffiths et al., 1980). In a similar procedure, lorazepam was not chosen more often than a placebo; in fact, at higher doses, participants chose a placebo more frequently than lorazepam or diazepam (de Wit, Johanson, & Uhlenhuth, 1984; Johanson & Uhlenhuth, 1980).

In a similar study, participants were selected for high anxiety levels and given the choice between diazepam and a placebo. The highly anxious participants reported that the capsules containing the diazepam reduced their anxiety, but they did not choose the diazepam capsule more frequently than a placebo. This finding suggests that relief from anxiety is not a motivation for benzodiazepine self-administration and that highly anxious people are not particularly at risk for benzodiazepine abuse (de Wit & Johanson, 1987), although other experiments have not found this latter effect (McCracken, de Wit, Uhlenhuth, & Johanson, 1990).

It has been demonstrated that moderate alcohol users and people with a history of sedative-hypnotic and alcohol abuse would choose benzodiazepines more frequently than a placebo (de Wit & Griffiths, 1991; Evans et al., 1996). In another study, people chose benzodiazepines when the choice was reliably followed by a task that required relaxation and earned them some money (Silverman et al., 1994).

SELF-ADMINISTRATION EXPERIMENTS. In a study conducted by Roland Griffiths and colleagues (Griffiths, Bigelow, & Lieberson, 1979) at the Johns Hopkins University School of Medicine, pentobarbital was made available to male volunteers in an experimental hospital ward setting. The participants, all of whom had a history of sedative drug abuse, could earn an administration of a drug by riding an exercise bicycle for 15 minutes. Five of the seven participants continued to self-administer doses of 90 mg (a high level) of pentobarbital over the 10 days of the experiment, indicating that the drug acted as a positive reinforcer in humans. The same experiment also showed that participants would not self-administer a placebo. Diazepam was self-administered by some participants but not as frequently or as reliably as the barbiturate.

Outside the Laboratory

Outside the laboratory, humans show two patterns of benzodiazepine self-administration apart from use for legitimate medical conditions. In the legal or *iatrogenic* (physician-caused) pattern, the drug is prescribed for its effects as an aid to sleep or anxiety problems and is then continued unnecessarily, or the dose is escalated. In the street-use pattern, the drugs are obtained illegally and are taken at high doses. Of these two patterns, the first is more common.

IATROGENIC USE. Benzodiazepines are widely prescribed for a variety of symptoms. In many cases, the prescription and use are entirely consistent with appropriate treatment of medical conditions; however, the use of these drugs often changes in nature and may cause problems for the patient in a couple of different ways. As we have seen, if they are prescribed at too high a dose or for too long, they can cause physical dependence and require special treatment to avoid withdrawal when the drug is discontinued. In addition, a patient may become motivated by the reinforcing effects of the drug and may start exhibiting an inappropriate amount of behavior toward obtaining the drug in increasing amounts. Such a patient may learn exactly how to tailor a medical history so that a physician will predictably prescribe the desired

drug or may go "doctor shopping" to find a compliant physician. Some patients may refuse to stop taking a drug and not consider alternative therapies, even though the drug is causing adverse side effects or the doctor recommends stopping. Other signs include a tendency to escalate doses, requests for early refills of the prescription because the prescription was "lost," and so on.

According to the popular stereotype, the typical Valium user is a well-educated, middle-class, suburban housewife who is denied personal or professional fulfillment by her husband and family. In fact, this does not appear to be the case. The Balter survey found that typical long-term users of anxiolytic benzodiazepines tended to be over 50, female, and suffering from substantial anxiety and some significant chronic health problem, such as heart disease or arthritis. This survey showed that, in general, most of the people who are receiving long-term benzodiazepines are receiving them for legitimate medical reasons—usually anxiety. Mellinger, Balter, and Uhlenhuth (1984) showed that at least half of long-term users suffered from high levels of psychic distress (anxiety).

Survey results indicate that large numbers of people who report severe symptoms of anxiety do not report the use of benzodiazepines. Given this information, some observers have concluded that benzodiazepines are underused rather than overused because there appear to be many people who could benefit from benzodiazepine use but are not receiving benzodiazepine treatment (Uhlenhuth, de Wit, Balter, Johanson, & Mellinger, 1988).

The extent of abuse or misuse of the benzodiazepines is not well understood. In one study, 176 people were referred to an outpatient clinic for assessment of benzodiazepine abuse. Fifty-six percent used benzodiazepines in clinically appropriate doses but did so longer than recommended by their physician. Others who took doses larger than prescribed did so in combination with other substances, such as alcohol, opioids, and cannabis (Juergens, 1993). In another study of 136 clinic clients who were found to be benzodiazepine abusers, less than 0.5% abused benzodiazepines alone. Most were well-educated Caucasian females more than 30 years old, and they received their benzodiazepines legally from a physician. Diazepam was the preferred benzodiazepine, particularly by primary cocaine and opioid users (Malcolm, Brady, Johnston, & Cunningham, 1993). The use of alprazolam and diazepam is a particular problem for many people on methadone maintenance (Sellers et al., 1993), although some research shows that heroin addicts and those on methadone maintenance have a distinct preference for flunitrazepam (Woods & Winger, 1997).

Because flunitrazepam appears to be different from other benzodiazepines in terms of its potential for recreational use, a number of researchers have attempted to discover if there is anything different about it that causes this effect. So far, no special property of flunitrazepam has become apparent (Mintzer & Griffiths, 1998; Woods & Winger, 1997).

STREET USE. When used for recreational purposes, the benzodiazepines are most often taken in conjunction with some other drug. Often that drug is alcohol, but, surprisingly, it has been reported that 60 to 70% of patients on methadone maintenance use benzodiazepines (often to boost the effects of the methadone). Laboratory data also support the claim that diazepam will enhance the subjective and physiological effects of opioids (Griffiths & Sannerud, 1987), although one study showed that diazepam did not alter the blood levels of methadone and vice versa (Preston, Griffiths, Clone, Darwin, & Gorodetzky, 1986).

Figure 7-3 shows the use of sedative-hypnotics (barbiturates; Panel A) and anxiolytics (Panel B) by male and female college students in the United States from 1980 to 2010. The graphs represent the number of students who reported using this class of drugs within the past year when it was not prescribed to them by a physician. Use of both sedatives and tranquilizers was high in the early 1980s but then declined until the mid-1990s. Following that decline, drug use rose steadily until the mid-2000s before it again started to decline. Prevalence of reported use is similar between men and women (Johnston, O'Malley, Bachman, & Schulenberg, 2011).

SELF-ADMINISTRATION IN NONHUMANS

Like humans, rats and monkeys will readily work to give themselves infusions of all types of barbiturates, although it appears that the short-acting barbiturates may maintain higher rates of responding than the longer-acting barbiturates (Winger, Stitzer, & Woods,

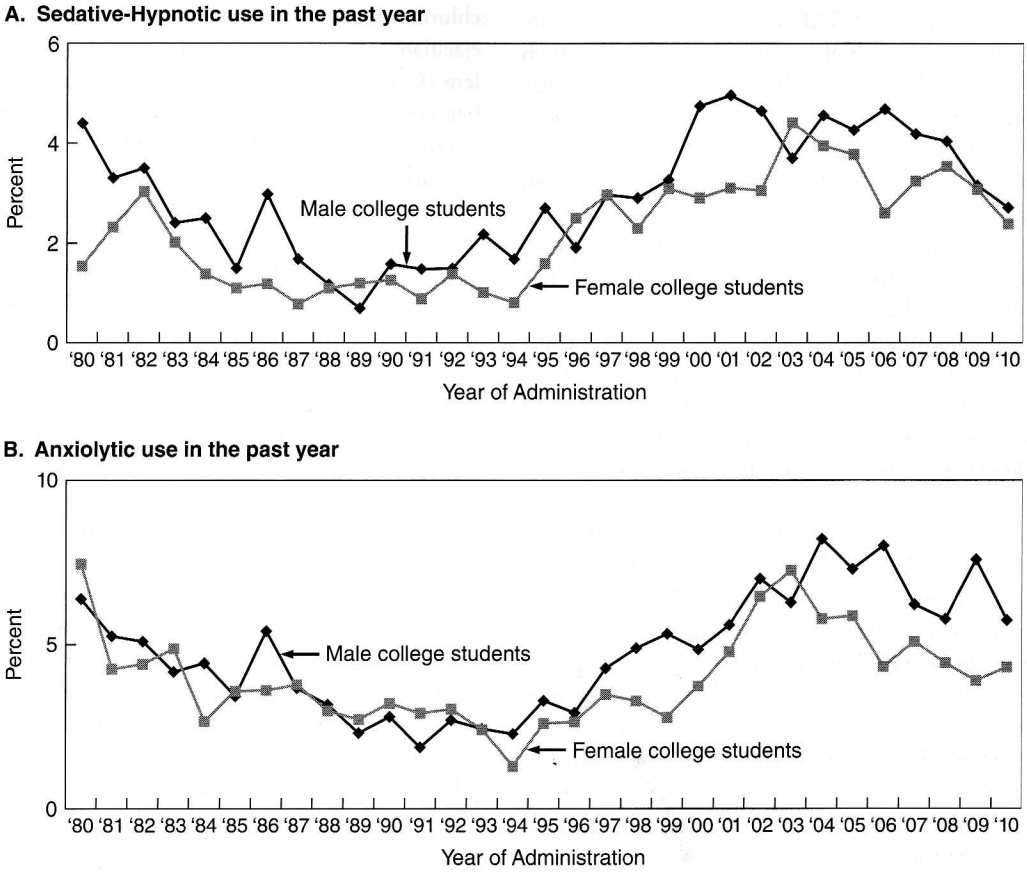

FIGURE 7-3 Trends in the number of male and female college students who reported using a sedative-hypnotic (barbiturate) or an anxiolytic within the past year without a prescription from a doctor. Panel A (top) shows sedative-hypnotic use, and Panel B (bottom) shows anxiolytic use. (Data from Johnson et al., 2011)

1975). Response patterns maintained by barbiturates on fixed interval (FI) and fixed response (FR) schedules are similar to typical response patterns maintained by other reinforcers and take place at doses that do not appear to cause physical dependence (Kelleher, 1976).

Laboratory animals will also self-administer benzodiazepines both intravenously and orally (Rowlett, Platt, Lelas, Atack, & Dawson, 2005; Stewart, Lamaire, Roche, & Meisch, 1994). Currently, there are many demonstrations of self-administration of both short- and long-acting benzodiazepines (Gerak et al., 2001; Griffiths, Lucas, Bradford, Brady, & Snell, 1981), although short-acting benzodiazepines like triazolam maintain higher rates of responding than long-acting benzodiazepines (Griffiths et al., 1981). Where comparisons have been made, the positive reinforcing effects of benzodiazepines are not as robust as those of barbiturates (Griffiths, Lamb, Sannerud, Ator, & Brady, 1991) and benzodiazepines that do not modulate activity of α_1-containing $GABA_A$ receptor complexes are less reinforcing than those that do (Rudolph & Knoflach, 2011). In intravenous self-administration studies using rhesus monkeys, Rowlett and colleagues (Rowlett et al., 2005; Rowlett & Leas, 2007) found that the breaking point on a progressive ratio schedule of reinforcement was highest for the α_1-subunit modulating drugs, diazepam, midazolam, and zolpidem, and lower for a drug (L-838417) that antagonizes α_1 subunits but acts as a partial agonist at α_2, α_3, and α_5 subunit-containing $GABA_A$ receptor complexes. This finding suggests that anxiolytics and sedative-hypnotics that selectively target

α_1 subtype-containing $GABA_A$ receptors may be more reinforcing and have higher abuse potential, although efficacy at α_2 and α_3 subtypes has also been shown to play a role in benzodiazepine abuse (Ator, Atack, Hargreaves, Burns, & Dawson, 2010).

The reinforcing effects of the benzodiazepines, even long-acting ones, can be enhanced by a period of exposure to the drug or to other barbiturates or benzodiazepines. In one study, Harris, Glaghorn, and Schoolar (1968) gave rats a choice between drinking a solution of chlordiazepoxide and drinking pure water. The rats always chose water. Then, for 25 days, the rats had to drink the chlordiazepoxide in order to obtain food. After this period of forced consumption, the rats showed a preference for the chlordiazepoxide, even when the alternate choice was water. Other research has shown that the effect of prior exposure does not depend on the development of physical dependence (Ator & Griffiths, 1992).

Taken together with the human choice and self-administration laboratory studies that show reinforcing effects in people with a history of sedative-hypnotic abuse, it appears that, at least for the longer-acting benzodiazepines administered orally, a period of forced consumption greatly enhances the reinforcing effect of the drug. In this respect, benzodiazepines are very different from the barbiturates, which are very powerful reinforcers right from the start in humans and nonhumans.

Subjective reports and epidemiological studies suggest that flunitrazepam may have a higher potential for use than any other benzodiazepine because it is preferred by many users, but self-administration and drug discrimination studies with laboratory animals have been unable to find any difference between the effects of flunitrazepam and other short-acting benzodiazepines like midazolam and triazolam (Gerak et al., 2001). It has also been noted that people on methadone maintenance seem to use benzodiazepines to "boost" methadone's subjective effect. In one study using baboons, self-administration of flunitrazepam was enhanced in animals who were administered methadone concurrently (Ator, Griffiths, & Weerts, 2005).

HARMFUL EFFECTS

Reproduction

Initially, it was thought that the benzodiazepines interfered with the menstrual cycle and fertility in women, but such concerns have not been substantiated. In males, chlordiazepoxide has been reported to cause a failure to ejaculate, but this does not appear to be a common problem (Greenblatt & Shader, 1974). In fact, there have been reports that the benzodiazepines improve reproductive success in previously infertile couples.

Early epidemiological studies suggested that the benzodiazepines might cause birth defects in humans. These effects have not been confirmed (Eros, Czeizel, Rockenbauer, Sorensen, & Olsen, 2002), but there is evidence of behavioral teratogenic effects in rats. In one study with rats, pups born to mothers injected with diazepam during the third (last) week of gestation showed absence of locomotion responses and the acoustic startle responses seen in normal rats (Kellogg, Tervo, Ison, Paisi, & Miller, 1980). In fact, it appears that exposure to benzodiazepines in utero affects the reaction of animals to various stressors, and these effects may be different at different developmental stages throughout the life span and may even extend into old age (Kellogg, 1988).

Withdrawal symptoms have been reported in infants when the mothers used normal therapeutic doses of diazepam during pregnancy. The withdrawal symptoms—tremors, irritability, and hyperactivity—are similar to withdrawal from opioids. They start 2.5 to 6 hours after delivery and can be treated with barbiturates (Rementiria & Bhatt, 1977). Even benzodiazepines given during labor have been reported to affect the newborn infant by depressing respiration, creating a reluctance to feed, and decreasing the ability to maintain normal body temperature (floppy baby syndrome). Apgar scorers (ratings of cardiac and respiratory functioning at birth) are also depressed. The drug has been detected in the blood of a baby up to 8 days after delivery (Cree, Meyer, & Hailey, 1973).

As with most drugs, it is probably unwise to take benzodiazepines at any time during pregnancy or even if pregnancy is possible. This could be a serious problem because benzodiazepines are prescribed much more frequently for women than for men.

Overdose

The main reason why benzodiazepines have replaced the barbiturates is that they are much safer. The major danger from barbiturate use is overdose, either accidental or deliberate. At one time, more than 15,000 deaths per year in the United States resulted from barbiturate overdose; without doubt, the majority of these were suicides.

Benzodiazepine overdoses are not as dangerous as barbiturate overdoses. About 12% of drug overdose emergencies in the United States involve the benzodiazepines, but because benzodiazepines do not cause significant respiratory depression, the outcomes of benzodiazepine overdoses are seldom fatal, and there seem to be no lasting effects. Doses as high as 2,250 mg of chlordiazepoxide have been tolerated with symptoms of sleep and drowsiness. There is no deep coma or severe respiratory depression, and the victims can usually be awakened (Greenblatt & Shader, 1974). Most symptoms disappear within 48 hours. Deaths due solely to benzodiazepine overdose are more likely to result from the shorter-acting drugs like nitrazepam, temazepam, and flunitrazepam (Drummer & Ransom, 1996). Hospital emergency rooms will often use flumazenil, the benzodiazepine receptor antagonist, to treat benzodiazepine overdoses.

Although the benzodiazepines are relatively safe by themselves, they intensify the effect of other depressants, such as alcohol and the barbiturates. The benzodiazepines can be, and frequently are, fatal when combined with high doses of alcohol (Torry, 1976).

TREATMENT

Anyone wishing to discontinue using the benzodiazepines after a long period of use should not attempt it alone because the withdrawal can be severe and may involve convulsions, which require medical treatment. Withdrawal should be done under medical supervision with the aid of a physician who appreciates the problem. Although withdrawal can usually be accomplished on an outpatient basis, hospitalization may be necessary, especially for patients with a history of seizures, psychotic episodes, or high doses of the drug (Higgitt et al., 1985).

The approach to detoxification from a benzodiazepine is similar to detoxification from other sedative drugs and alcohol. The best way to proceed is to gradually reduce the daily dose of the benzodiazepine, a technique called *GDR, gradual dose reduction*. Withdrawal should be conducted over an 8 to 12 week period and be completed in no more than 6 months (Lader, 2011). This is most successfully done in conjunction with counseling, group therapy, or Cognitive Behavioral Therapy, and careful monitoring of the patient's withdrawal symptoms. It is important that the patient be told exactly what symptoms to expect and how long they will last. It is sometimes helpful to also seek social support from self-help groups and members of the family. The patient should be taught various strategies for coping, not only with the withdrawal but also with the re-emergence of the symptoms for which the benzodiazepine was prescribed in the first place (Colvin, 1983). The most intense withdrawal and the greatest anxiety and panic are experienced while the last few milligrams of the drug are being withdrawn (Lader, 2011; Smith & Wesson, 1983). Treatment of iatrogenic physical dependence is usually successful: 88 to 100% of patients stop their benzodiazepine use (Higgitt et al., 1985).

When withdrawal has been managed, various therapies may be attempted, but it is important to match the patient with an appropriate therapeutic strategy. Options include group therapies with people who have similar problems, education, family involvement, a 12-step program similar to Alcoholics Anonymous in which participants are encouraged to "work" a program of recovery, and the support of peer groups and a physician who understand the process.

An illegal user seldom abuses benzodiazepines except as an adjunct to some other addiction, such as alcohol, heroin, or amphetamine, and treatments usually focus on the primary addiction.