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Tranquilizers and Sedative-Hypnotics

INTRODUCTION

The term *tranquilizer* or *anxiolytic* is applied to drugs that are used therapeutically to treat agitation and anxiety. 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 these 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 or benzodiazepines have also been used as sedative-hypnotics or tranquilizers. They include older drugs like *meprobamate* (Miltown) and *methaqualone* (Quaalude), which were widely used in the 1960s but are no longer used today, and newer drugs like *abecarnil* and *alpidem* and a class of drugs sometimes called the *Z drugs*, which include *zolpidem*, *zopiclone*, and *zaleplon*, which were introduced in the late 1990s. The hypnotic, sedating, and tranquilizing properties of all these drugs arise from the same neural mechanism. For the most part the medical use of the drug (i.e., whether it is prescribed as a tranquilizer or as a sedative-hypnotic) is determined 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 tranquilizers. The newer drugs and the Z drugs, however, are now able to target specific symptoms.

Tranquilizers and sedative-hypnotics share some properties with alcohol (Chapter 6), with inhaled solvents, and with other substances generally called depressants or general anesthetics (see Chapter 8). Although they have other effects on neuronal function, all these drugs facilitate the functioning of the inhibitory transmitter *gamma-aminobutyric acid* (GABA).

GHB (gamma-hydroxybutyrate) is a peculiar substance that occurs naturally in the body and shares many properties and could well have been included with the sedative-hypnotics but 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 16.

HISTORY

Before the development of the barbiturates, physicians of the nineteenth century had only a few substances that they could use to calm people

down 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 tranquilizers.

Over the years, thousands of different barbiturates were synthesized, and about 50 have been marketed. Compounds containing barbiturates have been recommended in the treatment of no less than 77 different disorders ranging from arthritis to bed-wetting (Reinisch & Sanders, 1982). By the 1990s, however, benzodiazepines had replaced barbiturates in almost all their medical uses, with only a few exceptions. Phenobarbital is still prescribed to prevent seizures. Butalbital is also used in combination with drugs such as aspirin, caffeine, acetaminophen, and codeine in analgesic preparations such as Fioronal and Fioricet for headaches, and some very short-acting barbiturates are used as anesthetics. The use of barbiturates as sedative-hypnotics has not entirely disappeared. In 1995, phenobarbital appeared in 8.2 percent of sedative-hypnotics sold worldwide (J. Woods & Winger, 1997).

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.

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 a tranquilizer. 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 two 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. One of these 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 tranquilizers, and they also differ in their speed of action. Apart from diazepam and chlordiazepoxide, common anxiolytic benzodiazepines are *lorazepam* (Ativan), *chlorazepate* (Trannxene), *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.

One benzodiazepine is of particular interest. That is *flunitrazepam* (Rohypnol). Although recreational use of benzodiazepines is not extensive, as was the use of barbiturates, this benzodiazepine is reported to be widely used on the street. 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 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*. It also has the reputation of being a *date rape drug* that is slipped into the drinks of young women who are then sexually assaulted.

Drugs that are neither barbiturates or benzodiazepines have been developed. Methaqualone and meprobamate were marketed in the 1960s, but they were widely abused and are no longer used. Several newer ones have also been developed. These are the so-called Z drugs: *zopiclone* (Systemic or Imovane), *zolpidem* (Ambiem), *zaleplon* (Sonata), and *abecarnil* (J. Woods, Katz, & Winger, 1995).

Recent trends in prescribing show an overall decrease in prescriptions for benzodiazepines since a peak in the mid-1970s (Griffiths & Sannerud, 1987, p. 1536). There has been an increase in the use of short-acting benzodiazepines that do not have active metabolites and a decrease in the use of long-acting benzodiazepines such as diazepam that have active metabolites (Busto, Isaac, & Adrian, 1986). Although the use of benzodiazepines as tranquilizers is declining, until recently their use as sedative-hypnotics has remained stable (J. Woods et al., 1995). Since their introduction in their late 1990s, the Z drugs have been slowly replacing the benzodiazepines in the treatment of insomnia, especially in North America.

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 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 (J. Woods & Winger, 1997, p. 3S).

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 benzodiazepins 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, which is 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 oxazepam and triazolam, is much faster, about 1 to 5 hours (Wilder & Bruni, 1981, p. 109). 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, p. 1141; 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 percent after a small drink of alcohol (Desmond, Patwardham, Schenker, & Hoyumpa, 1980).

Zaleplon has an extremely short half-life of about 1 hour (Julien, 2001).

NEUROPHYSIOLOGY

The neurophysiology of the barbiturates and benzodiazepines is fairly well understood. Their effects are mediated primarily by their ability to modify the effects of the inhibitory transmitter GABA (see Chapter 4). GABA has two types of receptor sites: $GABA_A$ and $GABA_B$ receptors.

The $GABA_A$ receptor site is directly linked to a gated chloride ion channel in a large protein molecule known as the *GABA receptor–chloride ionophore complex*. (An *ionophore* is another name for an ion channel.) When GABA is released at a synapse, its interaction with the $GABA_A$ receptor directly opens the chloride channel (Haefely, 1983; Paul, 2000). The open channel permits negatively charged chloride ions to flow in and out of the cell in response to changes in the membrane potential caused by excitatory neurotransmitters, and this tends to stabilize the membrane, making the neuron more difficult to fire. In this way, GABA acts as an inhibitory transmitter (see Figure 7-1). GABA receptors are found all over 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, believed to be responsible for preventing too much excitation to develop that could result in seizures.

The barbiturates and benzodiazepines do not modify the effects of GABA by altering the levels of GABA or by interacting directly with its receptor site. Instead, the barbiturates and the benzodiazepines each have their own receptor sites on the GABA receptor–chloride ionophore complex. When barbiturates and benzodiazepines activate their receptors, there is an increase in the ability of GABA occupying the $GABA_A$ receptor to open the chloride ionophore. Drugs that do this

are described as *positive $GABA_A$ modulators*. Some drugs like abecarnil and alpidem have a low affinity for the benzodiazepine receptor and have a weak effect. Others, like diazepam, flunitrazepam, midazolam, and triazolam, have a high affinity and a correspondingly greater effect.

The benzodiazepines have the ability only to make GABA more effective; they do not alter the operation of the ionophore directly. At low doses, the barbiturates have the same effect, but at higher doses, the barbiturates seem able to open the ionophore by themselves. Therefore, there is an upper limit on the inhibitory effect of the benzodiazepines 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 on the brain stem. 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 the reason why the benzodiazepines have replaced the barbiturates as tranquilizers and sedative-hypnotics.

As you can see from Figure 7-1, the $GABA_A$ receptor–ionophore is a large complex molecule. It is made up of five subunits that are proteins, or chains of amino acids folded into a complex unit. Each of these subunits is created by a different gene, and there is considerable variability in the composition of each subunit. There are three main subunits designated alpha (α), beta (β), and gamma (γ). There are six varieties of alpha (α_{1-6}), and three each of beta and gamma. These are put together in a variety of combinations, making

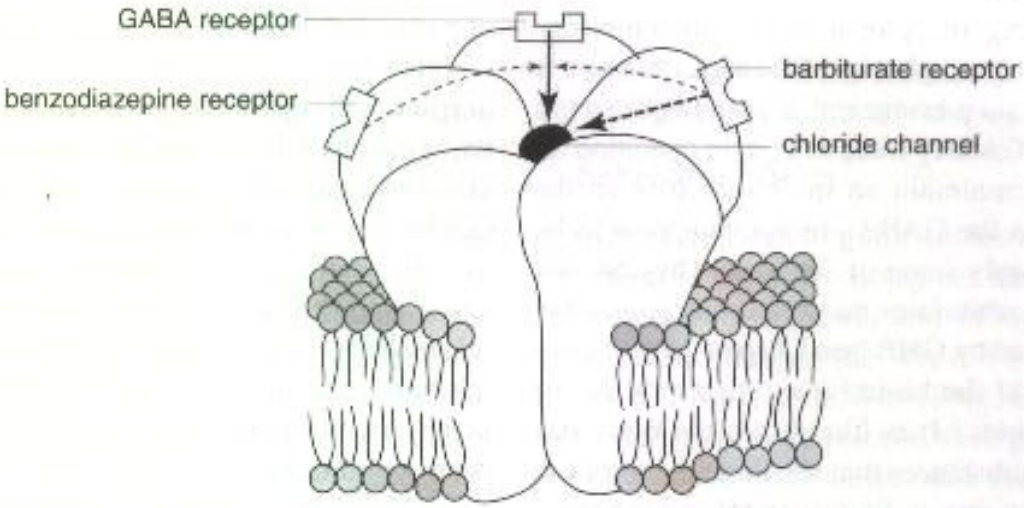

Figure 7-1 A schematic drawing of the GABA receptor–chloride ionophore complex. Three receptor sites are shown: a GABA receptor, a barbiturate receptor, and a benzodiazepine receptor. The solid arrow indicates that the GABA receptor can open the ionophore when it is occupied. The dark, dashed arrow indicates that the barbiturate receptor can also open the ionophore but only at high doses. The light, dashed arrows indicate that both the benzodiazepine and the barbiturate receptors can enhance the ability of GABA to open the ionophore. When the ionophore is open, it permits chloride ions (Cl^-) to pass in and out of the cell and makes it more difficult for excitatory neurotransmitters to depolarize the membrane.

many different types of $GABA_A$ receptors possible. What is important is that different configurations of the receptor are associated with different parts of the brain and mediate different functions. For example, the α_1 subtype exists in systems that seem to be responsible for sedation, and the α_2 subunit exists in systems that are responsible for the anxiolytic effects (Möhler, Fritschy, Crestani, Hensch, & Rudolph, 2004).

For the most part, different benzodiazepines affect these receptor subtypes the same way, but the newer Z-type drugs act differently at each subtype. Both zolpidem and zaleplon appear to be effective at the receptors with an α_1 subunit but have a lower affinity for receptors with the α_2 subunit. Therefore, they can act as sedatives without involving the antianxiety mechanisms. Conversely, new drugs are being developed that reduce anxiety without making a person sleepy or interfering with driving by acting at different receptor subtypes (Möhler, Fritschy, & Rudolph, 2002; Rush, 1998). As a result of this line of research many new drugs with selective actions and few side effects are being developed

The $GABA_B$ receptor also has an inhibitory effect but uses a completely different mechanism. It releases a second messenger that opens a potassium channel. The $GABA_A$ receptors are in operation all the time and maintain an inhibitory tone in the brain, whereas the $GABA_B$ receptors appear to be in operation only some of the time. They are not affected by barbiturates and benzodiazepines but may be affected by GHB (see Chapter 16).

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 increase inhibitory tone, making the organism less sensitive to the physiological and possibly cognitive effects of stress and distress (Hommer, Skolnick, & Paul, 1987, p. 982; 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 have the opposite of the usual benzodiazepine effect; they decrease GABA's ability to open the ionophore, 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 have this effect and induce seizures (Ticku & Olsen, 1978).

Even though many of the effects of the benzodiazepines and barbiturates can be understood in terms of their modulation of the effects of GABA, their neurophysiology is complex, and other transmitters and neuromodulators may be involved. For example, the benzodiazepines also 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 10).

Interestingly, the barbiturates and the benzodiazepines are reported to decrease dopamine activity in the nucleus accumbens, exactly the opposite effect of most reinforcing drugs. If this is so, how can they be reinforcing? The effect of dopamine on the neurons of the nucleus accumbens is known to be inhibitory; when dopamine is released, the cells in the nucleus accumbens are inhibited, and so is their output. There are GABA receptors in the nucleus accumbens, and GABA is also inhibitory, so it is likely that GABA has the same effect on these cells that dopamine does, that is, it causes reinforcement (Wise, 1998).

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, p. 5; 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.

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, p. 1539). 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 et al., 1999). A number of studies have failed to demonstrate any rebound insomnia after flunitrazepam (J. 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 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 subjects, 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 opiate 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).

Benzodiazepines are effective anxiolytics or tranquilizers (i.e., they reduce anxiety in anxious individuals). This is one of their major clinical uses, but they are effective in only 60 to 70 percent of cases. There appear to be a number of factors that can modify their clinical effectiveness. These include current and past exposure to various forms of stress (Haller, 2001).

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 (J. R. 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. 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. Memory effects do not seem to show tolerance and may persist for months after the drug is discontinued. One reason why flunitrazepam is reputedly used as a date rape drug 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 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 administration of the benzodiazepine receptor blocker flumazinil (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 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 were 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 (J. Woods & Winger, 1997). In an attempt to reduce these residual effects, the benzodiazepines 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, and 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 also shown that a 10-mg dose of diazepam will increase collisions in a simulated driving task. This impairment is also greatly increased by alcohol (Linnoila & Hakkinen, 1974). 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).

Many studies show that the benzodiazepines 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 has effects, but neither zolpidem nor zopiclone did (Bocca et al., 1999). Similar residual effects have been reported with flurazepam but not lormetrazepam, 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 that is 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 tiazolam appear to be more potent than other benzodiazepines (J. 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). It has been shown, however, that alcohol will 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 in rats trained to discriminate alcohol occurs (Rush, 1998).

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 (A. 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 (A. 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, recent 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 as sleeping pills to avoid next-day residual effects, but it seems that these benzodiazepines 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, p. 232).

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).

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; L. B. Hollister, Motzenbecker, & Degan, 1961) (see Chapter 6). 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 percent 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 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 EEG 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 the 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 Type

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 while 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). D. E. 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; D. E. Smith & Wesson, 1983). It is also not clear how many users of benzodiazepines at therapeutic doses have withdrawal symptoms; estimates range from 15 to 44 percent (Higgitt, Lader, & Fonagy, 1985). 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

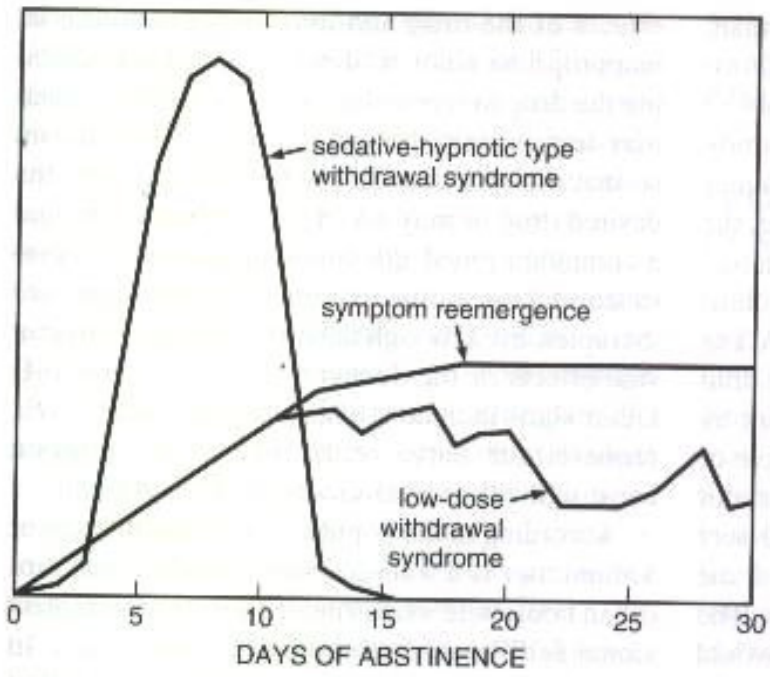

Figure 7-2 Two types of withdrawal symptoms that may be seen after use of the benzodiazepines. The sedative-hypnotic type of withdrawal has severe symptoms but lasts only a few days. The low-dose benzodiazepine withdrawal symptoms are less intense but last much longer and seem to come and go in cycles.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

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 reemergence—the expression of symptoms that were present before the drug was started and were suppressed while the drug was being used. 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 subjects 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, subjects 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 subjects chose capsules containing amphetamine much more often than a placebo, but they did not choose diazepam more often than a placebo (Griffiths, Bigelow, & Henningfield, 1980). In a similar procedure, lorazepam was not chosen more often than a placebo; in fact, at higher doses, subjects chose a placebo more frequently than lorazepam or diazepam (de Wit, Johanson, & Uhlenhuth, 1984; Johanson & Uhlenhuth, 1980).

In a similar study, subjects were selected for high anxiety levels and given the choice between diazepam and a placebo. The highly anxious subjects 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 (K. Silverman, Mumford, & Griffiths, 1994).

Self-Administration Experiments. In a study conducted by Roland Griffiths and his 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 subjects, 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 subjects 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 subjects would not self-administer a placebo. Diazepam was self-administered by some subjects 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, opiates, and cannabis (Juergens, 1993). In another study of 136 clinic clients who were found to be benzodiazepine abusers, less than 0.5 percent 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 opiate 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 (J. 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; J. 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 percent of patients on methadone maintenance use benzodiazepines (often to boost the effects of the methadone) (see Chapter 12). Laboratory data also support the claim that diazepam will enhance the subjective and physiological effects of opiates (Griffiths & Sannerud, 1987, p. 1537), although one study showed that diazepam did not alter the blood levels of methadone and vice versa (Preston, Griffiths, Clone, Darwin, & Gorodetzky, 1986).

National surveys in the United States indicated that the illicit use of sedatives and tranquilizers steadily declined from 1975 to 1992, but between 1992 and 2004, the number of students in grade 12 reporting the use of sedatives and tranquilizers within the past 30 days more than doubled, exceeding the levels of the early 1980s. In 2004, 3.1 percent of grade 12 students reported using a tranquilizer within the past 30 days (Johnston, O'Malley, Bachman, & Schulenberg, 2005).

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, 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 takes place at doses that do not appear to cause physical dependence (Kelleher, 1976).

Early self-administration research with benzodiazepines had difficulty demonstrating that benzodiazepines were reinforcing, but later research has shown that laboratory animals will self-administer this class of drugs both intravenously and orally (B. S. Stewart, Lamaire, Roche, & Meisch, 1994). The problem may have been that early research used benzodiazepines with rather slow onset and long duration of action. (In general, drugs with these properties are difficult to establish as reinforcers.) Currently, there are many demonstrations of self-administration of both short- and long-acting benzodiazepines (Griffiths, Lamb, Sannerud, Ator, & Brady, 1991; Gerak et al., 2001), although short-acting benzodiazepines like triazolam maintain higher rates of responding than long-acting benzodiazepines (Griffiths, Lucas, Bradford, Brady, & Snell, 1981). Where comparisons have been made, the positive reinforcing effects of benzodiazepines are not as robust as those of barbiturates (Griffiths et al., 1991).

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, R. T. 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).

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, p. 231). 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 have not been confirmed (Eros et al., 2002), but there is evidence that they may have behavioral teratogenic effects in rats. In one study with rats, it was shown that pups born to mothers injected with diazepam during the third week of gestation showed an absence of locomotion responses and of the acoustic startle responses seen in normal rats (Kellogg, Tervo, Ison, Paisi, & Miller, 1980). In fact, it appears that exposure to benzodiazepines in the uterus 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 opiates. They start 2 1/2 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 percent

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, p. 251). 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. If only the low-dose benzodiazepine withdrawal symptoms are anticipated, the best way to proceed is gradually to reduce the daily dose of the benzodiazepine. This is most successfully done in conjunction with counseling 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 seek social support from self-help groups and members of the family. The patient should also be taught various strategies for coping, not only with the withdrawal but also with the reemergence 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 (D. E. Smith & Wesson, 1983). Treatment of iatrogenic physical dependence is usually successful: 88 to 100 percent of patients stop their benzodiazepine intake (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.

CHAPTER SUMMARY

- Tranquilizers are used to treat agitation and anxiety, and sedative-hypnotics are used to sedate people and help them sleep (i.e., they are sleeping pills).
- The benzodiazepines are a class of drugs that was developed in the 1950s and became popular during the 1960s and 1970s for the control of anxiety and insomnia. Benzodiazepines replaced the barbiturates because they are much safer. There are newer drugs introduced in the late 1990s called Z drugs that appear to be replacing the benzodiazepines.

- These drugs are absorbed readily after oral administration. They may also be injected, depending on the medical reason the drug is being used. Their speed of absorption depends on their lipid solubility. Highly lipid-soluble drugs are redistributed into body fat.
- Benzodiazepines and barbiturates enhance the action of GABA, an inhibitory transmitter found widely throughout the brain. They act as their own receptors, which are located on the $GABA_A$ receptor–chloride ionophore complex. This action potentiates the ability of GABA to stabilize the cell membrane. As a result, they are called positive $GABA_A$ modulators. At higher doses, barbiturates but not benzodiazepines are able to open the ion channel directly.
- The benzodiazepines and barbiturates essentially have similar effects and the speed of action determined their use; fast-acting drugs were used as sedative-hypnotics, while longer-acting drugs were used as anxiolytics.
- The GABA receptor–ionophore complex is made of five different subunits, and there are many different varieties of subunits. Different subunits are located in receptors in different sites that control different systems. The Z drugs appear to selectively affect different subunits, so different drugs can specifically target different symptoms.
- The effects of the benzodiazepines on human performance are similar to those of alcohol. Some of these effects are still evident on the day following the use of barbiturates and benzodiazepines as sleeping pills, although the individual may not be aware of the effects. Some of the newer sedative-hypnotics like zopiclone do not appear to have this residual effect. High doses of barbiturates but not benzodiazepines cause death from respiratory depression, which results from a depression of the respiratory centers in the medulla.
- In low doses, the benzodiazepines cause decreases in arousal and vigor and increases in fatigue and confusion. They also decrease feelings of anxiety—their chief medical use. They interfere with memory and slow reaction time, and the drug impairs other skills, including driving. This effect is potentiated by alcohol.
- The benzodiazepines can cause amnesia for events that occur while they are in effect and have an effect on explicit memories.
- There have been ample demonstrations that the benzodiazepines increase behaviors suppressed by punishment. This effect in nonhumans predicts the antianxiety effect of these drugs in humans.
- Tolerance develops to many of the effects of these drugs, including their therapeutic effects.
- There are two separate patterns of withdrawal from the benzodiazepines: (a) the sedative-hypnotic type, similar to withdrawal from alcohol and the barbiturates, and (b) low-dose benzodiazepine withdrawal, which emerges slowly after therapeutic doses have been stopped. The symptoms of anxiety, panic, irregular heartbeat, and memory impairment come and go in cycles of about 10 days and may last for 6 months to a year.
- Benzodiazepines have reinforcing properties in both humans and nonhumans and are readily self-administered. In humans, there are two patterns of use: (a) iatrogenic or physician-caused use and (b) illegal street use. The illegal pattern is characterized by episodic binges. Benzodiazepines are frequently used in conjunction with other drugs such as heroin, cocaine, or alcohol. Flunitrazepam (Rohypnol) appears to be the most highly preferred benzodiazepine for street use, but researchers have not been able to find anything distinctive about it that can explain this preference.
- Because of their lethal effects, the barbiturates have caused many accidental poisonings. Benzodiazepines are much safer but can be fatal when combined with high doses of alcohol.