Five Commonly Used Drugs

- **LO 15.7** Describe the health hazards associated with smoking tobacco.
- **LO 15.8** Describe the health hazards associated with alcohol consumption and the various stages of the full-blown alcohol withdrawal syndrome.
- **LO 15.9** Explain the health effects of marijuana and the mechanism of action of THC.
- **LO 15.10** Describe the health hazards associated with the consumption of cocaine and other stimulants.
- **LO 15.11** Describe the health hazards associated with the consumption of opioids and the opioid withdrawal syndrome.

Comparing the Health Hazards of Commonly Used Drugs

- **LO 15.12** Explain why it is difficult to determine causality in studies of the health hazards of drugs.
- **LO 15.13** Compare the direct health hazards of alcohol, tobacco, marijuana, heroin, and cocaine.

Early Biopsychological Research on Addiction

- **LO 15.14** Explain the physical-dependence and positive-incentive perspectives of addiction.
- **LO 15.15** Describe the intracranial self-stimulation (ICSS) paradigm.
- **LO 15.16** Describe two methods for measuring the rewarding effects of drugs.
- **LO 15.17** Explain the role of the nucleus accumbens in drug addiction.

Current Approaches to the Mechanisms of Addiction

- **LO 15.18** Describe the three stages in the development of a drug addiction.
- **LO 15.19** Describe two sets of findings that have challenged the relevance of drug self-administration studies.
- **LO 15.20** Explain the significance of the case of Sigmund Freud.

Drug addiction is a serious problem in most parts of the world. Globally, more than 1 billion people are addicted to nicotine; more than 76 million are addicted to alcohol; more than 40 million are addicted to illegal drugs; and many millions are addicted to prescription drugs (Degenhardt & Hall, 2012). Pause for a moment and think about the sheer magnitude of the problem represented by such figures—more than a billion addicted people worldwide. The incidence of drug addiction is so high that it is almost certain that you or somebody dear to you will be adversely affected by drugs.

This chapter introduces you to some basic **pharmacological** (pertaining to the scientific study of drugs) principles and concepts, compares the effects of five commonly used drugs, and reviews the research on the neural mechanisms of addiction. You likely already have strong views about drug addiction; thus, as you progress through this chapter, it is particularly important that you do not let your thinking be clouded by preconceptions. In particular, it is important that you do not fall into the trap of assuming that a drug's legal status has much to say about its safety (see Nutt, King, & Nichols, 2013). You will be less likely to assume that legal drugs are safe and illegal drugs are dangerous if you remember that most laws governing drug use in various parts of the world were enacted in the early part of the 20th century, long before there was any scientific research on the topic.

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Case of the Drugged High School Teachers

People's tendency to equate drug legality with drug safety was once conveyed to me (JP) in a particularly ironic fashion: I was invited to address a convention of high school teachers on the topic of drug misuse. When I arrived at the convention center to give my talk, I was escorted to a special suite, where I was encouraged to join the executive committee in a round of drug taking—the drug being a special single-malt whiskey. Later, the irony of the situation had its full impact. As I stepped to the podium under the influence of a psychoactive drug (the whiskey), I looked out through the haze of cigarette smoke at an audience of educators who had invited me to speak to them because they were concerned about the unhealthy impact of drugs on their students. The welcoming applause gradually gave way to the melodic tinkling of ice cubes in liquor glasses, and I began. They did not like what I had to say.

Basic Principles of Drug Action

This module focuses on the basic principles of drug action, with an emphasis on **psychoactive drugs**—drugs that influence subjective experience and behavior by acting on the nervous system.

Drug Administration, Absorption, and Penetration of the Central Nervous System

LO 15.1 Compare the various routes of drug administration.

Drugs are usually administered in one of four ways: oral ingestion, injection, inhalation, or absorption through the mucous membranes of the nose, mouth, or rectum. The route of administration influences the rate at which and the degree to which the drug reaches its sites of action in the body.

ORAL INGESTION. The oral route is the preferred route of administration for many drugs. Once they are swallowed, drugs dissolve in the fluids of the stomach and are carried to the intestine, where they are absorbed into the bloodstream. However, some drugs readily pass through the stomach wall (e.g., alcohol), and these take effect sooner because they do not have to reach the intestine to be absorbed. Drugs that are not readily absorbed from the digestive tract or that are broken down into inactive *metabolites* (breakdown products of the body's chemical reactions) before they can be absorbed must be taken by some other route.

The two main advantages of the oral route of administration over other routes are its ease and relative safety. Its main disadvantage is its unpredictability: Absorption from the digestive tract into the bloodstream can be greatly influenced by such difficult-to-gauge factors as the amount and type of food in the stomach.

INJECTION. Drug injection is common in medical practice because the effects of injected drugs are strong, fast, and predictable. Drug injections are typically made *subcutaneously* (*SC*), into the fatty tissue just beneath the skin; *intramuscularly* (*IM*), into the large muscles; or *intravenously* (*IV*), directly into veins at points where they run just beneath the skin. Many drug-addicted persons prefer the intravenous route because the bloodstream delivers the drug directly to the brain. However, the speed and directness of the intravenous route are mixed blessings; after an intravenous injection, there is little or no opportunity to counteract the effects of an overdose, an impurity, or an allergic reaction. Furthermore, many drug users develop scar tissue, infections, and collapsed veins at the few sites on their bodies where there are large accessible veins.

INHALATION. Some drugs can be absorbed into the bloodstream through the rich network of capillaries in the lungs. Many anesthetics are typically administered by *inhalation*, as are tobacco and marijuana. The two main shortcomings of this route are that it is difficult to precisely regulate the dose of inhaled drugs, and many substances damage the lungs if they are inhaled chronically.

ABSORPTION THROUGH MUCOUS MEMBRANES. Some drugs can be administered through the mucous membranes of the nose, mouth, and rectum. Cocaine, for example, is commonly self-administered through the nasal membranes (snorted)—but not without damaging them.

Drug Action, Metabolism, and Elimination

LO 15.2 Explain the ways in which drugs can influence the nervous system and how they are eliminated from the body.

DRUG PENETRATION OF THE CENTRAL NERVOUS SYSTEM. Once a drug enters the bloodstream, it is carried to the blood vessels of the central nervous system. Fortunately, a protective filter, the *blood–brain barrier* (see Chapter 3), makes it difficult for many potentially dangerous bloodborne chemicals to pass from the blood vessels of the CNS into the extracellular space around CNS neurons and glia.

MECHANISMS OF DRUG ACTION. Psychoactive drugs influence the nervous system in many ways. Some drugs (e.g., alcohol and many of the general anesthetics) act diffusely on neural membranes throughout the CNS. Others act in a more specific way: by binding to particular synaptic receptors; by influencing the synthesis, transport, release, or deactivation of particular neurotransmitters; or by influencing the chain of chemical reactions elicited in

postsynaptic neurons by the activation of their receptors (see Chapter 4).

DRUG METABOLISM AND ELIMINATION. The actions of most drugs are terminated by enzymes synthesized by the *liver*. These liver enzymes stimulate the conversion of active drugs to nonactive forms—a process referred to as **drug metabolism**. In many cases, drug metabolism eliminates a drug's ability to pass through lipid membranes of cells so that it can no longer penetrate the blood–brain barrier. In addition, small amounts of some psychoactive drugs are passed from the body in urine, sweat, feces, breath, and mother's milk.

Drug Tolerance, Drug Withdrawal Effects, and Physical Dependence

LO 15.3 Describe how the body becomes tolerant to drugs and the process of drug withdrawal. Explain what it means to be physically dependent on a drug.

DRUG TOLERANCE. **Drug tolerance** is a state of decreased sensitivity to a drug that develops as a result of exposure to it. Drug tolerance can be demonstrated in two ways: by showing that a given dose of the drug has less effect than it had before drug exposure or by showing that it takes more of the drug to produce the same effect. In essence, what this means is that drug tolerance is a shift in the *dose-response curve* (a graph of the magnitude of the effect of different doses of the drug) to the right (see Figure 15.1).

There are three important points to remember about the specificity of drug tolerance.

- One drug can produce tolerance to other drugs that act by the same mechanism; this is known as **cross tolerance**.
- Drug tolerance often develops to some effects of a drug but not to others (e.g., Castello et al., 2014). Failure to understand this second point can have tragic consequences for people who think that because they have become tolerant to some effects of a drug (e.g., to the nauseating effects of alcohol), they are tolerant to all of them. In fact, tolerance may develop to some effects of a drug while sensitivity to other effects of the same drug increases. Increasing sensitivity to a drug is called **drug sensitization**.

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- Drug tolerance is not a unitary phenomenon; that is, there is no single mechanism that underlies all examples of it (Littleton, 2001). When a drug is administered at doses that affect nervous system function, many kinds of adaptive changes can occur to reduce its effects.

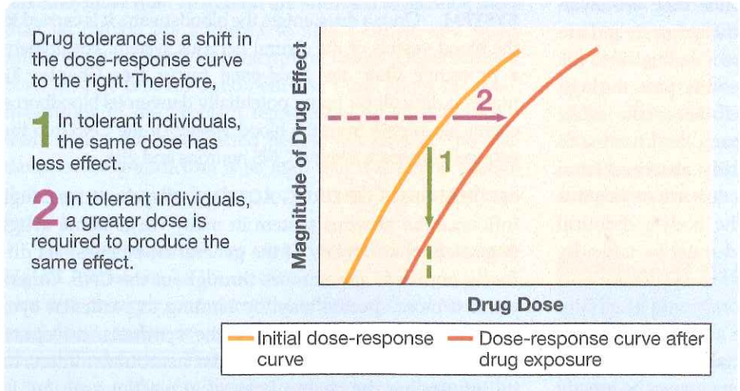
Two categories of changes underlie drug tolerance: metabolic and functional. Drug tolerance that results from changes that reduce the amount of the drug getting to its sites of action is called **metabolic tolerance**. Drug tolerance that results from changes that reduce the reactivity of the sites of action to the drug is called **functional tolerance**.

Tolerance to psychoactive drugs is largely functional. Functional tolerance to psychoactive drugs can result from several different types of adaptive neural changes (see Treistman & Martin, 2009). For example, exposure to a psychoactive drug can reduce the number of receptors for it, decrease the efficiency with which it binds to existing receptors, or diminish the impact of receptor binding on the activity of the cell. At least some of these adaptive neural changes are the result of epigenetic mechanisms (e.g., Ghezzi et al., 2013; Liang et al., 2013).

DRUG WITHDRAWAL EFFECTS AND PHYSICAL DEPENDENCE After significant amounts of a drug have been in the body for a period of time (e.g., several days), its sudden elimination can trigger an adverse physiological reaction called a **withdrawal syndrome**. The effects of drug withdrawal are virtually always opposite to the initial effects of the drug. For example, the withdrawal of anticonvulsant drugs often triggers convulsions, and the withdrawal of sleeping pills often produces insomnia. Individuals who suffer withdrawal reactions when they stop taking a drug are said to be **physically dependent** on that drug.

Clinical Implications

Figure 15.1 Drug tolerance is a shift in the dose-response curve to the right as a result of exposure to the drug.



Clinical Implications What do you think the withdrawal reaction might be when one suddenly stops taking an antidepressant medication after having taken it for many years?

The fact that withdrawal effects are frequently opposite to the initial effects of the drug suggests that withdrawal effects may be produced by the same neural changes that produce drug tolerance (see Figure 15.2). According to this theory, exposure to a drug produces compensatory changes in the nervous system that offset the drug's effects and produce tolerance. Then, when the drug is eliminated from the body, these compensatory neural changes—without the drug to offset them—manifest themselves as withdrawal symptoms that are opposite to the initial effects of the drug.

The severity of withdrawal symptoms depends on the particular drug in question, on the duration and degree of the preceding drug exposure, and on the speed with which the drug is eliminated from the body. In general, longer exposure to greater doses followed by more rapid elimination produces greater withdrawal effects.

Watch this video on MyPsychLab

CHALK IT UP! DRUG TOLERANCE, WITHDRAWAL EFFECTS, AND PHYSICAL DEPENDENCE

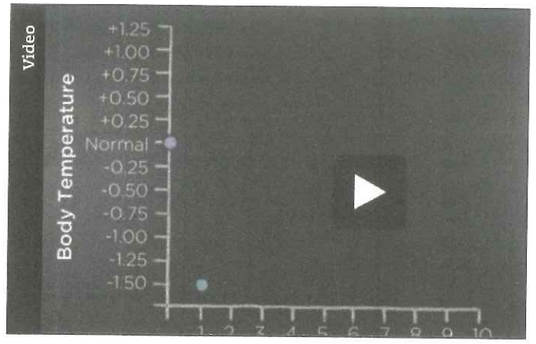
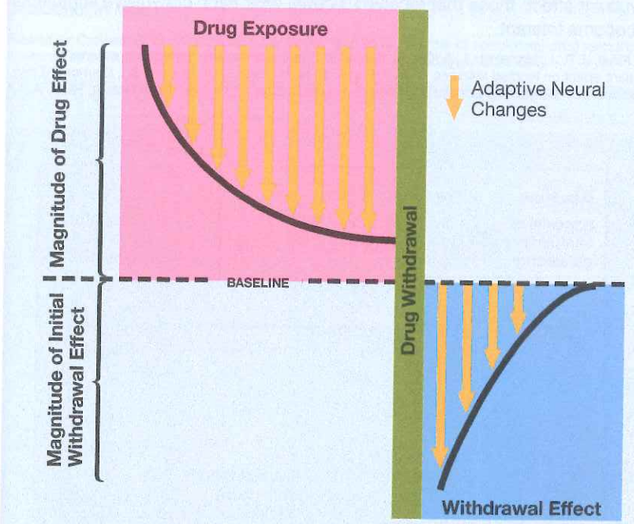


Figure 15.2 The relation between drug tolerance and withdrawal effects. The same adaptive neurophysiological changes that develop in response to drug exposure and produce drug tolerance manifest themselves as withdrawal effects once the drug is removed. As the neurophysiological changes develop, tolerance increases; as they subside, the severity of the withdrawal effects decreases.



Drug Addiction: What Is It?

LO 15.4 Define drug addiction.

Drug-addicted individuals are habitual drug users, but not all habitual drug users are drug-addicted individuals. **Drug-addicted individuals** are those habitual drug users who continue to use a drug despite its adverse effects on their health and social life, and despite their repeated efforts to stop using it.

The greatest confusion about the nature of drug addiction concerns its relation to physical dependence. Many people equate the two: They see addicted persons as people who are trapped on a merry-go-round of drug taking, withdrawal symptoms, and further drug taking to combat the withdrawal symptoms. Although appealing in its simplicity, this conception of drug addiction is inconsistent with the evidence. Addicted individuals sometimes take drugs to prevent or alleviate their withdrawal symptoms, but this is often not the major motivating factor in their addiction. If it were, drug-addicted individuals could be easily cured by hospitalizing them for a few days, until their withdrawal symptoms subsided. However, most addicted individuals renew their

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drug taking even after months of enforced abstinence. This is an important issue, and it will be revisited later in this chapter.

Drugs are not the only substances to which humans become addicted. Indeed, people who risk their health by continually bingeing on high-calorie foods or risk their economic stability through compulsive gambling clearly have an addiction (see Clark, 2014; Ko et al., 2013; Robbins & Clark, 2015). Although this chapter focuses on drug addiction, other addictions—such as food, gambling, and Internet addictions—may be based on similar neural mechanisms.

Role of Learning in Drug Tolerance

An important line of psychopharmacologic research has shown that learning plays a major role in drug tolerance. In addition to contributing to our understanding of drug tolerance, this research has established that efforts to understand the effects of psychoactive drugs without considering the experience and behavior of the subjects can provide only partial answers.

Research on the role of learning in drug tolerance has focused on two phenomena: contingent drug tolerance and conditioned drug tolerance. These two phenomena are discussed in the following sections.

Contingent Drug Tolerance

LO 15.5 Explain contingent drug tolerance.

Contingent drug tolerance refers to demonstrations that tolerance develops only to drug effects that are actually experienced. Most studies of contingent drug tolerance employ the **before-and-after design**. In before-and-after experiments, two groups of subjects receive the same series of drug injections and the same series of repeated tests, but the subjects in one group receive the drug before each test of the series and those in the other group receive the drug after each test of the series. At the end of the experiment, all subjects receive the same dose of the drug followed by a final test so that the degree to which the drug disrupts test performance in the two groups can be compared.

My colleagues and I (Pinel, Mana, & Kim, 1989) used the before-and-after design to study contingent tolerance to the anticonvulsant effect of alcohol. In one study, two groups of rats received exactly the same regimen of alcohol injections: one injection every 2 days for the duration of the experiment. During the tolerance development phase, the rats in one group received each alcohol injection 1 hour before a mild convulsive amygdala stimulation so that the anticonvulsant effect of the alcohol could be experienced on each trial. The rats in the other group received their injections 1 hour after each convulsive stimulation so that the anticonvulsant effect of the alcohol could not be experienced. At the end of the experiment, all of the subjects received a test injection of alcohol, followed 1 hour later by a convulsive stimulation so that the amount of tolerance to the anticonvulsant effect of alcohol could be compared in the two groups. As Figure 15.3 illustrates, the rats that received alcohol on each trial before a convulsive stimulation became almost completely tolerant to alcohol's anticonvulsant effect, whereas those that received the same injections and stimulations in the reverse order developed no tolerance whatsoever to alcohol's anticonvulsant effect. Contingent

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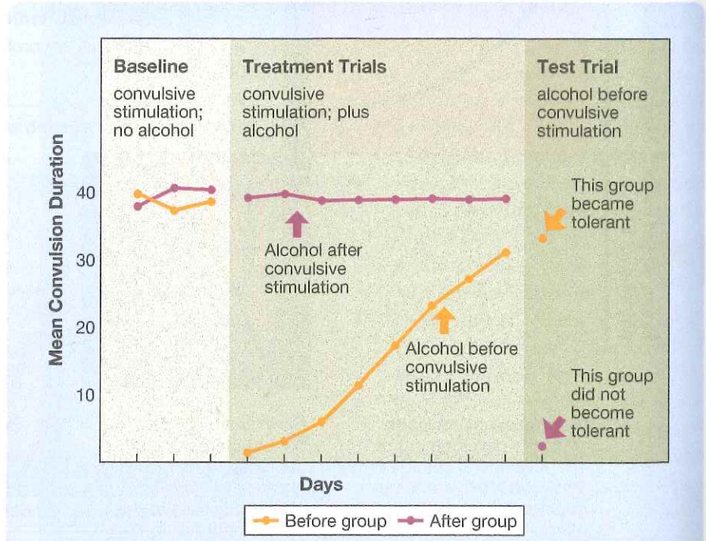
Figure 15.3 Contingent tolerance to the anticonvulsant effect of alcohol. The rats that received alcohol before each convulsive stimulation became tolerant to its anticonvulsant effect; those that received alcohol after each convulsive stimulation did not become tolerant.

(Based on Pinel, J. P. J., Mana, M. J., & Kim, C. K. (1989). Effect-dependent tolerance to ethanol's anticonvulsant effect on kindled seizures. In R. J. Porter, R. H. Mattson, J. A. Cramer, & I. Diamond (Eds.), *Alcohol and seizures: Basic mechanisms and clinical implications* (pp. 139–149). Philadelphia, PA: F. A. Davis.)



drug tolerance has been demonstrated to many other drug effects in many species, including humans (see Wolgin & Jakubow, 2003).

Conditioned Drug Tolerance

LO 15.6 Describe conditioned drug tolerance and conditioned compensatory responses.

Whereas studies of contingent drug tolerance focus on what subjects do while they are under the influence of drugs, studies of conditioned drug tolerance focus on the situations in which drugs are taken. **Conditioned drug tolerance** refers to demonstrations that tolerance effects are maximally expressed only when a drug is administered in the same situation in which it has previously been administered (see Siegel, 2011).

In one demonstration of conditioned drug tolerance (Crowell, Hinson, & Siegel, 1981), two groups of rats received 20 alcohol and 20 saline injections in an alternating sequence, one injection every other day. The only difference between the two groups was that the rats in one group received all 20 alcohol injections in a distinctive test room and the 20 saline injections in their colony room, while the rats in the other group received the alcohol in the colony room and the saline in the distinctive test room. At the end of the injection period, the tolerance of all rats to the *hypothermic* (temperature-reducing) effects of alcohol was assessed in both environments. As Figure 15.4 illustrates, tolerance was observed only when the rats were injected in the environment that had previously been paired with alcohol administration. There have been dozens of other demonstrations of the *situational specificity of drug tolerance*: The effects are large, reliable, and general.

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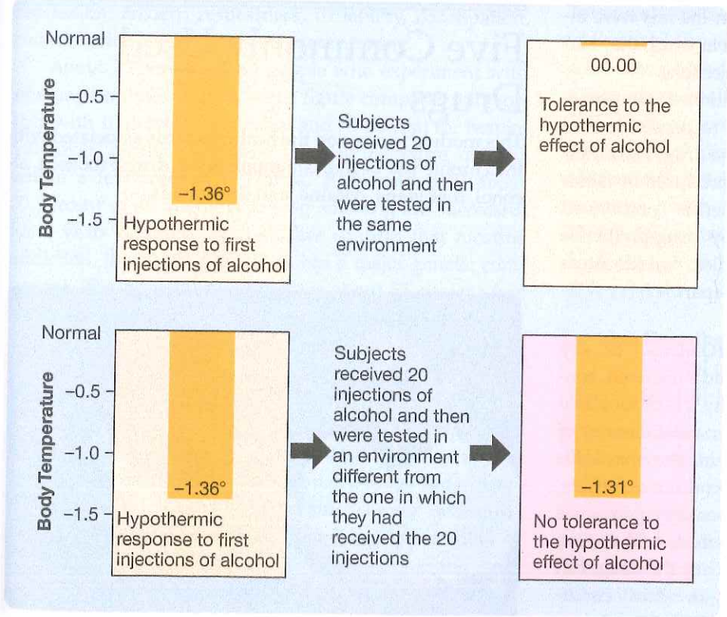
The situational specificity of drug tolerance led Siegel and his colleagues to propose that drug users may be particularly susceptible to the lethal effects of a drug overdose when the drug is administered in a new context. Their hypothesis is that drug users become tolerant when they repeatedly self-administer their drug in the same environment and, as a result, begin taking larger and larger doses to counteract the diminution of drug effects. Then, if the drug user administers the usual massive dose in an unusual situation, tolerance effects are not present to counteract the effects of the drug, and there is a greater risk of death from overdose. In support of this hypothesis, Siegel and colleagues (1982) found that many more heroin-tolerant rats died following a high dose of heroin administered in a novel environment than died in the usual injection environment. (Heroin, as you will learn later in this chapter, kills by suppressing respiration.)

Siegel views each incidence of drug administration as a Pavlovian conditioning (see Chapter 5) trial in which various environmental stimuli (e.g., particular rooms, drug paraphernalia, or other drug users) that regularly predict the administration of the drug are conditional stimuli and the drug effects are unconditional stimuli. The central assumption of the theory is that conditional stimuli that predict drug administration come to elicit conditional responses opposite to the unconditional effects of the drug. Siegel has termed these hypothetical opposing conditional responses **conditioned compensatory responses**. The theory is that conditional stimuli that repeatedly predict the effects of a drug come to elicit greater and greater conditioned compensatory responses; and those conditioned compensatory responses increasingly counteract the unconditional effects of the drug and produce situationally specific tolerance.

Figure 15.4 The situational specificity of tolerance to the hypothermic effects of alcohol in rats.

(Based on Crowell, C. R., Hinson, R. E., & Siegel, S. (1981). The role of conditional drug responses in tolerance to the hypothermic effects of ethanol. *Psychopharmacology, 73,* 51–54.)



Alert readers will have recognized the relation between Siegel's theory of drug tolerance and Woods's theory of mealtime hunger, which you learned about in Chapter 12. Stimuli that predict the homeostasis-disrupting effects of

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meals trigger conditioned compensatory responses to minimize a meal's disruptive effects in the same way that stimuli that predict the homeostasis-disrupting effects of a drug trigger conditioned compensatory responses to minimize the drug's disruptive effects.

Thinking Creatively What other external stimuli, besides the drug-administration environment, do you think might serve as effective conditional stimuli for the development of conditioned drug tolerance?

Most demonstrations of conditioned drug tolerance have employed **exteroceptive stimuli** (external, public stimuli, such as the drug-administration environment) as the conditional stimuli. However, **interoceptive stimuli** (internal, private stimuli) are just as effective in this role. For example, both the thoughts and feelings produced by the drug-taking ritual and the drug effects experienced soon after administration can, through conditioning, come to reduce the full impact of a drug (Siegel, 2008). This point about interoceptive stimuli is important because it indicates that just thinking about a drug can evoke conditioned compensatory responses.

Although tolerance develops to many drug effects, sometimes the opposite occurs, that is, drug sensitization. *Drug sensitization*, like drug tolerance, can be situationally specific (e.g., Singer et al., 2014). For example, Anagnostaras and Robinson (1996) demonstrated the situational specificity of sensitization to the motor stimulant effects of amphetamine. They found that 10 amphetamine injections, one every 3 or 4 days, greatly increased the ability of amphetamine to activate the motor activity of rats—but only when the rats were injected and tested in the same environment in which they had experienced the previous amphetamine injections.

Drug withdrawal effects and conditioned compensatory responses are similar: They are both responses that are opposite to the unconditioned effect of the drug. The difference is that drug withdrawal effects are produced by elimination of the drug from the body, whereas conditioned compensatory responses are elicited by drug-predictive cues in the absence of the drug. In complex, real-life situations, it is nearly impossible to tell them apart.

THINKING ABOUT DRUG CONDITIONING. In any situation in which drugs are repeatedly administered, conditioned effects are inevitable. That is why it is particularly important to understand them. However, most theories of drug conditioning have a serious problem: They have difficulty predicting the direction of the conditioned effects. For example, Siegel's conditioned compensatory response theory predicts that conditioned drug effects will always be opposite to the unconditioned effects of the drug, but there are many documented instances in which conditional stimuli elicit responses similar to those of the drug.

Ramsay and Woods (1997) contend that much of the confusion about conditioned drug effects stems from a misunderstanding of Pavlovian conditioning. In particular, they criticize the common assumption that the unconditional stimulus (i.e., the stimulus to which the subject reflexively reacts) in a drug-tolerance experiment is the drug and that the unconditional responses are whatever changes in physiology or behavior the experimenter happens to be recording. They argue instead that the unconditional stimulus is the disruption of neural functioning that has been directly produced by the drug, and that the unconditional responses are the various neurally mediated compensatory reactions to the unconditional stimulus, which the experimenter may or may not be recording.

This change in perspective makes a big difference. For example, in the previously described alcohol tolerance experiment by Crowell and colleagues (1981), alcohol was designated as the unconditional stimulus and the resulting hypothermia as the unconditional response. Instead, Ramsay and Woods would argue that the unconditional stimulus was the hypothermia directly produced by the exposure to alcohol, and the compensatory changes that tended to counteract the reductions in body temperature were the unconditional responses. The important point about all of this is that once one determines the unconditional stimulus and unconditional response, it is easy to predict the direction of the conditional response in any drug-conditioning experiment: The conditional response is always similar to the unconditional response.

Thinking Creatively

Five Commonly Used Drugs

This module focuses on the health hazards associated with the chronic use of five commonly used drugs: tobacco, alcohol, marijuana, cocaine, and the opioids.