CHAPTER

15

Hallucinogens, Phantasticants, and Club Drugs

A variety of drugs with different mechanisms of action are discussed in this chapter. At one time, they might have all been referred to as *hallucinogens*. While it may be true that many of these drugs can cause hallucinations, often they are not taken in high enough doses to do so—other effects seem to be important to the user.

Many of these drugs have profound subjective and emotional effects. They make the user feel in touch, either with others around them or with their inner selves; feel closer to God or the universe; or feel ecstatic. They can also enhance the enjoyment or appreciation of music and social situations. A variety of other names have been suggested that describe some of these other common effects, names that include *phantasticants*, *psychedelics* ("mind manifesters"), *entactogens* ("touching within"), and *empathogens* ("empathy enhancers"). The latter three were proposed in an attempt to describe the effect of these drugs on personal insights and empathy. Due to the nature of these subjective effects, it has been suggested that certain drugs of this type could be useful tools in psychotherapy (Metzner, 1993). Because the mental state created by some of these drugs is superficially similar (and sometimes almost identical) to certain forms of psychosis, the name *psychotomimetics* ("psychosis mimics") is also sometimes used. More recently, some of these drugs have become associated with the club scene and are used to enhance the pleasure of music, dancing, and being with others. When used this way, they are referred to as *club drugs*.

LSD AND THE MONOAMINE-LIKE DRUGS

The molecular structure of many drugs with hallucinogenic and phantasticant properties bears a resemblance to the monoamine neurotransmitters: serotonin, dopamine, and norepinephrine. *LSD (lysergic acid diethylamide)* and many other drugs are similar to serotonin, which is an indoleamine. Mescaline has a structure similar to the catecholamines, dopamine and norepinephrine. Even though they differ somewhat in structure, there is a considerable overlap between the effects of these *indoleamine-like* and *catecholamine-like* drugs, so they can be discussed together. In the next section we will discuss MDMA (ecstasy), which has certain chemical properties of both mescaline and amphetamines as well as similar behavioral effects.

Indoleamine-like drugs have effects that are similar to LSD and differ mainly in potency and duration of action. These include *psilocybin*, the ingredient in magic mushrooms; *lysergic acid amide*, found in morning glory seeds; *DMT*, found in the bark of a tree in the jungles of South and Central America; *bufotenine*, found in plants and in the venom of toads from the *Bufo* genus;

and *harmine* and *harmaline*, which are found in a tropical vine that grows in South America and is used by the native peoples in the area to make an intoxicating drink (McKim, 2003).

Mescaline is a catecholamine-like drug. It too has many effects in common with LSD but is about 1/2,000th as potent. It is the active ingredient in a cactus known as the *peyote* (*Lephophora williamsii*), which is native to the deserts of Mexico and the southwestern United States. The peyote is a small, spineless cactus that barely sticks out of the ground and has a thick, tuberous root. It has been used for centuries by Native Americans in rituals and religious ceremonies.

Since LSD is the most widely used and studied member of the monoamine-like drugs, it will be discussed in detail as a representative of this class. In fact, it also shares some effects with ecstasy and other drugs in this chapter.

History of LSD

LSD is a synthetic drug; however, a number of similar chemicals occur naturally in the *ergot fungus* that infects grains, especially rye. During the Middle Ages in Europe, there were outbreaks of what is now called *ergotism*, a reaction caused by eating fungus-infected grain. There were two kinds of effects caused by different fungi. One kind severely constricted blood flow to the limbs and made the person feel excessively warm. This eventually led to gangrene, and the limb would fall off. In 1039, a religious order was formed in France to treat people afflicted with this kind of ergotism. The patron saint of this order was St. Anthony, and the disease became known as *St. Anthony's fire* because of the sensation of heat. The other type of ergotism was characterized by convulsions, delirium, and hallucinations. That these afflictions were caused by the fungus was not discovered until more than 700 years later, in 1777. In fact, St. Anthony's fire was caused by derivatives of lysergic acid in the ergot fungus.

The story of LSD begins in the twentieth century. One of the effects of the lysergic acid derivatives in ergot was contractions of the uterus, a fact that was known to midwives who used it to aid women in childbirth. This prompted Albert Hofmann of the Sandoz Laboratories in Basel, Switzerland, to experiment with the derivatives of lysergic acid in the hope of finding a new medicine. He had no inkling that he was dealing with a hallucinogen. In 1938, he synthesized a series of lysergic acid compounds but found none of them particularly interesting and went on to other things. Five years later, in 1943, Hofmann made a new batch of the twenty-fifth derivative (which he called LSD-25) and tried some new experiments, but he began to feel very peculiar and had to go home. He suspected that the reason for his strange sensations was that he had accidentally taken some of the LSD-25. To test this theory, a few days later he deliberately ingested 0.25 mg (250 micrograms, μg), which he thought was an extremely small dose. His plan was to start with a dose so small that it would have no effect and slowly work up, but he did not know the extreme potency of LSD. A quarter of a milligram is a rather large dose and is more than sufficient to cause a significant hallucinatory effect. Hofmann experienced the first LSD trip.

Sandoz Laboratories did not know what to do with LSD, so the drug was distributed for testing to laboratories in Europe and the United States. It was thought that it might be useful in the treatment of mental disorders and alcoholism or at least as a means of studying psychotic behavior. Some researchers, like Humphry Osmond at the University of Saskatchewan, believed that LSD offered the power to provide great personal insights and possessed considerable psychotherapeutic potential. LSD was used in experiments in mental hospitals and laboratories until the mid-1960s, when it broke out of the laboratory and into the street.

Timothy Leary, a research professor in the Department of Social and Human Relations at Harvard University, was always considered by his colleagues to be a bit unconventional and radical in his views. The psychedelic revolution began for Leary in 1960. While he was in Mexico, he ate some mushrooms containing psilocybin, which caused him to have a "full-blown conversion experience." When he returned to Harvard, he and his colleague, Richard Alpert, distributed psilocybin to as many people as they could convince to take it. In 1961, they tried LSD, started a new religion, and adopted LSD as a sacrament. In 1963, Leary and Alpert were dismissed from Harvard, a move that generated considerable publicity for them and the drug. They coined the phrase that was to become the philosophy of the hippie movement of the 1960s: "Turn on, tune in, drop out."

LSD had its heyday during the 1960s and early 1970s, the years of the hippie movement, which reached

its peak at the Woodstock Music Festival in 1969. LSD has not vanished since then, but the pattern of its use is now somewhat different. In the 1960s, LSD was used as a true psychedelic—high doses were consumed in order to achieve vivid hallucinations and personal or cosmic insights. Using these high doses was not always a pleasurable experience. It has been suggested that drug users, since that time, are not as interested in insight as they are in pleasure (Baumeister & Placidi, 1983).

LSD is now taken in smaller doses and used more as a phantasticant or entactogen than as a hallucinogen. The effect is a euphoric high similar to that of marijuana, and powerful mind-altering states are neither desired nor achieved.

Dosage and Sources

LSD is sold as hits. In the 1970s, a typical hit contained about 100 μg of LSD with a range of 0 to 300 μg (James & Bhatt, 1972). The minimum dose required to produce a full psychedelic experience with visual hallucinations is often cited as 200 μg. Although the average dose does not appear to have changed much over time, there has always been great variation in the dosage available in a hit.

Hits of LSD have traditionally been absorbed in blotting paper, which may be plain or printed with various cartoons or mosaic patterns. More recent variations include the *gel tab*, LSD in gelatin that is set in molds of various shapes, or flat squares called *window panes*. LSD is also now available in candies or tiny pills called *microdots*. There is usually a larger dose of LSD in gelatin than in blotting paper because the gelatin protects the drug from deterioration caused by light and exposure to air. Mescaline is acquired from the dried *heads* of the peyote cactus and can be consumed orally or soaked in water to create an intoxicating drink. The typical effective dosage of mescaline is 200 to 400 μg.

Pharmacokinetics

LSD is usually taken orally and is effective between 30 and 90 minutes after ingestion. Only 1% of the drug ever reaches the brain. The half-life of LSD is approximately 175 to 300 minutes in humans (Aghajanian & Bing, 1964; Papac & Foltz, 1990). It is metabolized extensively in the liver, and its metabolites are secreted into the digestive system in the bile and excreted in feces. Mescaline is also readily absorbed from the digestive system and has a similar half-life (Brown, 1972).

Effects on the Body

There are few consistent physical side effects of LSD; the most common is dilation of the pupils. Nausea, changes in body temperature, and increased heart rate have also been reported. Mescaline often causes a period of nausea during the early stages of its effect.

Neurophysiology

Even though LSD has been around for a long time and has been studied extensively, its effects on the nervous system are still not clear. While it acts as a serotonin receptor blocker in the peripheral nervous system, in the central nervous system it appears to be a selective agonist at some serotonin receptors, particularly the 5-HT_{2A} receptor. This is also true for other indoleamine-like and catecholamine-like hallucinogens. Their effects on 5-HT_{2A} receptors are one of the few that all these drugs have in common. It has been suggested that, in cortical neurons specifically, LSD and other hallucinogenic compounds trigger a particular intracellular signaling cascade that is distinct from other 5-HT_{2A} receptor agonists (González-Maeso et al., 2007). This appears to be one of the reasons these compounds can trigger hallucinations.

There are three regions of the brain that seem to be involved in the hallucinogenic effect: the locus coeruleus (LC), the cortex, and the raphe nuclei. The LC receives input from many sensory sources throughout the body, including the raphe nuclei. It sends axons to almost every area of the brain including the cortex, where it promotes the release of NE (see Chapter 4). It is involved in fear and emotional responses and appears to function as a novelty detector. Stimulation of 5-HT_{2A} receptors by both indoleamine- and catecholamine-like hallucinogens can suppress output of the LC, although it occurs through different mechanisms. In addition, these drugs enhance the response of the LC to novelty. This might explain the common effects of hallucinogenic drugs on perception. After taking mescaline, for example, people often report that it is like seeing things for the first time.

In the cortex, these drugs change the response of large glutamatergic neurons to synaptic input by increasing

the duration of excitatory action potentials. This effect is mediated through serotonin synapses and is most prominent in the medial prefrontal cortex, where there is a large concentration of 5-HT_{2A} receptors. This area of the cortex is instrumental in information processing and perception.

The raphe nuclei are clustered in the brainstem and function to release serotonin in the rest of the brain. It has been found that LSD acts as a 5-HT_{1A} receptor agonist in the raphe system, where it inhibits neuronal firing and serotonin release (Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008). Because the LC receives input from the raphe nuclei via serotonin neurons, suppression of the raphe system by hallucinogenic drugs may be the precursor to LC suppression and the resulting effects.

Subjective Effects

HALLUCINOGENIC EFFECT. How does a scientist go about studying hallucinations? Hallucinations are, by definition, in the realm of subjective experience, and one of the first principles of scientific inquiry is that all scientific data must be public and observable to anyone. It is, however, possible to study the verbal reports of people who are experiencing or have experienced hallucinations. Heinrich Kluver (1966) combined reports of subjects in his own experiments on mescaline and those of other researchers and noticed that there were consistencies. Mostly, these people described vivid visual images, and the researchers were aware that the images were not real. If they closed their eyes, they would see these images against a black background; if they opened their eyes, the images would be projected on whatever they were looking at. Kluver noticed that the images were frequently geometric, and he identified some common patterns: a grating or lattice; a cobweb; a tunnel, funnel, or cone; and a spiral. Kluver remarked that images of these types also appear in fever deliriums, insulin hypoglycemia, and states that occur just before drifting off to sleep (*hypnogogic states*). Unfortunately, what Kluver described was only the first of two stages of imagery; the second stage, described by others, is more complex and involves meaningful images of people, animals, and places. Even during this phase, there are some common elements among individuals. For example, 60 to 70% of all subjects report seeing small animal or human figures that are friendly and caricature-like, and 72% of all subjects report religious imagery.

Despite the great interest surrounding these observations, no comprehensive, systematic, or scientific work on them was attempted until the 1970s. The problem was tackled by Ronald Siegel (Siegel & Jarvik, 1975) from the University of California in Los Angeles (UCLA). Siegel adopted a variation of the technique of trained introspection, which had been used by the early German schools of psychology. Siegel trained his observers to use a code to describe their experiences. They were able to code images, colors, and movement by using a series of letters and numbers that could be quickly expressed. Following this training, Siegel gave participants a series of blind tests in which they were administered placebos or any of a number of drugs in random order and left in a darkened room to report their experiences. Neither the participants nor the researchers scoring the imagery codes knew what drug had been given.

Whereas the participants given placebos saw a predominance of random forms, those getting the hallucinogenic drugs saw far more lattice and tunnel forms, confirming the observations of Kluver. During control sessions, participants saw primarily black and violet forms, but in hallucinogenic sessions, they saw more colors, ranging into the yellow, orange, and red end of the spectrum. Finally, in all conditions, aimless and pulsating movement was reported, but in hallucinogenic sessions there was an increase in "explosive" movement.

After demonstrating that all of these drugs appeared to create similar types of images, Siegel was also able to show that, at higher doses, people sometimes go through a phase where they see themselves being swept up into their own hallucination. This is followed by a stage where the images lose their geometric quality and become meaningful pictures of real objects. These images can change rapidly, as fast as 10 times a second, but the changes are not without a pattern. Each image appears to be related to the one before it. Figure 15-1 illustrates this point. Siegel also noted that the images during this stage were related to the participant's surroundings; for example, sounds such as footsteps induced an image of someone walking. Another interesting finding was that the colors appeared to shift from the blue end of the spectrum to the red end as the effect of the drug increased in intensity.

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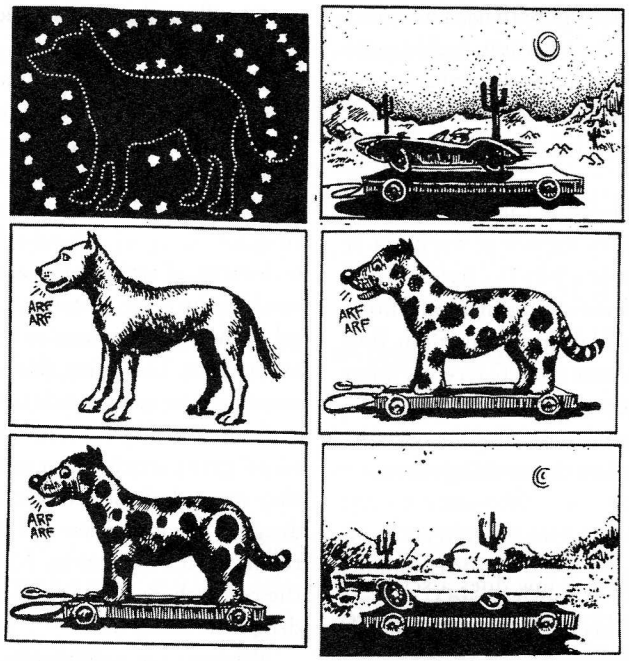

FIGURE 15-1 This series of drawings (viewed from top to bottom, column by column) illustrates the systematic changes in complex meaningful imagery reported after taking mescaline. Note that each scene contains an element of the previous one. (Pen and ink drawings by David Sheridan. From Siegel & Jarvik, 1975)

Because all these drugs have such similar effects, Siegel wondered whether the similarities might be due to cultural factors since all his subjects came from a similar culture (UCLA). To answer this question, he visited a remote tribe of Huichol Indians in the Sierra Madre range of Mexico. These Indians make brightly colored pictures of their peyote visions from colored yarn. Siegel found that the experiences represented by the Huichols in their yarn pictures were very similar to those reported by the subjects in his laboratory.

Siegel postulated that the nature and structure of hallucinations must be determined by the nature and structure of the visual system and the brain, not by the drug, because (a) these hallucinatory experiences are similar among vastly different drugs; (b) the experiences resemble the effects produced by other nondrug hallucinations, such as those from fever, hypoglycemia, and migraine headaches; and (c) the experiences are similar between cultures. In other words, the hallucinations are a result of nonspecific interference in brain functioning; the drug intensifies what might be considered normal background noise in the perceptual systems, and this noise is then organized, by the normal processes of perception and cognition, into images and patterns (Siegel, 1977; Siegel & Jarvik, 1975).

Siegel's study addressed only the visual property of the hallucinogenic experience, but LSD can cause entactogenic and empathogenic effects as well. These experiences often have a profound effect on emotions, insights, and feelings, which are not as easily studied and can be conveyed only by less scientific modes of expression, as we shall see.

PHANTASTICANT AND PERCEPTUAL EFFECTS. Hallucinogenic drugs can cause users to feel that the experiences they are having are of great emotional or worldly significance. Often these experiences can be spiritual in nature. For this reason, drugs

like LSD have been widely used in traditional religious ceremonies. The spiritual nature of the hallucinogenic experience is described here by R. Gordon Wasson (1972) in this account of his participation in a Mazatec Indian psilocybe mushroom rite:

> It permits you to see more clearly than our perishing mortal eyes can see, vistas beyond the horizons of this life, to travel backwards and forwards in time, to enter other planes of existence, even (as the Indians say) to know God. It is hardly surprising that your emotions are profoundly affected and you feel that an indissoluble bond unites you and the others who have shared in this sacred agape. All that you see during this night has a pristine quality; the landscape, the edifices, the carvings, the animals—they look as though they had come straight from the Maker's workshop. (p. 197)

Another commonly reported experience is the greatly enhanced pleasure derived from viewing art and, especially, listening to music:

> Ordinarily I am not particularly susceptible to music. This time, lying on the cot, I became acutely aware of the Montoya record playing. This was more than music: the entire room was saturated with sounds that were also feelings—sweet, delicious, sensual—that seemed to be coming from somewhere deep down inside me. I became mingled with the music, gliding along with the chords. Everything I saw and felt was somehow inextricably interrelated. This was pure synesthesia, and I was part of the synthesis. I suddenly "knew" what it was to be simultaneously a guitar, the sounds, the ear that received them, and the organism that responded, in what was the most profoundly consuming aesthetic experience I have ever had. (Richardson in Aanonsen & Osmond, 1970, p. 53)

ENTACTOGENIC AND EMPATHOGENIC EFFECTS. Another commonly reported effect is that the hallucinogens seem to provide insight into one's past and one's own mind, revealing repressed thoughts and unrecognized feelings. Such insights are similar to those that psychoanalysis attempts to achieve through psychotherapy. It was this effect that inspired Humphry Osmond to suggest that hallucinogens might be useful tools in psychotherapy and prompted the use of the term *entactogenic* ("touching within") to describe this effect. Here is a description of the experiences of psychologist Bernard Aaronson, who took LSD as part of an experiment:

> We sat on the bench under the trees and talked about the loneliness of being, and talked about how people are forever needing things they expect you to provide. For what seemed a long time, I cried as I have not cried since I was a baby, for all the people in the world who need things and whose needs cannot be met. I cried too for all the people around me that I botched in the giving or to whom I cannot give because I am depleted . . . . I expressed great hostility toward both my parents and with H.'s help analyzed my feelings as they derived from my relationship with each of them. I analyzed my relationship with my next older brother, and examined the meaning in my life of my relationship with that friend whom I love the most. (Aaronson & Osmond, 1970, pp. 47–48)

A more complete account of the subjective experiences of hallucinogens is beyond the scope of this book. A good selection of accounts of drug experiences may be found in Grinspoon and Bakalar (1979b).

Perception

As we have seen, people who use LSD frequently report that their perceptions are much keener and that their sight and hearing have become more acute. There have been a few studies of the effects of LSD on visual sensory thresholds, but their results are not consistent. In general, however, impairments of sensory functions attributable to LSD are reported more often than improvements (Hollister, 1978).

Although it is clear that LSD increases the enjoyment of music, it has not yet been established whether there are any changes in auditory thresholds. The perception of the passage of time is distorted in most individuals; however, the direction of distortion is not consistent. In most cases, time is perceived as slowing down (10 seconds seem more like 20), but in some experiments the reverse has been reported (Hollister, 1978).

Behavior and Performance

One of the difficulties with measuring human performance under the influence of hallucinogens is maintaining the motivation of the participant to cooperate. Like marijuana, hallucinogens frequently cause people to become inattentive to the task and so caught up in internal experiences that they lose their motivation to perform, as well as they are able, tasks that they may feel are irrelevant at the time. The available data show mostly that LSD impairs reaction time. Functioning on intellectual tasks is also impaired. Like THC, LSD causes a deficit in short-term, or working, memory. Other impairments are seen in problem-solving and cognitive functions such as mental addition and subtraction, color naming, concentration, and recognition (Hollister, 1978).

Claims have been made that LSD-like hallucinogens improve creativity, but again, as with THC, these are difficult to substantiate experimentally. There is little doubt that LSD changes the sort of work done by artists, but it is debatable whether these changes are improvements.

Tolerance

In humans, tolerance to the effects of LSD and related drugs develops rapidly. When LSD is taken repeatedly for 2 or 3 days, tolerance develops and the drug no longer produces the desired effect. This tolerance dissipates quickly, however, and sensitivity returns within a week. This is one reason why these drugs are seldom taken continually. The ability of LSD to disrupt the operant behavior of nonhumans also shows rapid tolerance. Cross-tolerance has been observed between LSD, psilocybin, and mescaline but not between LSD and d-amphetamine or THC (Brown, 1972). Such tolerance appears to be mediated by the downregulation of the serotonin 5-HT_{2A} receptor (Gresch, Smith, Barrett, & Sanders-Bush, 2005).

Withdrawal

No withdrawal symptoms for LSD or any similar drugs have been documented. This may be because the drugs are seldom taken continuously for any period of time and do not lead to physical dependence. However, some issues can persist for a short time after use is stopped, such as flashbacks or residual perceptual distortions.

Self-Administration

NONHUMANS. It is widely accepted that LSD and similar monoamine-like hallucinogens are not self-administered by nonhumans. In fact, they appear to have aversive effects, and it has been demonstrated that laboratory animals will work to avoid being given LSD. In one experiment, rhesus monkeys learned to press a lever to turn off a stimulus that normally preceded an infusion of LSD and, thus, prevented the infusion (Hoffmeister & Wuttke, 1975). Nevertheless, a study done in 2004 did show transient self-administration of DMT, mescaline, and psilocybin in some monkeys with a history of self-administering MDMA (discussed later in this chapter; Fantegrossi, Woods, & Winger, 2004). This suggests that the occasional use of these drugs may be reinforcing in some individuals. This may explain why, outside the laboratory, there are reports that nonhumans will, from time to time, consume plants that contain LSD-like drugs.

HUMANS. The self-administration of hallucinogens like LSD in human cultures is almost universal and very ancient, but its use is different from the use of most other drugs. First, these drugs are never continuously consumed. They are indulged in sporadically and on special occasions. The use of hallucinogens in most cultures is usually associated with religious ceremonies. In many cultures, these drugs are taken only by priests and shamans for the purpose of divination, talking to the dead, or seeking direction from a deity. Even in modern Western culture, hallucinogens are usually taken episodically. Unlike other heavily used drugs such as alcohol, LSD use, for most people, does not increase over time. This may be due in part to the rapid development of tolerance that occurs when individuals use LSD continually.

LSD use among teenagers in the United States remained fairly high throughout the 1990s but has since been steadily declining. In 2009, 6.8% of individuals aged 18 to 25 reported lifetime use of LSD and 0.3% reported using LSD within the past 30 days (Substance Abuse and Mental Health Services Administration, 2010).

Harmful Effects

Psilocybin, LSD, and mescaline are not very toxic. There are no recorded cases of anyone dying from an

overdose of any of these drugs. However, the media has focused attention on behaviors, which may be provoked by the acute effects of hallucinogenic drugs. For example, stories appear occasionally about LSD users who jump out of windows because they believe that they can fly or commit murders under the influence of the drug. These events undoubtedly occur, but they are extremely rare and probably occur with no greater frequency under the influence of LSD than alcohol or any other drug.

A common effect of less concern is the *acute psychotic reaction* or *psychedelic crisis*, which occurs when the user is having an unpleasant experience or bad trip. During a psychedelic crisis, the user often forgets that their experience is drug-induced. Consequently, they can undergo reactions ranging from vague anxiety to prolonged terror or panic. Panic reactions are not normally seen in experienced users, are frequently a result of an unusually high dose (or mixture) of drugs, and do not constitute a serious medical emergency. Panicked users can usually be calmed down if put in close contact with someone who talks to them and reassures them that their state is drug induced. If their attention can be concentrated on this fact, the panic can usually be dispelled.

Another adverse effect of many hallucinogens is that some of their effects may be briefly experienced long after the drug has worn off. These episodes are commonly known as *flashbacks*, and the condition is listed in the *DSM-IV-TR* (2000) as "Hallucinogen Persisting Perception Disorder (Flashbacks)" (HPPD). In a similar effect, called *trailing phenomena*, objects seem to move in a jerky, discontinuous fashion as though being illuminated by stroboscopic light. These symptoms may occur unpredictably after a single use of LSD and normally last only a few seconds or minutes. It has been suggested that stress or the use of other drugs such as caffeine, alcohol, or marijuana may trigger these perceptual distortions (Halpern & Pope, 2003). The prevalence of individuals who display HPPD symptoms after one-time, or even chronic, use is likely very small, and there is insufficient evidence to establish a cause–effect relationship between hallucinogen use and development of HPPD. Though the condition exists, its development is likely contingent on numerous other factors than just hallucinogen use alone.

ECSTASY AND SYNTHETIC MESCALINE-LIKE DRUGS

The structure of the mescaline molecule has been altered to form a family of drugs that is a combination of catecholamine-like hallucinogens and amphetamines. These drugs are all synthetic. Much of this research was done in the hope of finding drugs with medically useful properties, and many were created. So far, these substances have been used exclusively in the drug subculture. Perhaps the best known of these is ecstasy.

The term *ecstasy* usually refers to *MDMA* (3,4-methylenedioxymethamphetamine) but may also refer to a mixture of *MDMA*, *MDEA* (N-ethyl-3,4-methylenedioxyamphetamine), and *MDA* (3,4-methy lenedioxyamphetamine), drugs with similar potencies and effects (Kalant, 2001). MDMA was originally synthesized by the Merck drug company and patented in 1914. It was never developed or used for any purpose until the late 1960s, when it first appeared on the drug scene (Siegel, 1986). MDMA may also be known on the street as *X*, *Adam*, *MDM*, *M&M*, and *e*.

During the 1960s, many other synthetics were invented and manufactured in clandestine labs in an attempt to circumvent the law, which identified only specific chemicals as illegal. At that time, slight changes in the molecule could make a drug legal until such time as there was specific legislation against it. Such drugs have become known as *designer drugs*, and they appeared on the street with a variety of names such as DMA, DOM, DOET, and so on. For the most part, these substances are more potent and considerably more toxic than mescaline, and they cause more unpleasant side effects, such as headaches and nausea. Unlike commercially developed drugs, many designer drugs were not screened for adverse effects, and some had extremely toxic effects and caused a number of deaths. Many of these designer drugs have virtually disappeared, but some, like ecstasy, are still around and are still widely used.

Prior to July 1985, when it was reclassified by the governments of the United States, the United Kingdom, and Canada, some psychiatrists gave MDMA to their patients because it seemed to enhance intimacy and communication between the patient and the therapist (the terms *entactogen* and *empathogen* were invented with ecstasy in mind; Adler, Abramson, Katz, & Hager, 1985; Verebey, Alrazi, & Jaffe, 1988). When it was reclassified

in 1985, its use, even for psychotherapeutic purposes, was banned because it was discovered that the drug had neurotoxic effects; it was shown that a dose of about four times the normal effective dose causes a depletion of serotonin in the brains of rats 1 week after a single administration, a finding now confirmed in humans (Baggott, Jerome, & Stuart, 2001).

Ecstasy is sold in white or colored tablets that may or may not be marked with a symbol. Each pill may contain up to 100 mg or more of MDMA and may also contain varying amounts of MDEA, MDA, PMA (paramethyoxyamphetamine), and MBDB (3,4-methhlenedioxy-phenyl-N-methylbutanamine). A review of the purity of ecstasy tablets showed that in the late 1990s, as many as 20% of tablets did not contain MDMA at all; many contained only drugs like caffeine, ephedrine, or ketamine. However, these purity problems have not persisted into the 2000s, and non-MDMA tablets are now infrequent (Parrott, 2004).

Pharmacokinetics

Ecstasy is typically taken orally and reaches a peak concentration in the bloodstream 2 hours after ingestion. The majority of the drug is either excreted unchanged in the urine or metabolized to MDA. It has a half-life of about 8 hours, thus taking about 40 hours for 95% of the drug to be eliminated. For this reason, many of its effects persist for several days after use.

Ecstasy is most often used by teens and young adults attending dance clubs or raves, although its use is associated with an increasing number of other activities such as sex. It produces a marked increase in wakefulness, endurance, energy, a sense of euphoria, an increased sense of well-being, sharpened sensory perception, greater sociability and extroversion, and a heightened sense of closeness to other people. As with LSD, these effects are subject to rapid acute tolerance, which generally means that ecstasy is unlikely to be used continuously. As with LSD, this tolerance dissipates within a few days.

Neurophysiology

Ecstasy and similar synthetics increase transmission at synapses that use serotonin, norepinephrine, and, to a lesser extent, dopamine. It works primarily by causing the release of the neurotransmitter and blocking transmitter reuptake. Ecstasy also affects the release of *oxytocin*, a hormone involved in bonding and building trust (Dumont et al., 2009). This neurophysiological effect may be the cause of ecstasy's empathogenic and entactogenic properties.

Behavior and Performance

A dose of 75 to 100 mg of ecstasy induces a state similar to that caused by marijuana or low doses of phencyclidine (PCP), with no hallucinations, and an enhanced awareness of emotions and sensations—effects similar to the entactogenic effects described earlier in the section on LSD (Lamb & Griffiths, 1987; Siegel, 1986).

Short-term, physiological effects of ecstasy include increased body temperature, perspiration, headache, pupil dilation, and muscular tension, which causes jaw clenching and tooth grinding (*bruxism*). Once the acute effects of ecstasy have subsided, several after effects are often reported, including difficulty in concentration, irritability, insomnia, fatigue, and depression similar to the crash or comedown after the use of amphetamine and cocaine (see Chapter 10).

Discriminative Stimulus Properties

Although not as much is known about mescaline and the synthetic mescaline-like drugs, it appears that increased serotonin activity is important in their stimulus effects. Rats trained to discriminate saline from MDMA will generalize the response to a serotonin (5-HT_{1A}) agonist. MDMA stimulus properties do not generalize to cocaine or mescaline.

Tolerance

Similar to LSD, psilocybin, and mescaline, tolerance to the effects of ecstasy develops rapidly in humans.

Self-Administration

NONHUMANS. It has been shown that, unlike LSD, MDMA is readily self-administered by primates (Lamb & Griffiths, 1987) and mice (Trigo, Panayi, Soria, Maldonado, & Robledo, 2006). Research with rhesus monkeys has shown that the reinforcing effects of MDMA are strongest at moderate doses, with lower doses and higher doses being ineffective reinforcers (Fantegrossi, Ullrich, Rice, Woods, & Winger, 2002).

In this experiment, the reinforcing effects of MDMA could be eliminated by administration of a drug that selectively blocked 5-HT_{2A} receptors, but this same drug did not eliminate the reinforcing effects of cocaine or methamphetamine. This suggests that the reinforcing effects of MDMA are mediated by a different mechanism than the psychomotor stimulants. Given this finding, it seems odd that other drugs that increase serotonin activity at 5-HT_{2A} receptors, such as LSD and the selective serotonin reuptake inhibitors (SSRIs), tend not to be self-administered.

HUMAN EPIDEMIOLOGY. The use of ecstasy increased steadily among young people in the United States and Europe throughout the 1990s until 2000. In the United States, ecstasy use increased in high school students, and the number of mentions of ecstasy in emergency room admissions roughly doubled between 1994 and 1999 (NIDA, 2001). A similar trend was seen in the United Kingdom and Canada (Morgan, 2000). Following this peak in 2000, when 3.6% of grade 12 students in the United States reported using the drug in the previous 30 days, ecstasy use underwent a drastic decline. In 2004, that figure dropped to 1.2%. This decline was accompanied with a general increase in perceived risk of using the drug (Johnston, O'Malley, Bachman, & Schulenberg, 2005). There are signs, however, that ecstasy use may be resurging. Ecstasy use in Canada and the United States has increased over the last 5 years, according to the U.N. World Drug Report (2010), and the trend will likely continue to rise. In the United Kingdom, rates of ecstasy use dropped about 1.4% from 2002 to 2008, showing a gradual decline (UNODC, *World Drug Report,* 2010).

Withdrawal

Ecstasy is known to have negative aftereffects; however, due to rapid development of tolerance, it is not taken repeatedly, and withdrawal effects are not seen.

Harmful Effects of Ecstasy

Earlier reports of dopamine neurotoxicity have been shown to be in error, but there is good evidence that, after chronic use, there is depletion of serotonin in the brain that is in proportion to the extent and intensity of use. What is not clear at this time is whether serotonin depletion is irreversible or due to receptor downregulation. There is considerable evidence from studies of chronic users that this depletion in serotonin plays out in behaviors known to be associated with serotonin. Chronic users show sleep disorders, persistent anxiety, impulsiveness, hostility, and selective impairment of memory and attention (Wareing, Fisk, & Murphy, 2000). The cognitive deficits seem to dissipate about 6 months after use is stopped, but the anxiety and hostility may remain for years. It is likely that any recovery is due to an upregulation of serotonin receptors or some other regulatory adjustment to compensate for the decreased serotonin activity in the brain (Morgan, 2000). The influence of ecstasy in precipitating depression is controversial, with some studies reporting a strong link and others not. In a review of the literature, Guillot (2007) found that, of the 22 studies reviewed, 11 reported increased depression scores associated with ecstasy use and the remaining 11 did not. Contributing to the confusion is the fact that ecstasy is rarely used in isolation; polydrug use tends to be the norm, making it difficult to attribute psychological symptoms to any particular drug. In addition, most users who demonstrated increased levels of depression reported that being diagnosed preceded their use of ecstasy (Guillot, 2007; Guillot & Greenway, 2006).

One of the more troubling and dangerous effects of ecstasy is the loss of heat regulation in the body, causing an increase in body temperature. This may not be serious in many circumstances, but at a rave where the user is dancing vigorously in a warm environment, it can cause symptoms similar to heatstroke, including muscle tissue damage, kidney failure, and liver damage. In addition, if one is dancing vigorously, this also causes profuse sweating, and the body can become dehydrated and lose large amounts of salt. Dancers often attempt to compensate by drinking water excessively, but doing this without replacing salt can dilute the blood and create an electrolyte imbalance. This in turn can cause organs, including the brain, to swell, resulting in seizures. In a 2009 review of the harmful effects of ecstasy, it was found that *hyperthermia* and *hyponatraemia* (electrolyte disturbance) were the most common causes of death related to ecstasy (Rogers et al., 2009).

Lethal Effects

The therapeutic index of ecstasy is about 15 (Gable, 2004); however, there is a great range of doses that have been known to cause death, some within the range

of recreational drug use. Death may result from a number of different mechanisms. Hyperthermia and hyponatraemia are two causes. In one study of 87 ecstasy-related deaths, 8 were related to the heart or circulatory system, 4 were caused by liver damage, 9 were caused by swelling of the brain resulting from blood dilution, 30 were caused by overheating, 14 were caused by suicide or accident, and in 22 cases the cause could not be determined (Kalant, 2001).

A complicating factor is that there is nothing in the way of quality control in the clandestine labs that manufacture ecstasy, and the pills may also contain amphetamine, ephedrine, and other substances like *PMA*. PMA was developed in a clandestine lab in Canada in the early 1970s and was distributed in the illicit drug market in the United States and Canada. This drug is extremely potent, second only to LSD, but it is also very toxic and has a therapeutic index of 2.5, making it very dangerous to use (Schmidt, 1987). A number of deaths were attributed to PMA before warnings could be spread about it.

In many ecstasy-related fatalities, other drugs have been consumed such as alcohol, amphetamines, or other club drugs like GHB or PMA. Using data from the General Mortality Register, it was calculated that the risk of death per person, per tablet of ecstasy, is 1 in 39,000 when combined with other drugs, but only 1 in 1.8 million when ecstasy is the sole drug used (Noller, 2009).

SALVIA

Salvia dinorum is a psychoactive plant that produces visions and dissociative effects, much like LSD and other hallucinogens. The plant is native to Oaxaca, Mexico, and has a long history of use in tribal ceremonies, as with many naturally occurring hallucinogens. *Salvinorin A*, the active compound in *Salvia dinorum*, is unique as it is the first known *diterpene hallucinogen*. Salvinorin A does not chemically resemble other psychoactive compounds like LSD and mescaline as they are alkaloid and contain nitrogen. Dried *Salvia dinorum* usually contains about 0.18% Salvinorin A (Ott, 1995) and, by mass, is one of the most potent natural hallucinogens. The effects of the drug can be present in doses as small as 200 μg, which is somewhat comparable to the effective dose of synthetic psychoactive drugs like LSD. Despite its potency, Salvinorin A has an extremely low toxicity, and rats chronically exposed to doses far in excess of effective human doses showed no harmful physiological damage (Mowry, Mosher, & Briner, 2003).

Neurophysiology

Salvinorin A has been identified as a highly selective kappa (κ)-opioid receptor agonist (Yan & Roth, 2004) and as a partial D_2 dopamine receptor agonist (Seeman, Guan, & Hirbec, 2009). Interestingly, it appears to have no action at the $5\text{-}HT_{2A}$ serotonin receptor, which is instrumental in the psychedelic response to the monoamine-like hallucinogens. It has been suggested that the hallucinogenic effects of Salvinorin A are modulated by its action at the κ-opioid receptor, though this is only speculation. Little research has been done in this regard, unlike with LSD.

Salvinorin A quickly crosses the blood–brain barrier and disperses throughout the central nervous system upon ingestion. The concentration of the drug is highest in the cerebellum as well as the visual cortex (Hooker et al., 2008), which may explain the hallucinogenic properties in addition to the problems integrating sensory experience and motor control while intoxicated.

Pharmacokinetics

After ingestion of salvia, the drug is effective only for a short time. The drug-induced experience can last anywhere from 5 to 30 minutes, which is extremely short in comparison to other common hallucinogens. The main metabolic product of Salvinorin A is *Salvinorin B*, which is an inert metabolite. The metabolism of Salvinorin A to Salvinorin B occurs very rapidly, which explains the brief duration of intoxication when salvia is ingested. Levels of Salvinorin B are undetectable in the urine of rhesus monkeys even shortly after ingestion, suggesting that the metabolite is either immediately cleared or stored in organs and tissue (Schmidt et al., 2005).

Behavioral Effects

Salvinorin A produces intense hallucinations, which are extremely subjective, and with that comes a host of varied behavioral and physiological effects. Some common effects include uncontrollable laughter, loss of motor coordination, changes in perception, emotional swings, and *synaesthesia* (where sensory pathways get crossed so that, for example, words are seen in color and music tastes

good). There have been many personal accounts of salvia intoxication, but no systematic studies have been done in humans to observe the effects of the drug. A recent study attempted to remedy this by observing unaltered, full-length videos of salvia "trips" posted on YouTube. Despite the many flaws inherent in this method, certain effects were consistently noted such as *hypomovement* (relaxed or slumped body position), *hypermovement* (uncontrollable laughter or restlessness), speech deficits, and emotional changes (Lange, Daniel, Homer, Reed, & Clapp, 2010).

Tolerance and Withdrawal

Repeated exposure to salvia does not appear to lead to the development of tolerance. In fact, most users report that higher doses are required initially, and the amount needed decreases for a short time after. Few users seem to report needing an increased dose over time and indicate that at higher doses the drug effect simply continues to intensify. This is distinct from nearly all other drugs and suggests that the mechanism of action is especially different from other hallucinogens. Tolerance to LSD can become pronounced in as little as 2 days.

By all accounts, discontinuing salvia use does not lead to unpleasant physical withdrawal symptoms. Again, there has been little research done in this regard, but most users report mild adverse effects such as headache, insomnia, and irritability.

DISSOCIATIVE ANESTHETICS: PHENCYCLIDINE AND KETAMINE

Phencyclidine, also known as *PCP*, is a synthetic drug that was developed and marketed in 1963 as an analgesic and anesthetic by the Parke-Davis Company. For these purposes, it proved very effective and safe because it did not depress blood pressure or heart and respiration rates. It caused a trance-like state rather than a loss of consciousness and has been classified as a *dissociative anesthetic* because it seemed to separate people from sensory experience. In 1965, it was withdrawn from the market because patients reported that while they were recovering from the drug, they experienced a delirium, disorientation, and agitation referred to as *emergence delirium*. The use of PCP was then restricted to nonhumans. It started to be sold on the street in 1965 under the names *crystal*, *angel dust*, and *hob*, but it did not become popular until after the 1960s.

Ketamine was first synthesized in 1962 and marketed in 1969 as a safer alternative to PCP. It is a more potent anesthetic, has a shorter duration of action than PCP, and has milder emergence effects. Ketamine continues to be used as an anesthetic for children and as a veterinary anesthetic under the names *Ketaset* and *Vetalar*. Its street names include *K*, *Special K*, and *kitkat*, and it is widely used as a club drug at dance clubs or raves. It also has the reputation of being used as a date rape drug.

Ketamine sold on the street is probably diverted from legitimate veterinary use. It comes in liquid form and is colorless and tasteless. It may be swallowed or injected. Often the liquid is heated and turned to a white powder that is snorted.

Pharmacokinetics and Dose

PCP and ketamine are weak, lipid-soluble bases and can be inhaled, injected, or taken orally. A moderate dose of PCP is 5 to 10 mg. The effects of PCP are felt within a minute of inhalation or intravenous injection and from 20 to 40 minutes after oral administration. Peak effects usually occur between 10 and 90 minutes, and the effects may last from 4 to 8 hours. Drug levels fall rapidly at first as the drug is absorbed into body fat; however, low levels may persist in the body for several weeks as the drug is released from body fat (Gorelick & Balster, 2000).

During oral administration, ketamine is slowly absorbed and subject to first-pass metabolism, so the drug is often administered intranasally. Ketamine is rapidly absorbed, and effects last from 35 to 40 minutes. A normal dose of ketamine is called a *bump* and contains about 75 to 125 mg. A typical oral dose of ketamine is 175 mg, and a typical intranasal dose is 50 mg (Gable, 2004).

Neurophysiology

The dissociative anesthetics appear to alter the functioning of norepinephrine, dopamine, acetylcholine, and serotonin, but it is believed that the principal effect responsible for their reinforcing properties is that they block NMDA receptors for glutamate and aspartate, which are excitatory transmitters in many parts of the brain, including the cortex. PCP and ketamine have a binding site embedded in the ion channels normally activated by NMDA receptors. When the binding site is

occupied by PCP or ketamine, the NMDA receptor ion channel is blocked, making these transmitters ineffective. This mechanism is thought to be similar to that of the alcohol molecule (Dinwiddie & Farber, 1995; Gorelick & Balster, 2000; see also Chapter 6). When the NMDA receptor is occupied by ketamine, especially in the frontal cortex, significant negative psychotic symptoms are present, as assessed by the Brief Psychiatric Rating Scale (Stone et al., 2008). These drugs appear to act as reinforcers by influencing glutamate activity, and thereby dopamine release, in the mesolimbic and mesocortical pathways in a manner similar to the barbiturates and benzodiazepines (see Chapter 7).

Behavior and Performance

The dissociative anesthetics are known to cause amnesia for events that occur while under the influence of the drug. Although no studies of the effects of PCP on memory in humans have been conducted, PCP does seem to be more disruptive of memory in nonhumans than LSD, THC, opioids, and other psychoactive drugs (Balster, 1987). It is known that NMDA receptors are vital in the formation of long-term memories, and so it is not surprising that NMDA antagonists like PCP and ketamine are powerful amnesic drugs. In addition, it has been demonstrated that PCP and ketamine induce a type of thought disorder very similar to that seen in schizophrenic patients (Gilmour et al., 2011).

PCP and ketamine are not hallucinogenic in the same sense as LSD. Taken at usual doses, the dissociative anesthetics cause relaxation, warmth, a tingling feeling, and a sense of numbness. There are euphoric feelings, distortions in body image, and a feeling of floating in space. When these effects wear off, they are sometimes followed by a mild depression that may last from 24 hours to a week. At higher doses, the user may become stuporous or even comatose. Psychotic behavior occurs frequently and may include anything from manic excitation to catatonia, in which the user assumes one position and does not move for a prolonged period of time. There may be sudden mood changes accompanied by laughing and crying; disoriented, confused, and delusional thought; drooling; and repetitive (stereotyped) actions. This psychotic state often disappears as drug levels decline, but sometimes the psychosis requires hospitalization and lasts for weeks.

Stimulus Properties

Dissociative anesthetics appear to have unique stimulus properties. Animals trained to discriminate PCP and ketamine do not generalize this response to any other class of drugs, including stimulants, depressants, and hallucinogens, and no drug has been shown to antagonize their stimulus properties. They generalize only to other drugs known to block NMDA receptors, such as dextromethorphan (see later in this chapter), indicating that this effect is likely the basis for their stimulus properties.

Tolerance

Like LSD, PCP is typically used sporadically. When the drug is used every day, tolerance develops, and there is some evidence of dependence and withdrawal symptoms (Grinspoon & Bakalar, 1979b). When users first try the drug, they need only a few puffs of a PCP-laced cigarette to get high, but within 2 to 6 weeks, they may require two joints to achieve the same effect. Tolerance also seems to develop to the analgesic effects in burn patients. Tolerance has also been demonstrated in nonhumans and appears to take place at physiological and behavioral levels rather than in pharmacokinetics (Balster, 1987; Gorelick & Balster, 2000). Rapid tolerance also develops to the reinforcing effects and discriminative stimulus properties of ketamine in rats (Rocha et al., 1996).

Withdrawal

Research with nonhumans has shown that there may be some withdrawal after continual use of PCP. The symptoms include vocalizations, grinding of the teeth, diarrhea, difficulty staying awake, anxiety, confusion, and tremors. No systematic studies of PCP withdrawal in humans have been done (Gorelick & Balster, 2000).

Self-Administration

NONHUMANS. PCP is self-administered by monkeys, dogs, baboons, and rats either by intravenous infusion or orally (Balster, 1987; Carroll, 1993; Griffiths et al., 1980). PCP injected directly into a part of the nucleus accumbens and the frontal cortex has been shown to be reinforcing, an effect that is not diminished by a dopamine antagonist, showing that this effect is independent

of dopamine transmission (Carlezon & Wise, 1996). It has also been demonstrated that ketamine is self-administered intravenously by both rats and monkeys (Moreton, Meisch, Stark, & Thompson, 1977).

HUMAN EPIDEMIOLOGY. Patterns of PCP use are similar to LSD. Most use is experimental or occasional, but unlike LSD, some occasional users become heavy chronic users. Unfortunately, even though tolerance does develop to the reinforcing effects of dissociative anesthetics, the tolerance is not severe enough to discourage continuous use as is the case with LSD (Linder, Lerner, & Burns, 1981).

Not until the decline of LSD in the 1970s did PCP use start to increase. Before PCP became popular in its own right, it was more widely used than most people suspected because it was often mixed with other drugs or sold as something different. While its use has declined, it is still popular in some metropolitan areas and among certain groups who continue to take it by itself or mixed with marijuana or cocaine (Gorelick & Balster, 2000). The small percentage of users has continued to decrease. In 2004 and 2008, roughly 0.5% of high school students in the United States reported using PCP within the past 30 days (Johnston et al., 2005; Substance Abuse and Mental Health Services Administration (2010). In the United Kingdom and Canada, the trend has been fairly stable at low percentages over the last few years.

Ketamine was little used until it entered the club scene in the 1980s when its popularity expanded. Its use, however, appears to have leveled off. Ketamine use among high school students in the United States has shown little change since 2000 with about 2% of grade 12 students reporting use within the past 12 months (Johnston et al., 2005).

Harmful Effects

PCP and ketamine have an unfounded reputation for causing violence and uncontrollable behavior. An examination of the literature on the drug has not found any systematic evidence that these drugs specifically cause violent or criminal behavior. It is true, however, that the psychotic state induced by large doses of dissociative anesthetics causes disorientation, agitation, and hyperactivity, and that these effects have the potential for injury to the individual and others nearby. However, PCP and ketamine do not seem to turn normal, innocent people into dangerous and violent criminals (Brecher, Wang, Wong, & Morgan, 1988; Gorelick & Balster, 2000). Laboratory research even suggests that PCP may have a taming effect on normally aggressive animals (Balster, 1987).

As with many other drugs of abuse, it appears that chronic ketamine use is associated with long-term neurological changes. In a recent study of chronic ketamine users, researchers observed a significant reduction in gray matter volume in the left superior frontal gyrus and the right middle frontal gyrus (Liao et al., 2011). Reduction in gray matter volume was correlated with the duration of use for both of the affected brain regions.

Long-lasting psychotic behavior has been reported after PCP use, even in individuals without any psychotic tendencies. This PCP psychosis may last several months in some individuals and is indistinguishable from schizophrenia as it includes both positive and negative symptoms.

Acute behavioral effects of PCP and ketamine can sometimes be responsible for injury and death. For example, because the drugs are anesthetics, rather severe injuries have been tolerated or self-inflicted without pain or any effort at avoidance. Although the exact frequency of this sort of event has not been documented, it is probably more likely to happen with PCP than with LSD and the other serotonin-like and norepinephrine-like hallucinogens.

GENETIC DAMAGE AND REPRODUCTION. PCP has been shown to slow the growth of the fetus, precipitate labor, and cause fetal distress. Children born to mothers who use PCP often show muscle stiffness, tremor, irritability, and impaired attention and behavior control that may last for several years, although it is difficult to be sure that these effects are due specifically to PCP since other maternal drug use is common (Gorelick & Balster, 2000). Also, usage of PCP and ketamine has been linked to widespread cell death in the developing rat brain. Blockage of NMDA receptors by PCP or ketamine for even a few hours during prenatal development appears to induce significant neurodegeneration (Ikonomidou et al., 1999).

Lethal Effects

A lethal dose of the ketamine is 25 times the effective dose for intranasal administration (Gable, 2004). Although toxic effects may vary, high doses cause coma, convulsions,

and respiratory arrest. Brain hemorrhage and kidney failure have also been reported. The lethal effects of PCP and ketamine are potentiated by the presence of depressant drugs, such as alcohol or barbiturates, in the body.

DEXTROMETHORPHAN

Dextromethorphan is a synthetic *antitussive* (cough-suppressant) drug, which is structurally similar to opioids. Many years ago, it was considered safe after research showed that it did not have as serious an abuse potential as opioids. However, more recently there have been numerous reports of people consuming large quantities of over-the-counter cough medicines such as Robitussin for their psychological effects, a practice sometimes called *roboing* (Darboe, Keenan, & Richards, 1996). This trend has led to more in-depth examination of dextromethorphan's behavioral pharmacology as well as *dextrorphan*, a metabolite of dextromethorphan.

Neurophysiology

Dextromethorphan and dextrorphan have been shown to be low-affinity NMDA receptor agonists, similar to PCP and ketamine. When bound, they act as ion channel blockers in a manner similar to alcohol and the dissociative anesthetics (see Chapter 4) and therefore have similar pharmacological properties. Dextrorphan has a greater affinity for the NMDA receptor than dextromethorphan and consequently has a much greater PCP-like effect. Dextromethorphan also affects the functioning of *sigma* receptors, a poorly understood class of receptors once believed to be a type of opioid receptor but later deemed to have no structural similarity to opioid receptors. Dextromethorphan is a Sigma-1 and Sigma-2 receptor agonist, though it appears to bind with higher affinity to the Sigma-1 receptor, which is found predominantly in the central nervous system (Weissman, Su, P., Hedreen, & London, 1988). Sigma-1 receptor activation has been linked with cough-suppression in guinea pigs (Brown, Fezoui, Selig, Schwartz, & Ellis, 2004), which may contribute to the antitussive effect of dextromethorphan. Interestingly, dextromethorphan has been used to decrease morphine-induced reward in rats through Sigma-1 receptor activity in the ventral tegmental area. These findings suggest that low doses of dextromethorphan could be used in the treatment of opioid addiction (Chen, Hsu, Huang, Lu, & Tao, 2011).

Pharmacokinetics

In most cases, dextromethorphan is converted rapidly to dextrorphan during first-pass metabolism through the liver. Because the effects of dextrorphan are greater than dextromethorphan, the most intense effects of consuming dextromethorphan may be delayed until this transformation occurs. Since first-pass metabolism is greatest after oral administration, oral consumption may be the most effective route of administration.

Population studies have shown that there is considerable individual variation in the ability to metabolize dextromethorphan to dextrorphan. Some individuals are rapid metabolizers and should be able to experience the effects of dextrorphan rapidly, but others are slow metabolizers, so the metabolite will not reach high levels, and the effects will be diminished. The cytochrome P450 enzyme plays a crucial role in the metabolism of dextromethorphan, and slow metabolizers tend to have low levels of this enzyme, specifically of the CYP2D6 variant. About 5 to 10% of Caucasians and 4% of African Americans are poor metabolizers (He, Daniel, Hajiloo, & Shockley, 1999). Such differences in metabolism can cause considerable individual variation in the effects of taking dextromethorphan.

Discriminative Stimulus Properties

Rats trained to discriminate dextromethorphan will generalize fully to PCP, though at a higher dose. Generalization is dose- and training-specific, and this has led researchers to believe that dextromethorphan and dextrorphan are not identical to PCP and other full NMDA receptor blockers (Holtzman, 1994).

Self-Administration

It appears that both rats and rhesus monkeys will readily self-administer both dextromethorphan and dextrorphan (Nicholson, Hayes, & Balster, 1999).

Behavioral Effects

NONHUMANS. The effects of dextromethorphan and dextrorphan have been investigated in rats. Dextromethorphan caused a decrease in locomotor activity, whereas dextrorphan caused an increase along with stereotyped behavior at higher doses. Some memory and learning impairment was seen with dextromethorphan

but not with dextrorphan. The two drugs appear to have different behavioral effects with dextromethorphan closely mimicking sedatives and dextrorphan resembling PCP and ketamine (Morgan, Porritt, & Poling, 2006).

HUMANS. Dextromethorphan has been used as a cough suppressant for over 30 years. At normal therapeutic doses it has few side effects and no PCP-like effects. However, selective serotonin reuptake inhibitors and monoamine oxidase inhibitors seem to increase the likelihood of unpleasant side effects (Ziaee et al., 2005). At higher doses, its effects are similar to PCP and ketamine; these include ataxia, dizziness, euphoria, tactile and visual hallucinations, altered time perception, and increased perceptual awareness.

GHB

GHB (gamma-hydroxybutyrate) occurs naturally in the body as a metabolite of gamma-aminobutyric acid (GABA) and acts as a neurotransmitter or neuromodulator (Castelli, 2008). When administered as a drug, it is rapidly absorbed, easily crosses the blood–brain barrier, and, in increasing doses, produces anxiolysis (anxiety reduction), sedation, and anesthesia (Castelli, 2008). The sodium salt of GHB, *sodium oxybate*, is sold under the trade name *Xyrem* as a treatment for narcolepsy. GHB has also been marketed in Italy as *Alcover*, a treatment for alcoholism. When sold on the street, it has many names, including *liquid X*, *GBH* (*grievous bodily harm*), *scoop*, *cherry meth*, *blue nitro*, *easy lay*, and more than 30 others (O'Connell, Kaye, & Plosay, 2000).

Initially, GHB was widely used in Europe as a medicine and in the United States as a dietary supplement. It received little attention from public health officials until the early 1990s, when its use became more widespread as a growth promoter among bodybuilders, as a sedative, and as a recreational drug used alongside ecstasy and ketamine as a club drug. GHB has also been identified as a date rape drug. In 1990, the U.S. Food and Drug Administration declared GHB unsafe and banned it from public sale.

The legal status of GHB remains unclear. In 2000, the U.S. attorney general was voted authority by the U.S. Congress to make GHB a Schedule I drug; that is, it has abuse potential but no medical use. However, when sold as Xyrem, GHB is classed as Schedule III drug. This is similar to the classification of Marinol, a preparation containing THC that has medical use (see Chapter 14). This ambiguity has not yet been resolved. In the United Kingdom, GHB was made a Class C drug (thought to have the least capacity for harm) as of 2003.

Pharmacokinetics and Dose

GHB and its precursor, *GBL*, are considered to be pharmacologically equivalent, except that GBL is more readily absorbed. When taken orally, GHB produces effects within 15 to 30 minutes and peak effects are reached between 25 and 45 minutes. It has a half-life of 30 to 50 minutes. Endogenous GHB is taken into cells via an active reuptake mechanism from the synaptic cleft, where it is rapidly metabolized. A minimum dose is about 10 mg/kg body weight and will produce muscle relaxation. A therapeutic dose for sleep is in the range of 15 to 30 mg/kg, and a high dose of 60 mg/kg will cause unarousable sleep or coma lasting for 1 to 5 hours. A lethal dose may be anywhere between 300 and 900 mg/kg. This gives it a therapeutic index of between 20 and 60.

In a recent review of 226 GHB-associated deaths, 94% were due to cardiorespiratory arrests and 65% involved coadministration of another drug (Zvosec, Smith, Porrata, Strobl, & Dyer, 2011).

Neuropharmacology

GHB binds to at least two receptor types in the CNS: the GHB receptor and, at high concentrations (higher than those that occur naturally in the body), the $GABA_B$ receptor. However, the GHB binding site on the $GABA_B$ receptor is distinct from that of GABA itself (Castelli, 2008; Wu et al., 2004). GABA does not bind to the GHB binding site on the $GABA_B$ receptor complex. The GHB receptor is part of a complex that has its effect by releasing a second messenger inside the membrane. Even though there are high levels of endogenous GHB outside the CNS, all GHB receptors appear to be inside the CNS. The highest densities of GHB receptors are found in the hippocampus and regions of the cortex, whereas the highest concentrations of GHB molecules are found in the substantia nigra and hypothalamus (Castelli, 2008). GHB also appears to have a modulatory effect on GABA levels, in some cases decreasing GABA, and, because it is also a GABA precursor, it can also increase GABA levels.

GHB acts both presynaptically and postsynaptically to modulate activity of other neurotransmitters. Its main effect seems to be on dopamine synapses, where it inhibits dopamine release and causes the accumulation of excess dopamine in the presynaptic neuron. It has also been reported that after a period of inhibition or at higher doses, there is a surge in dopamine activity.

Effects on Behavior

NONHUMANS. There are significant differences between GHB and the other drugs discussed in this chapter. GHB has sedative properties and, at high doses, acts as an anesthetic. The anesthetic state it induces appears to be more similar to a cataleptic state than anesthesia; brainwaves show seizure-like activity that can be blocked with anticonvulsant drugs. The nonresponsive state achieved at high levels of GHB is more similar to a petit mal seizure than anesthesia. At higher doses, jerks and seizure-like activity can be seen.

Cognitive deficits after prolonged GHB use have been observed in nonhumans that are distinct from amnesia during and after drug use. Deficits in spatial learning and memory were observed in adolescent rats that were thought to be due to a decrease in NMDA receptor expression after chronic administration (Sircar, Wu, Reddy, Sircar, & Basak, 2011).

HUMANS. Users report that GHB causes alcohol-like intoxication without a hangover. They report increased feelings of relaxation and euphoria. GHB is sometimes used in conjunction with alcohol and various club drugs like ketamine and ecstasy to enhance their effects. It is also reputed to be an aphrodisiac, increasing libido and enhancing sexual pleasure; however, such effects may be due to a reduction in sexual inhibition rather than a true aphrodisiac quality.

Amnesia for events both during and after drug use has also been reported (Miotto et al., 2001). At higher doses, before passing out, people show many of the signs of alcohol intoxication, they appear confused, speech is incoherent, and they have poor balance and coordination. Driving ability is clearly impaired (Couper & Logan, 2001).

EFFECTS ON SLEEP. Unlike the barbiturates and benzodiazepines (or almost any other drug, for that matter), GHB normalizes sleep patterns and increases stages 3 and 4 and REM sleep. This effect is the basis for its development as a treatment for narcolepsy. In narcolepsy, normal sleep does not occur at night, so the narcoleptic falls into uncontrollable sleep during the day. The benzodiazepine and barbiturate hypnotics alter normal nighttime sleep patterns and are consequently not useful, but GHB appears to be an effective treatment.

ANXIOLYTIC PROPERTIES. There is conflicting evidence in the literature that GHB has anxiolytic effects. Drugs that increase punished behavior are often subject to abuse. A recent study showed that GHB increases punished responding to an extent comparable to pentobarbital, suggesting that it does indeed have antianxiety effects that might contribute to its abuse liability (Frawly & McMillan, 2008).

Drug State Discrimination

Animals trained to discriminate GHB from saline only partially generalize to morphine, LSD, and chlordiazepoxide; generalize even less to amphetamine and ethanol; and do not generalize at all to barbital and PCP-like compounds, indicating a unique subjective effect.

Any generalization to other drugs seems to be highly dose specific. At high training doses of GHB, animals will generalize to drugs that are $GABA_B$ agonists, suggesting that this effect is probably responsible for its subjective effect, but at low doses, the subjective effect appears to be mediated by its activity at its own receptor. Similarly, alcohol-trained rats generalize only to GHB at a very narrow range of intermediate doses.

Self-Administration

GHB will create a place preference in rats, but this learning requires more trials than with cocaine. In nonhuman primates, GHB has been shown to have abuse potential, but a history of self-administration may be important (Goodwin, Kaminski, Griffiths, Ator, & Weerts, 2011). On the other hand, there is evidence that GHB will reduce the self-administration of alcohol in both rats and humans, with humans reporting a reduction in craving for alcohol. This may be a result of the dopamine-blocking effect of GHB, but this effect needs further study.

Human Epidemiology

While there are little data available on the extent of GHB use, a 2002 survey of 16- to 23-year olds revealed that the prevalence of overall lifetime use is approximately 0.05%

(Wu, Schlenger, & Galvin, 2006). The Drug Abuse Warning Network is a system that tracks drug use by the number of times it is mentioned in cases seen in hospital emergency rooms in the United States and Canada. In 1992, there were 20 mentions of GHB, but in 1998 it was mentioned on nearly 1,300 occasions. This cannot be taken as an indication of how often the drug is used, but it does suggest a drastic increase in use. Prevalence of GHB use among high school students in the United States does not appear to have changed much since legislation was introduced in 2000 to make it a Schedule I drug.

Tolerance and Withdrawal

Tolerance develops to the motor-impairing effects of GHB in rats following high doses for 9 days. These rats were cross-tolerant with alcohol on the same effect. Tolerance has also been demonstrated to the sedating and anesthetic effects of GHB.

In humans, continual GHB use several times a day can lead to tolerance and dependence, after which a sudden reduction in use can lead to withdrawal symptoms including anxiety, tremor, agitation, delirium, and hallucinations (van Noorden, Kamal, de Jong, Vergouwen, & Zitman, 2010).

GHB will alleviate alcohol withdrawal symptoms in humans and nonhumans and has been used therapeutically in Italy to treat alcohol withdrawal and dependence. GHB is also effective in reducing withdrawal effects from opiates.

MEPHEDRONE

Mephedrone, or *4-methylephedrone*, is a synthetic stimulant and empathogenic drug that belongs to the ampethamine and cathinonine classes. Mephedrone is a relatively new drug and did not gain popularity until 2007 when it began to be sold and distributed online. The intended effects of mephedrone are similar to those of khat, MDMA, cocaine, and amphetamines as it creates a feeling of euphoria, increased energy, confidence, elevated mood, and decreased hostility. Users can swallow, snort, smoke, or inject the drug. Although the exact neurological method of action is not known, it appears that mephedrone interacts with dopamine and serotonin transporters and blocks the reuptake of these neurotransmitters (Martínez-Clemente, Escubedo, Pubill, & Camarasa, 2011).

Similar to other drugs in its class, mephedrone is most popular among young adults (18 to 25 years), especially those involved in the club scene. In a survey by a British clubbing magazine, *Mixmag*, mephedrone was the fourth most popular drug among the over 2,200 readers who were surveyed. Possible reasons for the rapid increase in popularity include the convenience of online purchase and a decrease in purity and availability of drugs with similar intended effects. Because of its popularity among young clubbers, it is likely to be used alongside alcohol and other stimulant drugs.

Harmful Effects

The toxicology of mephedrone has not been fully established. As of January 2011, the LD_{50} of mephedrone was not known. Because of the lack of scientific testing and short history of use, the long-term effects are also not known. Les King, former drug advisor to the British government, has said, "All we can say is [mephedrone] is probably as harmful as ecstasy and amphetamines. . ." (reported by Reed, 2010). An analysis of patients admitted to the ER for medical reasons related to self-reported mephedone use revealed that 53.3% of patients experienced anxiety, 40% tachycardia, and 20% seizures (Wood, Greene, & Dargan, 2011).

Legal Status

Since 2008, many countries have passed legislation making the sale, possession, and manufacture of mephedrone illegal. As of December 2010, the European Union made the drug illegal across Europe. In Australia and New Zealand, it is controlled indirectly as it is treated as an analog of other controlled substances. Drugs controlled in this fashion are substantially similar to, and thereby treated as if, they are in fact another illegal substance intended for sale, possession, or manufacture for human consumption. Until recently, similar means of enforcement existed in the United States; however, many individuals exploited this loophole and legally sold mephedrone as plant food or bath salts. The U.S. Drug Enforcement Administration (DEA) declared an emergency scheduling authority as of September 2011 that will make mephedrone and two other synthetic substances (MDPV and methylone) illegal for a minimum of 1 year. During this time, the DEA will perform further studies to determine if mephedrone should be made permanently illegal, and if so, how it should be scheduled.