The Pharmacology of Hallucinogens

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CHAPTER 14

CHAPTER OUTLINE

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DEFINITION

Hallucinogens are chemically divergent substances primarily used for their potential to profoundly alter the processing of cognitive, perceptual, and emotional understanding of self and reality (1). Hallucinogenic substances derived from plant materials have been ritualistically employed for millennia in religious and shamanic contexts (2). More recently, hallucinogenic drugs are being studied for psychotherapeutic uses.

"Hallucinogen" is the most widely accepted term for describing these mind-altering chemicals. It was first introduced in the French psychiatric literature in the early 1930s (3) and, by the 1950s, referred to mescaline, LSD, and adrenochrome (4). The term is not ideal because it overemphasizes perceptual changes at the expense of the often more significant changes in thought, cognition, affectivity, and body experience. Sensory changes are not the most characteristic effects produced by these compounds, as other classes of drugs also produce hallucinations, for example, stimulants. Hallucinations can be defined as "non–object-bound sensory phenomena" (5) that may include simple and complex visual and auditory hallucinations in the classical sense, misperceptions, misidentifications, illusions, paresthesias, synesthesias, and enhanced mental imagery. Most hallucinogens produce visual alterations of perceived objects and pseudohallucinations, which are understood by the subject as not based in reality. The term "psychedelic" (i.e., mind manifesting) was coined by the psychiatrist Humphry Osmond to characterize substances capable of liberating perception from cultural conditioning, providing an opening to the transcendent qualities of being human and enabling humans to better understand themselves and their relationships with the world.

Because the effects of these substances are quite dependent on the environment/setting, their effects vary significantly under controlled or therapeutic circumstances versus under unsupervised conditions.

SUBSTANCES INCLUDED

A number of substances have been categorized as hallucinogens or hallucinogen-like: (a) the classical hallucinogens (e.g., mescaline, psilocybin, lysergic acid diethylamide or LSD, dimethyltryptamine or DMT); (b) the entactogenic phenylalkylamines (e.g., methylenedioxyamphetamine [MDA], MDMA, methylenedioxyethylamphetamine, [MDE]), termed "entactogens" because they have distinctive emotional and social effects; (c) the anticholinergic dissociatives (atropine, hyoscyamine, scopolamine); and (d) the dissociative anesthetics/miscellaneous (phencyclidine or PCP, ketamine, salvinorin A). Table 14-1 presents a partial list of these compounds.

Table 14-1

Classical hallucinogens possess an arylalkylamine skeleton of the indolealkylamine or phenylalkylamine type. Agents from this class do not necessarily produce identical effects. However, all bind at 5-HT_2 serotonin receptors, and where known, all are 5-HT_{2a} receptor agonists or partial agonists. Indolealkylamines include LSD, psilocybin, and DMT. Hallucinogenic phenylalkylamines include mescaline; 4-bromo-2,5-dimethoxyphenethylamine (2-CB); the less-studied trimethoxyamphetamine; 2,5-dimethoxy-4-bromoamphetamine; and 2,5-dimethoxy-4-n-propylthiophenethylamine (2-CT-7). Salvinorin A, derived from the plant *S. divinorum*, has clear-cut hallucinogenic effects, but an unknown mechanism of action. It became a widely used hallucinogenic drug during the last decade (6).

A somewhat separate and newer group of substances that are often included in the category of hallucinogens are the so-called entactogens like MDMA and MDE. These usually do not induce major alteration in sensory perceptions, although they may be considered hallucinogenic in terms of significant alterations/expansions of conscious awareness

TABLE 14-1 MAJOR HALLUCINOGENS (PARTIAL LIST)

CLASS	CHEMICAL NAME	COMMON OR STREET NAME	SOURCE	DOSAGE	ROUTE	DURATION OF ACTION	MAJOR NEUROBIOLOGIC TARGET	NOTES
Indolealkylamines	LSD	LSD, acid, blotter	Synthetic	50–200 μg	PO	8–14 h	5-HT_{2a} partial agonist	Distributed on small squares of blotting paper, drops of liquid, gel caps, small pills
	Psilocybin	Magic mushrooms, shrooms	*Psilocybe cubensis*, *Psilocybe azurescens*, and many other subspecies; synthesis	10–50 mg, 1–5-g dried mushroom; quite variable	PO	4–8 h	5-HT_{2a} partial agonist	Psilocybin is converted in the body to psilocin, the actual active hallucinogen. Continued shamanic use in Mexico. Bruising of mushroom turns blue.
	DMT	DMT, yopo, cohoba, "businessman's trip"	*Psychotria viridis*, *Anadenanthera peregrina*, *Mimosa hostilis*, and many other natural sources; synthesis	5–40 mg	Smoked, inhaled snuff	30–60 min	5-HT_{2a} partial agonist	Continued Amazonian shamanic use
	Ibogaine	Ibogaine	*Tabernanthe iboga*	200–300 mg	PO	12+ h	Likely 5-HT_{2a} partial agonist	Religious sacrament; long-acting metabolites may contribute to purported antiopioid withdrawal benefits.
Phenylalkylamines	3,4,5-Trimethoxyphenylethylamine	Mescaline, peyote, San Pedro	*Lophophora williamsii*, *Echinopsis panachoi*, other cacti; synthesis	200–500 mg, 10–20 g or 5–10 dried peyote buttons, 1-kg fresh *E. pachanoi*	PO	6–12 h	5-HT_{2a} partial agonist	Religious sacrament
Entactogenic phenylalkylamines	3,4-Methylenedioxymethamphetamine	MDMA, ecstasy, X, XTC, rolls, molly	Synthesis	80–150 mg	PO	4–6 h	5-HT release and depletion	Mildly hallucinogenic at high doses
	3,4-Methylenedioxyamphetamine	MDA, love drug, Adam	Synthesis	75–160 mg	PO	4–8 h	5-HT release and depletion	
	4-Bromo-2,5-dimethoxyphenethylamine	2C-B, nexus	Synthesis	5–30 mg	PO	4–8 h	Unknown	
Other	Salvinorin A	Salvia, sally D, diviner's sage	*Salvia divinorum*	250–750 mg (smoked), 2–10 g dried leaves (PO)	Smoked, PO	30–60 min (smoked), 1–3 h (PO)	Kappa opioid selective agonist	Atypical hallucinogen; no longer found in the wild

of self and others. The term "entactogen" was coined by the medicinal chemist David Nichols (7) for these substances, which have neurobiologic and subjective effects distinct from the classical hallucinogens. Entactogen refers to drugs that "produce a touching within," derived from the roots "en" (Greek, within), "tactus" (Latin, *touch*), and "gen" (Greek, *produce*) to describe effects of decreased anxiety and increased trust, self-acceptance, and openness (7).

This chapter deals mainly with the most clinically relevant hallucinogenic substances like LSD, psilocybin, DMT, mescaline, MDMA, and salvinorin A.

METHODS OF USE AND ABUSE

No other recreational drug class (such as alcohol, opiates, and cannabis) enjoys a philosophical underpinning in Western society as does LSD. LSD has been touted as having a purpose other than simply to get intoxicated. For its users, the psychedelic experience is about enhancing and expanding perception, offering a new way to see the world as it really is. "[My] heightened awareness saw through the static, one-dimensional, ego-constricted, false front which is the consciousness-contracted reality of the everyday world. This was no evasive flight from, but a deep probe into reality" (8). LSD appears to provide a numinous experience unmediated by a religious hierarchy or sacred texts. Those primarily attracted to LSD were creative individuals who sought out novelty, change, and insight into the human condition (9).

Since the mid-1960s, hallucinogens have been recreational drugs popularly consumed on a broad scale, with all the possible complications that can result from inappropriate use (10). The 1990s witnessed a cautious resurgence of academic research with "mind-manifesting" (i.e., psychedelic) substances, especially toward the neurobiologic and clinical effects of psilocybin, ketamine, DMT, and the entactogens (11).

Hallucinogenic substances influence information flow throughout the brain, thereby inducing an altered state of mind that affects conceptual cognition, affectivity, and sensory processing. Some of these actions might induce a specific matrix of brain alterations that could be beneficial for neuropsychiatric disorders. The notion that some of these substances have significant potential as medical and psychological treatments has emerged over the last decade. Their specific value may lie in the short-term rearrangement of brain activity, rather than in tonic long-term action as from antidepressants, psychostimulants, and neuroleptics. In successful cases, these substances do not primarily compensate for or suppress symptoms but rather precipitate forms of healing in a more direct and causal manner (e.g., MDMA-assisted therapy for posttraumatic stress disorder [PTSD]) (12,13). Nevertheless, these complex effects are very sensitive to extrapharmacologic variables and remain experimental.

Clinical Uses

More than 10,000 subjects received LSD (and other hallucinogens) from 1950 to the mid-1960s in controlled research settings, resulting in several thousand research papers (14). During this time, the most prevalent substances were called "psychedelic drugs," used for enhancing creativity (15,16), deschematizing perceptual processes (17), inducting "experimental psychoses" (18), education of psychiatric staff through temporary self-experience of quasipsychotic states (19,20), and experimental exploration of religious and mystical experiences (21,22). Another important application was psycholytic therapy, where lower dosages (of LSD or psilocybin) were used to induce a dream-like state with affective and sensory activation to access unconscious material for therapeutic processing in psychoanalytic settings. The American concept of psychedelic therapy used the induction of mystical experiences by high doses for transformation of personality traits (23,24). These therapeutic approaches were later abandoned, not for reasons of safety (25,26) or lack of efficacy but because of criminalization of the substances.

Currently, there is renewed interest in psilocybin and LSD as experimental tools for elucidating neural mechanisms of consciousness (27,28), for the treatment of cluster headache (29), and in psychotherapy with the terminally ill (30,31). Beyond a few experimental applications, no clinical use of DMT, mescaline, or salvinorin A has been documented in the scientific literature. Recent studies of the psychotherapeutic utility of MDMA report significant clinical improvement in double-blind, placebo-controlled trials of MDMA-assisted psychotherapy for patients with PTSD (12,13).

Nonmedical Use, Abuse, and Dependence

Nonmedical use and abuse of hallucinogens in Western culture started in the mid-1960s and was initially linked to the social turmoil of the 1960s student movement ("hippies"). Since that time, hallucinogens became readily accessible to Western populations. In these typically less-structured/"permissive" settings, use of these compounds often resulted in careless experimentation. Especially because of user inexperience with these drugs, a mass wave of complications resulted, which then established their new image as dangerous drugs (32,33). These complications resulted not rarely in indirect medical (e.g., physical accidents) and/or psychological emergencies (e.g., brief psychotic reactions and suicidality), causing emergency department visits (10,34). The overall rates of abuse and dependence are considered low compared to other substances (35) with relative risk of dependence apparently greater in users with very early age of onset of hallucinogen use (10 to 11 years) (36).

Discussing hallucinogen abuse with patients requires an understanding of the rewarding properties of these drugs, as well as their potential risks. It is ineffective to offer only a one-sided discussion about psychiatric comorbidity without expressing awareness of what the users value within their experiences, whether rooted in spiritual–religious or "recreational" pursuits.

Hallucinogen use disorder as listed in the *DSM-V* (formerly dependence in the *DSM-IV*) and ICD-10 is characterized by (mild, moderate, or severe) patterns of compulsive

and repeated drug use despite the knowledge of significant harm caused by the activity. Mild hallucinogen use disorder is equivalent to the DSM-IV criteria for hallucinogen abuse. Hallucinogen use very rarely leads to the development of typical dependence syndromes, such as seen with opiates or alcohol. As a class, the hallucinogens lack significant direct effect on the dopamine-mediated reward system; animals cannot be trained to self-administer these compounds (37). In contrast to users of other substances of abuse, hallucinogen users do not experience withdrawal symptoms, and therefore, this trait is not a criterion for diagnosing hallucinogen dependence. In general, tolerance rapidly increases when hallucinogens are used with frequency, exponentially so with daily use.

The diagnosis of hallucinogen use disorder should be considered when patients report using hallucinogens despite evidence and knowledge of harm as a result of this use. Polydrug use is common in clinical settings, so the differential diagnosis often includes other substance use or substance-induced disorders. Schizophrenia, bipolar, and schizoaffective disorder should also be ruled out in these patients (38).

HISTORICAL FEATURES

Psychoactive substances derived from plant materials have been used ritualistically for millennia. Hallucinogens were primarily used for religious and shamanic purposes. Evidence suggests that Soma of the 3,500-year-old Hindu-Aryan Rig Veda and the Kykeon of ancient Greece's Eleusinian Mysteries may have been botanical hallucinogens (39). Hallucinogens play a prominent role in the cultures of Mesoamerican people. Psilocybin-containing mushrooms were originally employed as shamanic sacraments by some Native tribes of Mexico. Indeed, ayahuasca remains an important spiritual medicine of many Native people of the Amazon Basin. The peyote cactus (*L. williamsii*), containing the hallucinogen mescaline, has been venerated for over 3,000 years by the Huichol and Tarahumara ethnic groups of northern Mexico and is the sacrament of the Native American Church (NAC) in the United States and Canada, the largest faith among Native people of North America with some 300,000 adherents (40). Native use was not clearly protected in the United States until the American Indian Religious Freedom Act Amendments of 1994 (39). Many native people of Latin America have used DMT for spiritual purposes for hundreds of years through to the present. It is prepared as a powdered snuff from the seeds of *Anadenanthera peregrina* and the bark of *Virola sp.* trees and as "ayahuasca," a DMT-containing plant concoction, which is orally active. Salvinorin A is a diterpene alkaloid and is found in the mint *S. divinorum*, a plant initially only cultivated in Oaxaca, Mexico, where it has been used for spiritual and divinatory purposes (39).

LSD was synthesized in 1938, and its psychoactive effects were accidentally discovered in 1943. It was used during the 1950s and 1960s as an experimental drug in psychiatric research for producing the so-called experimental psychosis and in psychotherapeutic procedures ("psycholytic" and "psychedelic therapy"). After the discovery of its intense psychoactive effects in miniscule amounts, it became a force of intense interest in psychiatric research and stimulated the discovery of the neurotransmitter systems and their functions in the brain (14). From the mid-1960s onward, it became an illegal drug of abuse.

3,4-Methylenedioxymethamphetamine (MDMA or "Ecstasy"/"Molly") was first synthesized in 1912. It was tested by the military in a search for "truth drugs" in the 1950s. During the mid-1960s, the American chemist Alexander Shulgin synthesized MDMA in search for a psychotherapeutic drug but did not realize the full spectrum of its psychoactive effects. After he discovered its unique effects in 1977, he distributed it in psychotherapeutic circles (41). By the early 1980s, MDMA use rapidly expanded in popularity, and MDMA was listed in 1986 as a Schedule I drug on an international level, but the appropriate committee of the WHO recommended research into the "therapeutic potential of this interesting substance" (42).

EPIDEMIOLOGY

The 2010 National Survey on Drug Use and Health (NSDUH) estimated that almost 37.5 million Americans (14.8%) over age 12 ingested a hallucinogen at least once in their lifetime (43). The NSDUH estimates of the number of users in 2009 combined with the 2009 data from the National Estimates of Drug-Related Emergency Department Visits from the Drug Abuse Warning Network (DAWN) (44) show how rarely emergency medical attention is sought as a percentage of active users for hallucinogens compared to other illicit substances. Excluding data on the dissociative "hallucinogen" PCP, less than 1% of hallucinogen users had an emergency department visit related to their hallucinogen use in 2009 (compared with 5.5% of methamphetamine users, 8.8% of cocaine users, and 35.2% of heroin users) (35).

LSD is still the most widely used hallucinogenic drug; 23.3 million Americans used LSD at least once in their lifetime (35). Since the 1970s, there is no decline in its use, especially in the United States and central Europe (45). A renewed interest in the substance was registered at the end of the 1990s in the United States and central Europe (46). *Psilocybe* mushrooms appear to be the most common hallucinogen consumed in the previous year among new hallucinogen users (35). Mescaline has never been synthesized and distributed for illicit purposes in the United States on a significant scale, and it is not mentioned in any drug abuse survey. The mescaline-containing peyote cactus plant use is protected by the American Indian Religious Freedom Act of 1994 and is almost solely consumed in religious ceremonies of the NAC. DMT was never a significant drug of abuse. Since the 1960s, it was used only in tiny circles, and no significant abuse was reported up to today (35). *S. divinorum* is still legal in much of the United States. Today, an estimated

1.8 million people in the United States had tried this plant (35). The 2011 Monitoring the Future Survey reported an increasing trend with an annual prevalence of Salvia use in young adults at 2.5% (47).

Among young adults (15 to 34 years), lifetime prevalence estimates of LSD use in Europe range from 0.1% to 5.4%. In the few countries providing such data, lifetime prevalence estimates for hallucinogenic mushrooms among young adults range from 0.3% to 8.1% (48).

Some 15.9 million Americans have tried MDMA at least once in their life with 2.6 million trying it for the first time in 2010 (43). About 11.5 million Europeans have tried MDMA, and about 2 million have used it during the last year. Its use is concentrated among young adults in the age range of 15 to 25 years. Most countries report 2.1% to 5.8% lifetime prevalence of among the 15 to 34 age group range (48).

Hallucinogens in general show a more or less constant pattern of use and abuse, with MDMA showing a peak in the 1990 and a stable level since 2000 (35,48).

PHARMACOKINETICS AND PHARMACODYNAMICS

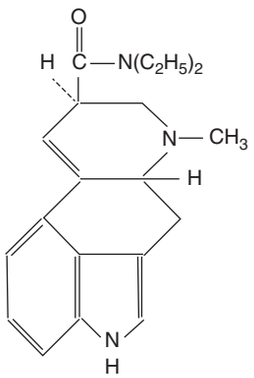
Lysergic Acid Diethylamide

LSD is a semisynthetic substance derived from lysergic acid as found in the parasitic rye fungus *C. purpurea*. LSD was synthesized in 1938, and its psychoactive effects were discovered in 1943. The molecule consists of an indole with a tetracyclic ring ($C_{20}H_{25}ON_3$) (Fig. 14-1).

LSD was used during the 1950s and 1960s as an experimental drug in psychiatric research and in psychotherapeutic procedures ("psycholytic" and "psychedelic" therapy). Pharmacologic research on LSD was extensive and produced nearly 10,000 scientific papers (14). Currently, there is renewed interest in LSD in the treatment of cluster headache and in psychotherapy with the terminally ill (31).

LSD is still the most widely illicitly used hallucinogenic drug based on total numbers of lifetime users (49). Though no physical damage results from its use, many psychiatric complications have been reported (10,45). Extent of use has remained essentially constant since the 1970s. The number of complications has declined presumably because of better-informed users and a reduction in the per unit dosage (now more commonly 50 to 100 μg).

In both its somatic and psychological effects, LSD is representative of most other hallucinogenic drugs. The pharmacology of LSD is complex, and its mechanisms of action are still not completely understood (37,50).



LSD-25

FIGURE 14-1 Ring structure of LSD-25.

Pharmacokinetics

Following oral administration, LSD is completely absorbed in the digestive tract (51,52). The threshold oral dose in humans is 0.5 to1.0 μg/kg (53). After 100 to 250 μg LSD, psychological and sympathomimetic effects reach their peak after 1.5 to 2.5 hours at a plasma level of 6 to 7 ng/mL (54). Over the next 8 hours, plasma levels gradually fall until only a small amount of LSD is present (55). The half-life of LSD in humans is 175 minutes (55,56). The distribution of LSD across tissue and organ systems is yet to be quantified for humans. In cats, parenterally administered LSD at 1 mg/kg yields highest concentrations in the gallbladder and plasma (57,58). The presence of considerable amounts in the brain and cerebrospinal fluid (CSF) of rats and cats indicates that LSD may easily cross the blood–brain barrier (57). Two studies evaluating a two-compartment model found that the correlation of the neuropsychological effects of LSD and tissue concentrations could be linear, logarithmic–linear, or neither (59,60).

Pharmacodynamics

LSD-induced sympathetic stimulation is evidenced by pupillary dilation and slight increases in heart rate (+5 to 15/bpm) and blood pressure (10 to 15 mm Hg systolic) (61,62); other more inconsistent signs are slight blood sugar elevation (63,64) and, rarely, a minimal increase in body temperature. There is a broad variation in somatic reactions to LSD; increased parasympathetic tone with bradycardia and hypotension may occur in some cases (61,65). Slightly increased perspiration may occur. Respiration remains unchanged. Initial nausea, decreased appetite, temporary mild headache, dizziness, and inner trembling may occur in some subjects. The most consistent neurologic effect is an exaggeration of the patellar (and other deep tendon) reflexes. More unusual signs include slight unsteadiness of gait and ataxia (66). No evidence was found for changes in liver and renal functions, blood cells, and electrolytes (50,67,68). LSD increases serum growth hormone but does not alter serum prolactin levels (60).

Tolerance to autonomic and psychological effects of LSD occurs in humans after a few moderate daily doses (66,69,70). Reduction in receptor density is a possible mechanism for the development of tolerance to LSD (71).

There have been no documented human deaths from an LSD overdose due to toxicity (14). The lethal dose of LSD in humans is estimated to be 1,400 mg (72).

Subjective Effects

A moderate oral dose (75 to 150 μg) of LSD will significantly alter the state of consciousness, including stimulation of affect, enhanced capacity for introspection, and altered psychological functioning in the direction of hypnagogia and dreams (73). Typical perceptual changes include illusions, pseudohallucinations, and synesthesias, as well as alterations of thinking and time experience (Table 14-2). Changes of body image and ego function also often occur (74,75). Religious and mystical experiences may occur and can be produced reliably under controlled conditions (20–22).

While under the influence of LSD, performance decreases on tests of attention and concentration, recognition, and recall of various stimuli (76–78). Thinking processes can be affected at higher doses (>100 μg) of LSD (66,79). Time intervals are regularly overestimated (80). Studies of intellectual functioning under LSD have been interpreted as showing regression of intellectual functioning to an ontogenetically earlier state of development (i.e., 12 to 14 years of age) (81,82). There is no evidence for long-lasting impairments in performance after LSD intake (83).

The acute psychological effects of LSD last between 6 and 10 hours, depending on the dose (Fig. 14-2). Traumatic experiences (called "bad trips") can have long-lasting effects, including mood swings and, more rarely, flashback phenomena (10,84). Conversely, it has been shown that under controlled and supportive conditions, the hallucinogen experience may have lasting positive effects on attitude and personality in healthy humans (85,86).

TABLE 14-2 HALLUCINOGEN[a] INTOXICATION MAY INCLUDE A CLUSTER OF THE FOLLOWING

PHYSICAL EFFECTS[b]	PSYCHOLOGICAL EFFECTS
Typical (mild to very mild):	**Typical:**
Tachycardia	Intensification and lability of affect with euphoria, anxiety, depression, and/or cathartic expressions
Palpitation	Dream-like state
Slight hypertension or hypotension	Sensory activation with illusion, pseudohallucination,[c] hallucination, and/or synesthesia
Diaphoresis	Altered experience of time and space
Slight hyperthermia	Altered body image
Motor incoordination	Increased suggestibility
Tremor	Lassitude/indifference/detachment
Hyperreflexia	Acute cognitive alterations with loosening of association, inability for goal-directed thinking, and memory disturbance
Altered neuroendocrine functioning	**"Positive":**
Typical (mild to strong):	Sense of perceiving deeper layers of the world, oneself, and others ("consciousness expansion")
Mydriasis	Mystical experience
Arousal	Sense of profound discovery/healing
Insomnia	**"Negative":**
Occasional:	Psychosomatic complaint
Nausea	Impaired judgment
Vomiting	Derealization
Diarrhea	Depersonalization
Blurred vision	Megalomania
Nystagmus	Impulsivity
Piloerection	Odd behavior
Salivation	Paranoid ideation
	Suicidal ideation

[a]Indolealkylamine and phenylalkylamine hallucinogens only.
[b]Some effects are reactionary to psychological content (e.g., increased heart rate and nausea due to anxiety), and complaints can be dependent on factors such as mindset, setting, dose, and supervision. Intoxicated individuals may also desny physical impairment and/or claim increased energy, sharpened mental acuity, and improved sensory perception.
[c]A subject experiencing "pseudohallucinations" retains the capacity to recognize that these "novel" experiences are transient and drug induced, as opposed to true hallucinations in which no such discernment is possible.

Psilocybin

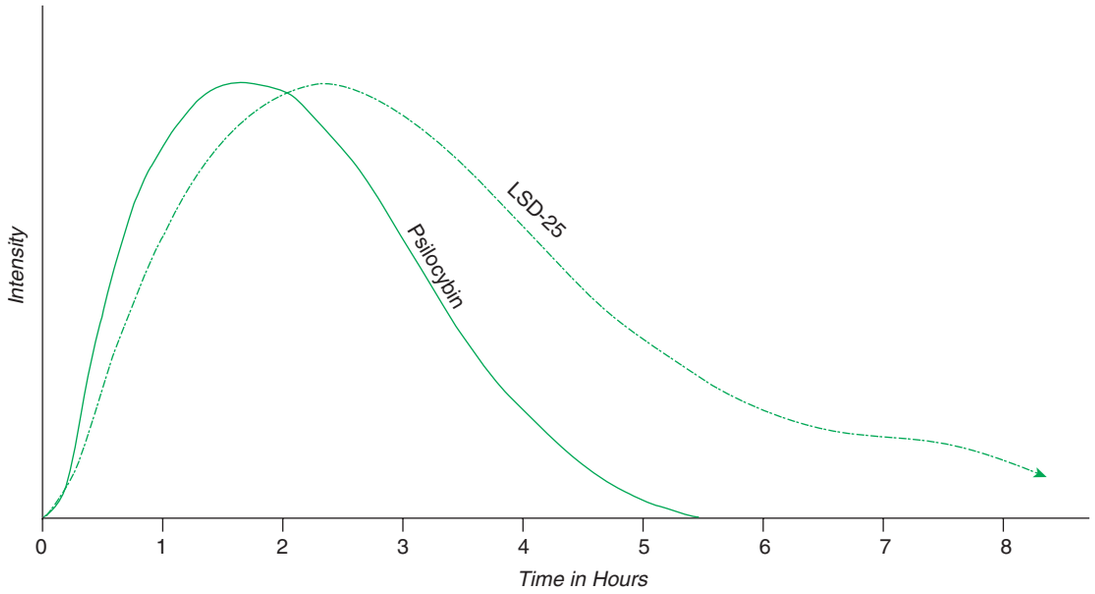
Total content of psilocybin varies with mushroom, subspecies, and preparation, but the most commonly used mushroom, *P. cubensis*, contains 5 to 11 mg psilocybin per gram of dried mushroom (87).

Pharmacokinetics

Psilocybin (4-phosphoryloxy-N,N-DMT) and its active metabolite psilocin (4-hydroxy-N,N-DMT) are substituted hallucinogenic indolealkylamines. Because its metabolite psilocin is the psychoactive molecule, psilocybin is better referred to as a prodrug.

Psilocybin is readily absorbed following oral administration and is widely distributed throughout the body (88,89). Holzmann (90) and Hasler (91) identified four metabolites of psilocybin, including psilocin.

Psilocybin and psilocin are detectable in plasma within 20 to 40 minutes following ingestion. Psychological effects occur with plasma levels of 4 to 6 μg/mL (90,91). The full effects occur within 70 to 90 minutes following oral doses of 8 to 25 mg. A significant first-pass effect can be assumed (91). After a rapid increase of psilocybin plasma levels, a plateau follows for about 50 minutes, after which there is a relatively slow decline, ending at about 360 minutes. The half-life of psilocybin is 163.3 ± 63.5 minutes (92). The mean elimination half-life of psilocin is 50 minutes. (90). Maximum plasma concentration occurs at approximately 80 minutes, although there is substantial individual variation in the time course of plasma concentration, which is not due to variability in conversion of psilocybin to psilocin (91). The elimination of the glucuronidated metabolites as well as unaltered psilocybin (3% to 10%) occurs through the



Q10

FIGURE 14-2 Clinical course of psychological effects with medium-range doses of the hallucinogens LSD and psilocybin. (Modified from Leuner H. Halluzinogene. Bern: Huber Publishers, 1981.)

kidneys. Approximately two-thirds of the renal excretion of psilocin is completed after 3 hours (91). Peak intoxication occurs approximately within the first 2 hours, diminishing over the subsequent 3 to 4 hours (see Fig. 14-2).

Even though significant tolerance is known to occur with repeated use of psilocybin, neither physical dependence nor a withdrawal syndrome develops (69,92). There is no direct death from psilocybin reported in the scientific literature.

Complications arising from use of psilocybin (e.g., severe panic reactions or "bad trips") resulting in emergency department visits occur with less frequency than with most other hallucinogens (93), possibly due to its short duration of action. Affected individuals may find the intoxication resolving before arriving at a hospital.

Pharmacodynamics

Neurovegetative effects within the usual dose range (10 to 25 mg orally) include mydriasis, slight acceleration in heart and breathing rate, and discrete hyperglycemic and hypertonic effects (88,94). Nausea and sleepiness can occur in the initial phase of intoxication. Electrolyte levels and liver enzyme activity are unaffected (95–97), as are endocrine cortisol, prolactin, and growth hormone levels (98). There is no evidence of mutagenic or teratogenic effects (88). Ingestion of *Psilocybe* mushrooms can cause nausea and vomiting, but serious toxicity has not been reported in humans. The predicted human lethal dose of psilocybin is 14,000 mg (72), which is equivalent to 4 kg of dried mushrooms, an amount unlikely to be consumed.

Subjective Effects in Humans

The psychopathologic phenomena induced by psilocybin are virtually identical to those of LSD (see above). At a moderate dose (12 to 20 mg orally), psilocybin produced an altered state of consciousness marked by stimulation of affect, enhanced ability for introspection, and altering of psychological functioning (28). Especially noteworthy are perceptual changes such as illusions, synesthesias, affective activation, and alterations of thought, time sense, and body experience.

Psilocybin selectively increased errors in the interference condition of the Stroop test. Neuropsychological findings suggest disrupting effects of psilocybin on both automatic and conscious response inhibition mediated by prefrontal functioning and impairment of attention, temporal estimation and reproduction, sensorimotor synchronization, tapping tempo, and reaction times (99–101).

Most psilocybin users display an erratic pattern of use. The intense consciousness-altering/consciousness-expanding (i.e., psychologically irritating) effects of psilocybin appear to limit frequency of its use. Daily consumption of psilocybin results in acute tolerance, and such users are virtually unknown in the scientific literature (102).

Dimethyltryptamine (DMT)

DMT is derived from various plant sources and animal venoms. DMT is also produced endogenously in humans in miniscule amounts (103). Despite much conjecture (104,105), its physiologic functions are still unknown, although it was recently found to be an endogenous sigma-1 receptor agonist (106).

Pharmacokinetics

DMT is quickly absorbed and distributed throughout the body and the brain (107,108). The assimilation of DMT into neurons is by active transport through the membranes (109). Maximal plasma levels of DMT are reached 2 minutes after IV administration and 107.5 minutes after oral intake of ayahuasca (110).

DMT is metabolized mainly by oxidative deamination and *N*-oxidation, catalyzed by monoamine oxidase. The main metabolites are indole acetic acid, dimethyltryptamine–nitrous oxide (DMT-NO), *N*-methyltryptamine indole acetic acid, and 5-hydroxy-indole acetic acid (111,112).

DMT and its metabolites are eliminated very quickly through the kidneys. After 30 to 70 minutes, no unchanged DMT is excreted in human urine, but 90% of its metabolites indole acetic acid and 5-hydroxy-indole acetic acid are excreted (113).

In contrast to other classical hallucinogens like LSD, psilocybin, or mescaline, DMT does not induce tolerance in humans (114).

Pharmacodynamics

After smoking (alone or on a substrate of tobacco, parsley, or marijuana) or via the intravenous route, initial effects occur in 30 to 60 seconds, peaking within 2 to 3 minutes, then clearing over the next 15 to 20 minutes (115,116). When ingested orally as the ayahuasca brew, effects commence after 30 to 60 minutes, peak within the first hour, and last for 3 to 4 hours (110). Ayahuasca is typically associated with a considerable amount of nausea and vomiting (117), which may alter its absorption.

High doses or overdoses of DMT may lead to seizure. Nausea and vomiting is common. Vegetative symptoms are predominant at IV doses of 0.05 to 0.1 mg/kg, whereas hallucinatory effects predominate at doses of 0.2 to 0.4 mg/kg (118). DMT significantly increases blood pressure (+15 to 30 mm Hg) and heart rate (+10 bpm), often combined with an oppressed feeling in the chest (115,119) and a sympathomimetic excitation syndrome with mydriasis, hallucinations, and overarousal. These effects are significantly less (BP +8 to 15 mm Hg, no change of heart rate) when DMT is ingested as ayahuasca (117,120). Respiration rate increases only slightly with oral intake (110). A slight rise in body temperature (+0.1 °C) was reported only with intravenous administration (115). Deep tendon reflexes are more active in two-thirds of subjects (119). Some subjects develop slight involuntary extrapyramidal movements (119,121). DMT increases secretion of prolactin, growth hormone, ACTH, and cortisol (110,115), as well as corticotropin and β-endorphin (115). There are no lethal intoxications documented in the literature (122,123). The LD50 dose in mice is 135 mg/kg IM (124).

Subjective Effects in Humans

Typical signs of DMT intoxication include dysphoria or euphoria, subjective impression of breathing difficulties, and sensory disturbances resulting in impaired performance in multiple domains including engaging in behaviors that are not based in response to true perceptions of reality. The psychological effects of DMT, especially when they appear very rapidly, as with smoking or intranasal insufflation, can be very frightening and may lead to severe unintended injuries because of disorientation, motor incoordination, and unrealistic thoughts and behaviors. Typical are dysphoria or euphoria and the subjective impression of breathing difficulties. Complications are very rare, especially by the oral route, and also may not appear in clinical settings because of the very short duration of action of DMT. The psychological effects of DMT are milder with orally ingested ayahuasca (than with the pure drug) and are very similar to those of LSD and psilocybin (see Table 14-2).

Virtually no studies examined DMT's effect on performance. Some disturbances in automatic and conscious mechanisms of information processing and attention have been observed (125).

Mescaline

The principal hallucinogenic compound of the peyote cactus, *L. williamsii*, is mescaline (β-3,4,5-trimethoxyphenethylamine), although over 60 other alkaloids are also found in peyote (126). Although mescaline is regularly mentioned as a "classical hallucinogen" in the scientific literature, its use as a recreational drug is rather limited (127,128). There have been virtually no seizures from significant amounts of synthetic mescaline in the United States, and it is almost never mentioned in statistics of emergency department visits (44). There are no serious physical complications or dependency syndromes from peyote or mescaline documented in the scientific literature (129). Evaluation of neurocognitive competence and psychological health of members of the NAC has shown them to perform as well as (and in some domains of mental health, better than) nonusing, healthy comparators (130).

Pharmacokinetics

Peyote contains at most 1.5% mescaline sulfate. The cactus has a bitter, acrid taste, often inducing nausea and vomiting. The usual human dosage is 200 to 400 mg of mescaline sulfate or 175 to 350 mg of mescaline hydrochloride (131). The average 76-mm (3.0-inch) button contains about 25 mg mescaline (126).

Mescaline taken orally is absorbed rapidly and completely in the gastrointestinal tract. Onset of effects is typically 30 to 45 minutes. Maximum concentration in brain builds up in 30 to 120 minutes (132). Peak intoxication occurs within 2 to 4 hours, wearing off over the subsequent 4 to 6 hours. Plasma level correlates with intensity of psychological effects (133).

Mescaline easily crosses the blood–brain barrier; up to 50% can be detected in the CSF but only miniscule amounts of its metabolites. Mescaline levels in CSF correlate with behavioral manifestations of the drug (132).

Plasma levels of metabolites peak after 3 hours and then decline to virtually zero after 12 hours. 81.9% is eliminated unaltered in the urine 24 hours after oral ingestion and 26.2% as the phenylacetic acid derivative (132). About half the dosage is excreted after 6 hours. Between 20% and 50% of mescaline is excreted in the urine unchanged, the rest being excreted as the carboxylic acid, a likely result of MAO degradation (134). Four metabolites have been identified in human urine: mescaline 55% to 60%;

3,4,5-trimethoxyphenylacetic acid 27% to 30%; *N*-acetyl-beta-(3,4,dimethoxy-5-hydroxyphenyl) ethylamine 5%; and *N*-acetylmescaline less than 0.1%. Five other metabolites have been partially characterized (132).

Complete tolerance develops gradually within a few days and builds with repeated usage, lasting for a few days (135).

No fatal intoxication from mescaline has been documented in the literature. The lethal human dose of mescaline is estimated to be 6,000 mg (72).

Pharmacodynamics

There is little high-quality physiologic research on mescaline (136). Somatic effects from mescaline intoxication include mydriasis, dizziness, diarrhea, nausea and vomiting, headache, dilated pupils, abdominal cramps, sweating, warm and cold sensations, and tremors and feelings of weakness. Gastrointestinal effects may be dependent on route of administration. No nausea, vomiting, abdominal cramps, headache, or feelings of weakness occur when the total mescaline dose is taken in several small increments (131). Increased blood pressure and heart rate were reported (137). Somatic effects are strongest in the first 1 to 2 hours, then subside, and replaced by the dream-like hallucinogenic state that lasts 5 to 12 hours, depending on the dose.

Secretion of prolactin and growth hormone occurs for a few hours, with peak increases at 90 to 120 minutes (138).

No serious somatic side effects or lethality has been reported from mescaline. There is no evidence of lasting cognitive or psychophysical effects with mescaline (130,139).

Subjective Effects in Humans

The typical mescaline intoxication is characterized by a dream-like state with enhanced alertness and affectivity; euphoric or dysphoric mood states; sensory–perceptual distortion; alterations of space and time sense; altered perception of color, sound, and shapes; complex hallucination; synesthesia; deconstructed perception; depersonalization; and ecstatic or mystical states of mind. Prominence of color is distinctive, appearing brilliant and intense. Recurring visual patterns observed during the mescaline experience include stripes, checkerboards, angular spikes, multicolored dots, and very simple fractals, which turn very complex (140). Aldous Huxley described these self-transforming amorphous shapes as like animated stained glass illuminated from light coming through the eyelids. Distortions of form and kaleidoscopic experiences apparently manifest more clearly with eyes closed and under low lighting conditions. "It apparently has a rather stronger hallucinatory and a somewhat weaker depersonalizing effect than the more potent LSD…" (141).

There is little research on neuropsychological performance under the influence of mescaline. Alberts (142) and Guttmann (143) demonstrated deficiencies in simple arithmetic performance, weight and time estimation, concentration, and language and memory performance. Disturbances of movement perception and space–time perception also occur.

Salvia Divinorum and Salvinorin A

Salvinorin A is a neoclerodane diterpene alkaloid. It is structurally unrelated to any other hallucinogen and is found in the mint plant *S. divinorum*.

Pharmacokinetics

No explicit pharmacokinetic evaluations of *S. divinorum* have been completed (144).

S. divinorum is most commonly inhaled by smoking the dried leaves or more concentrated leaf extracts. Other routes of administration include inhalation via volatilization or buccal absorption of tinctures (145).

If taken orally, leaves or extracts containing salvinorin A have a mild effect, often compared to cannabis (146). Salvinorin A is only minimally absorbed through the mouth (147); most is degraded in the gastrointestinal tract.

Pharmacodynamics

Salvinorin exerts its potent psychotropic actions through agonist action on the kappa opioid receptor (148,149). There is no evidence that it works on other receptor systems (150), but the endocannabinoid system may play a role in its effects (151).

If taken orally, leaves or extracts containing salvinorin A have a mild effect, often compared to cannabis (146). When smoked, its effects can be much more pronounced, depending on the dose. The psychological effects consist of mood changes and strange hallucinations that appear within seconds and may last from 30 minutes to more than 2 hours, depending on dose (152). When smoked in higher concentrations, salvinorin A produces a rapid and intense hallucinatory effect that typically lasts between 10 and 15 minutes and includes a "highly modified perception of external reality" (152). A recent double-blind study with smoked salvinorin A in healthy volunteers demonstrated peak drug effects after 2 minutes, which lasted for about 10 to 20 minutes, with a "coming down" phase of another 20 minutes (153).

Salvinorin A does not significantly increase heart rate or blood pressure. No serious physiologic symptoms occur with moderate to high doses (153,154). Users become less aware of their surroundings as dose increases, which may generate disorientation, incoordination, and potentially unrealistic self-destructive behavior. Loss of consciousness is common with higher doses. Typical recreational doses of salvinorin A increase plasma cortisol and prolactin (154). No obvious harmful physical effects were observed in clinical studies. Unpleasant aftereffects include tiredness, heaviness of head, dizziness, and "mental cloudiness" lasting 24 hours or more after use (155).

There are no reported cases of severe *S. divinorum* toxicity or deaths from overdose of salvinorin A (144,156). A key danger to the user's psychophysical integrity can be ego disintegration and anxiety reactions. These are limited by the brief duration of effects. Users seeking treatment sometimes report gastrointestinal and/or cardiovascular complaints (6).

There is little evidence of *S. divinorum* causing psychiatric dysfunction beyond acute effects (157). There are no reports of a withdrawal syndrome from salvinorin A. It appears to lower dopamine in the CNS (158). There is no evidence that salvinorin A leads to addictive behavior (159).

Subjective Effects in Humans

The most commonly reported desirable psychological effects of *S. divinorum* include laughter, happiness, separation from body, relaxation, and perceptual changes (157,160). There is a mild hallucinogenic effect, comparable to cannabis, from lower dosages of salvinorin A and a more dissociative pattern of effects from higher doses, with serious hallucinatory effects and loosening contact with reality. The latter consists of mood changes and hallucinations that appear suddenly within seconds and may last from 30 minutes to an hour or more, depending on dose (152). Some users describe experiencing themselves "as paint on the wall" and in other strange ways not reported with other hallucinogens. There is no significant euphoria (154), whereas dysphoria often occurs, which may partially explain its typical erratic use pattern. Hallucinogenic effects were comparable to those produced by intravenous DMT (115,155). Salvinorin A's very drastic consciousness-altering effects can't be compared easily to the "classic hallucinogens" like DMT or psilocybin because the perceptual world of the user is much more strangely altered than with virtually any other drug (152). Some researchers have described its central effect as "dissociation" often involving anxiety (152). Larger doses are typically aversive, and few people want to repeat the experience. The strange perceptual altering effects and lack of euphoria may also explain its pattern of intermittent use.

MDMA ("Ecstasy")

MDMA (3,4-methylenedioxymethamphetamine) was first synthesized by the German pharmaceutical company Merck in 1912. It was tested by the military in a search for "truth drugs" in 1953 (161). The American chemist Alexander Shulgin synthesized MDMA in search for a psychotherapeutic drug and discovered its unique effects in the late 1970s, when he started distributing it in psychotherapeutic circles. (41,162). MDMA was listed in 1986 as a Schedule I drug in the United States and slightly later in most other countries of the world. Soon afterward, it became a major drug of abuse, with a peak in the mid-1990s and a considerable mass of users to the present.

MDMA is not a classical hallucinogen but belongs to the "entactogens," a group of substances with a different profile of action than the classical hallucinogens such as LSD, psilocybin, and mescaline. Compared to the classical hallucinogens psilocybin, MDMA produces only minimal sensory effects (e.g., pseudohallucinations) but consistently increases feelings of elation. MDMA also has some amphetamine-like stimulant effects mediated through release or reuptake inhibition of dopamine and noradrenaline (7).

Pharmacokinetics

Maximum plasma levels after a typical oral dose of MDMA (1.6 mg/kg) are reached 1.5 to 2.5 hours after ingestion. Plasma levels decrease slowly over the following 10 hours. Excretion is more than 95% completed after 24 hours (163). A typical recreational dose (125 mg) has a half-life of 8.73 ± 2.27 hours (164).

The major enzymes involved in the metabolism of MDMA are the liver cytochrome P450 complex (CYP450, CYP2D6) and catechol-*O*-methyltransferase. There are slow metabolizers of MDMA (i.e., with low activity of CYP2D6), but the clinical significance of this is still a matter of debate. CYP2D6 is apparently easily saturated, reducing the likelihood that this is a source of individual variability in sensitivity to MDMA. The slow CYP2D6 metabolizer genotype is not considered a significant risk factor for acute MDMA toxicity (165,166). Complex, nonlinear pharmacokinetics result from inhibition of CYP2D6 and CYP2D8 by MDMA (167) and, in turn, results in higher than expected concentrations if the user takes consecutive doses (168).

Seven percent of ingested MDMA is metabolized into the psychoactive metabolite MDA. At typical recreational doses of MDMA, MDA does not usually reach concentrations associated with noticeable effects. All other metabolites are inactive, including 4-hydroxy-3-methoxymethamphetamine; 4-hydroxy-3-methoxyamphetamine; 3,4-dihydroxyamphetamine; and *N*-hydroxy-3,4-methylenedioxyamphetamine (169). MDMA and its metabolites are excreted as conjugated glucuronides and sulfates through the kidneys, but more than 50% of MDMA is excreted unchanged in urine (170).

Pharmacodynamics

The first effects of MDMA are usually experienced within 30 minutes after an oral dose of 85 to 150 mg. The majority of individuals claim peak effects between one-half to 1 hour after intake. Gender-specific sensitivity to MDMA's effects has been reported, with stronger effects in females (171). Stimulant effects occur soon after ingestion, including increased energy and elevated mood. Additional side effects include nausea, jaw clenching, muscle tension, and blurred vision. A "hangover" for some hours or even 1 to 2 days can occur, with symptoms of insomnia, fatigue, sore muscles, headache, and decreased mood.

Somatic effects of MDMA (100 to 125 mg orally) include loss of appetite, diaphoresis, and bruxism (172–174). Dose-dependent increased blood pressure from MDMA is between 20 to 35 mm Hg systolic and 10 to 20 mm Hg diastolic (167,175). MDMA increases heart rate around 10 to 20 bpm and body temperature by 0.3°C to 0.4°C (167,175). MDMA has significant dose-dependent effects on the endocrine system, with increases in cortisol, prolactin, vasopressin, and growth hormone (164,176,177). MDMA acutely affects immunologic function, with reduced CD4 T-cell count, increased NK cell count, and decreased lymphocyte proliferation. It also decreases the proinflammatory cytokine interleukin 2 (IL-2) and increases levels

of the anti-inflammatory cytokine interleukin 10 (IL-10) (178,179). The lethal oral dose of MDMA in humans is calculated to be 1,875 mg. (72).

Stimulant effects, as noted above, occur soon after ingestion, including increased energy and elevated mood. Additional side effects include nausea, jaw clenching, muscle tension, and blurred vision. A "hangover" for some hours or even 1 to 2 days can occur, with symptoms of insomnia, fatigue, sore muscles, headache, and decreased mood.

Intense pleasure and increased physical stamina are sought by dance party ("rave") consumers of MDMA. They like the euphoric and body-stimulating effects, which, combined with loud drumbeat-driven dance music, may result in ecstatic feelings. Side effects reported from such dance events are overexertion and elevated body temperature. As dehydration, hyperthermia, and tachycardia continue, individuals can collapse from a potentially life-threatening fever, cardiac arrhythmia, and extreme exhaustion. Fever may eventually lead to rhabdomyolysis and kidney failure (180). Use of methamphetamine and cocaine in combination with MDMA increases the risk of serotonin syndrome (181).

Subjective Effects in Humans

Liester et al. (182) interviewed 20 American psychiatrists who had experimentally ingested MDMA (100 to 200 mg). Most of the participants were prepared for MDMA intake and ingested it under quiet and discreet conditions. The results are summarized in Table 14-3.

In a questionnaire survey of 500 White American college students aged 18 to 25 years who claimed to have taken MDMA at least once, 97% described experiencing euphoria (183). The typical MDMA-induced state has been compared to the postorgasmic state (184).

TABLE 14-3 SUBJECTIVE EFFECTS OF MDMA (PERCENTAGE OF SUBJECTS WITH YES ANSWERS)

Altered perception of time	90%
Increased ability to interact with or be open with others	85%
Decreased defensiveness	80%
Decreased anxiety	65%
Decreased sense of separation or alienation from others	60%
Changes in visual perception	55%
Increased awareness of emotions	50%
Decreased aggression	50%
Aware of previously unconscious memories	40%
Decreased compulsiveness	40%
Decreased restlessness	30%
Decreased impulsivity	25%
Decreased anxious feelings	15%

Based on a study by Liester et al. (182)

Typical psychological reactions to MDMA in healthy, MDMA-naïve adult research volunteers include improved disposition, increased physical well-being associated with vague symptoms of derealization and depersonalization, impaired thinking, and occasional feelings of anxiety with no increase in psychomotor drive. The affective changes were, on the whole, positively received. Subjects described a greater attention to feelings, a higher degree of openness, and increased sense of closeness to others.

When medium range doses of MDMA (100 to 150 mg) are administered to healthy volunteers in a medically supervised setting, no health risks or significant complications have been reported (12,164,167,175,185). MDMA ingested recreationally may pose special risks to users (186). Heightened empathy and impulsivity may increase vulnerability to abuse. MDMA use may induce paranoid psychotic states, anxiety, and/or depression. In some affected individuals, symptoms may persist for days or weeks. The attribution of these effects to MDMA is subject to bias because of the concomitant use of other drugs, preexisting psychiatric symptoms, or a pertinent family history of psychiatric disease. Depressive symptoms in former MDMA users are usually mild and clinically insignificant.

When compared to the typical hallucinogens, the acute effect of MDMA (in medium range doses) on neuropsychological performance is minimal, as assessed with a variety of neuropsychological and psychomotor tests (187–190). In more complex and attention-demanding psychomotor tasks, such as car driving, acute MDMA (in typical recreational doses of 100 to 150 mg) decreased driving performance in some respects (191). Less automated aspects of driving behavior are only minimally impaired (192), perhaps due to conscious effort to compensate. In a naturalistic driving scenario, MDMA acutely decreased the subjective sense for risk taking (193).

Toxicity and Adverse Effects

Physical side effects of the clinically known indolealkylamines or phenylalkylamines are insignificant and do not lead to serious dysfunction of organ systems or brain damage (1,14,194–196). Their physiologic effects are usually very mild and limited to the acute phase of intoxication. Higher doses of pure smoked or injected DMT may be an exception. Hallucinogens induce no lasting damage or neurophysiologic alterations but can cause seizure and accidents from incoordination (195).

Adverse effects with the classical hallucinogens result mainly from "bad trips," that is, severe anxiety or paranoid reactions, or perceptual distortions delusions and hallucinatory effects. Accidents may happen because of distorted reality, especially with higher doses and potent substances like salvinorin A (10).

The only clinically significant long-term aftereffects, occurring in a minority of users (estimated 1% to 10%), are

the so-called flashbacks, that is, the reexperiencing of some fragments of the original hallucinogen experience (197). This may happen when a traumatic experience with a hallucinogen occurred previously. Several factors may contribute to experiencing a flashback, such as intoxication with cannabis or alcohol, being in the same circumstances, hearing the same music. Very few cases are documented of clinically significant and verified episodes of persisting flashbacks (84,198).

There is no evidence of lasting effects on neurocognitive functioning (14,28,83,199) or teratogenic effects of hallucinogens in man. Mutagenic effects of LSD were suggested by some early in vitro studies, but this has not been confirmed (200).

The situation is different with entactogens such as MDMA. High-dose regimens in animals suggested neurotoxicity, although the data are inconsistent, especially in humans (199,201,202). In overdose or in combination with other drugs and alcohol or with a very frequent dosage regimen, MDMA may cause lasting complications. Some chronic users report attenuation of drug effects, lack of attention, a feeling of depression, increased extroversion, reduced appetite, insomnia, and increased self-awareness (203).

Destructive effects of entactogens on the serotonergic system have been shown in animal studies, usually with very high doses (204). Chronic users of MDMA in combination with other psychoactive substances (e.g., alcohol, cannabis, cocaine, amphetamines) show decreased serotonin transporter density in the brain (205). Other indications of serotonergic neuron impairment depend on the cumulative doses (206). In contrast, people with lifetime use of 50 to 100 doses of MDMA and even heavier users exhibit no alteration in diverse neurometabolic and neuropsychological measures (199,207). Slight difficulties with memory processing have been reported in MDMA polydrug users (201).

Drug–Drug Interactions

Most prescribed medications do not significantly interact with the classical hallucinogens (14). Psychopharmacologic agents like tricyclic antidepressants and lithium may increase responses to LSD, while selective serotonin reuptake inhibitors (SSRIs) and MAO inhibitors decrease the subjective LSD response (50,208). Chronic tricyclic antidepressant administration was associated with subjective increases in physical, hallucinatory, and psychological responses to LSD.

There are few studies about MDMA complications from interactions with prescribed medications (209). MDMA and related compounds attenuate the effects of SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) (210,211). Serious complications from combinations of MDMA with antiretroviral agents are also reported (212).

Coingestion of other stimulants (e.g., amphetamines, modafinil, caffeine) may worsen side effects of MDMA and classical hallucinogens (213). LSD potentiates the effects of MDMA (214). The most common substances coused with MDMA are alcohol, cannabis, and stimulants (amphetamines and cocaine) (215,216). Stimulants are also neurotoxic to both serotonergic and dopaminergic neurons. Hence, they may act synergistically with MDMA and enhance its long-term adverse effects (213). Alcohol can prolong euphoric effects of MDMA (217) and attenuate MDMA-induced hyperthermia but does not alter cardiovascular effects (218). Cannabis is one of the drugs most commonly taken with MDMA. (216). Chronic coadministration of MDMA and cannabis may alter functioning of the immune system (219) and the endocrine system (220), but some of the effects reported for the combination of both drugs are similar to those of cannabis alone. Regular use of MDMA and methamphetamine has been reported to cause long-term neurologic changes. Their combined use reduces striatal dopamine transporters more than MDMA alone (221).

Virtually nothing is known about the interaction of salvinorin A with other pharmacologic agents (144).

NEUROBIOLOGY

Mechanisms of Action

Hallucinogens exert an activating effect on parts of the CNS due to their agonist properties at serotonergic, adrenergic, and dopaminergic neurotransmitter-modulated brain systems. The serotonergic system appears to be especially affected (37).

The classical hallucinogens (like LSD, psilocybin, DMT, and mescaline) have high affinity for 5-HT receptors (222,223). Radioligand-binding studies show that phenylalkylamine hallucinogens are highly selective for 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors, but not for 5-HT_1 receptors (224,225), which implies that their behavioral effects are likely exclusively 5-HT_2 mediated. Indolealkylamine hallucinogens are relatively nonselective for 5-HT receptors, displaying moderate to high affinity for 5-HT_1 and 5-HT_2 subtypes (225–227). They generally produce effects similar to their phenylalkylamine counterparts, but there is evidence that the psychopharmacologic profiles of these compounds are more complex (228).

The 5-HT_{2A} receptor appears to be the primary site of action, with significant modulation by other serotonergic sites including 5-HT_{2C} and 5-HT_{1A} receptors. Genetic or pharmacologic inactivation of 5-HT_{2A} receptors blocks behavioral effects in preclinical models, as well as subjective effects in humans (175,229). Further evidence for 5-HT_{2A} mediation comes from studies of tolerance. Daily administration of LSD and other hallucinogens selectively decreased 5-HT_2 receptor density in rat brain by down-regulation (230,231).

5-HT_{2A} receptors are most abundant in layer V pyramidal neurons (232). González-Maeso et al. (233) hypothesize that hallucinogenic 5-HT_{2A} agonists may interfere with normal gating functions of layer V cortex and may lead to dysfunction and altered cognition and sensory processing of this "output" cortex layer (234).

Hallucinogens enhance glutamatergic transmission in the cortex (235,236). The heaviest density of mGlu2/3 receptor

binding is found in the mPFC layers I and Va with a laminar distribution similar to 5-HT_{2A} receptors (237). Activation of 5-HT_{2A} leads to increased cortical glutamate levels (235,236) probably mediated by thalamic afferents (37), which may alter corticocortical and corticosubcortical transmissions. There is growing consensus that the glutamatergic and serotonergic systems interact in complex ways and regulate each other (238,239). This is supported by the observation that the stimulus effects of DOM and LSD in rats can be potentiated by ketamine (235,240). Glutamate release triggered by 2-HT_{2A} receptor activation may represent a final common pathway for the actions both of serotonergic and glutamatergic hallucinogens (241,242). The 5-HT_{1A} receptor might provide a link for this final common pathway (243).

5-HT_{2A} and 5-HT_{2C} receptors are very similar in terms of structure and function. Most hallucinogens are partial agonists at the 5-HT_{2C} receptor (244,245). Their stimulus effects are mediated by agonist activity at 5-HT_{2A} receptors and can be modulated by agonist activity at 5-HT_{2C} receptors (229). Activity at the 5-HT_{2C} receptor serves to attenuate many behavioral effects of hallucinogens (228).

Many indolealkylamine hallucinogens bind with higher affinity at other 5-HT receptors (e.g., 5-HT_{1A}, 5-HT_{1D}, 5-H_{T6}) than they do at 5-HT_{2A} receptors (37). Therefore, the activation of the 5-HT_{2A} receptor may be a necessary but not sufficient pharmacologic event. Some hallucinogens also interact with dopamine receptors and directly or indirectly activate dopamine pathways. Few studies have evaluated the dopaminergic effects of hallucinogens. There is evidence that LSD interacts with central dopamine D1 and D2 receptors (246), and some interactions of psilocybin with the dopamine system are shown in a dopamine-specific PET study in humans (247). However, most hallucinogens do not significantly interact with the dopamine system (228).

What are the functional implications of these receptor-mediated effects on brain activity? Aghajanian et al. (248) found a reduction in the firing rate in the dorsal raphe nucleus after LSD, DMT, or psilocin (249,250). This encouraged the hypothesis that ascending brainstem systems (e.g., serotonergic projections arising from the raphe) modulate neural activity in thalamocortical circuits in a nonspecific or global manner to trigger hallucinogenic activity. The 5-HT_{1A} receptor mediates this effect in the dorsal raphe nucleus. Indolealkylamine hallucinogens usually have a high affinity for the 5-HT_{1A} receptor (226,251), but phenylalkylamine hallucinogen, such as mescaline, has no relevant affinity for this receptor (252).

Alteration of thalamic function may play a central role in the changes to the CNS caused by hallucinogens. 5-HT_{2A} receptors are widely expressed in different regions of the thalamus (253,254). The thalamus, along with the amygdala, represents the major source of glutamate afferents innervating the neocortex. The reticular nucleus serves as a kind of gate for processing signals to the cortex (255,256) and other thalamic nuclei according to the demands of sensory input and attentional processing (257,258). 5-HT_{2A} receptor activation in the reticular thalamic nucleus as induced by hallucinogens might increase the level of inhibitory input to relay cells, which leads to a loss of sensory-specific inhibition of thalamic nuclei. This results in relay cells recruited into thalamocortical circuits without receiving adequate sensory input and the formation of coherent assemblies of thalamocortical oscillations that would be independent of afferent sensory inputs, that is, hallucinatory activity (258,259).

Future research could further clarify hallucinogenesis by better accounting for the compound effects in the CNS by hallucinogens as well as how hallucinogens potentially interfere with receptor conformational stabilization or induction effects on sites as implicated by previous research (228). Functional selectivity of hallucinogens for second- and third-messenger systems in agonist-specific signaling inside the cells may also become more important for explanatory models.

Entactogens

Amphetamines (including those that are entactogens) are potent dopamine-releasing agents (260). However, the psychoactive effects of entactogens are at most only minimally mediated via the dopaminergic system (7). It is possible that the blocking of norepinephrine reuptake contributes to entactogenesis because all entactogens exert this effect, albeit some insignificantly (261). The prevailing theory is that the psychoactive effects of entactogens are mediated by potent synaptic release as well as reuptake blockade of the neurotransmitter serotonin that, in turn, results in increased intrasynaptic serotonin (173,261). A comprehensive study found significantly distinct patterns of brain activation for the entactogen MDE, the amphetamine methamphetamine, and the classical hallucinogen psilocybin (98,262).

Alteration of Hemispheric Lateralization

Early experiments show a reversal of laterality induced by hallucinogens (263). More recent neuroimaging studies demonstrated an increase in metabolic activity and cerebral blood flow in the right hemisphere with mescaline (137), psilocybin (262,264), and DMT (265). Mandell (266) proposed a model to understand ecstatic and mystical experiences under the influence of hallucinogenic drugs as an "interhemispheric fusion" through the abolishment of oscillatory control of the brainstem–cortex axis induced by the activation of inhibitory serotonin receptors, which leads to a uniform activation of both hemispheres. Experiments with hallucinogens using the paradigm of binocular rivalry have been interpreted as supporting this model (267).

Functional Imaging Studies

LSD had no effect on general cerebral blood flow, vascular resistance, oxygen consumption, or glucose utilization in an early study using the nitrous oxide method (62).

The last two decades have seen neurofunctional studies with hallucinogens like psilocybin (262,264), DMT (120), and mescaline (137). When compared to each other, most of these studies gave inconsistent or incongruent results, which limits the plausibility of hypotheses developed to explain neurofunctional alterations during hallucinogen effects (259). The few results that were congruent across different studies show an activation of the right hemisphere, altered thalamic functioning, and increased metabolism in paralimbic structures and the frontal cortex. Some investigators found increased global brain metabolism (137,264), but others found no change (262,265). One recent fMRI/BOLD study showed decreased neuronal activity and cerebral blood flow in the anterior and posterior cingulate cortex and thalamus after administration of psilocybin (268). Functional connectivity analysis showed that the "hubs," that is, the relay stations, connecting related brain regions showed less activity. Therefore, they hypothesized an "unconstrained cognition" resulting from these changes. However, artifacts due to the irritating intravenous mode of drug administration and the strange and noisy environment of the fMRI scanner cannot be ruled out. Conflicting results from these studies and their interpretations are still a matter of debate (269).

The only comparative neurometabolic study of psilocybin, MDE, and methamphetamine revealed significantly different effects of these substances (262). Results from FDG-PET with psilocybin demonstrated a relative hypermetabolism in the prefrontal and inferior temporal regions of the right hemisphere, as well as in the subcortical regions. The most prominent deviation was found in the anterior cingulum, which had a metabolic increase of almost 10%. In the thalamus and left precentral region, there was a decrease in the metabolic rate. The ratio of cortical/subcortical metabolism was also reduced. The induced metabolic effects with MDE were partly comparable to those of methamphetamine and partly to those of psilocybin. MDE caused a metabolic increase in the cerebellum and a reduction of cortical metabolism, particularly in the frontal regions, comparable to the effects of methamphetamine. Despite globally reduced frontal activity after MDE administration, the anterior cingulum demonstrated a marked increase in metabolism (262).

In another FDG-PET study (189), MDMA significantly increased bilateral regional cerebral blood flow (rCBF) in the cerebellum, ventromedial prefrontal cortex, ventral anterior cingulum, and inferior temporal and medial occipital lobes, possibly due to activating tasks during the scanning session. Bilateral decreases of rCBF were observed in the precentral and paracentral lobes and dorsal and posterior cingulum, as well as in the superior temporal gyrus, insula, and thalamus. The most significant change was a unilateral decrease in activity in the left amygdala. This might be the neurophysiologic substrate of diminished anxiety and euphoria under the influence of MDMA.

Interpretation of research on the neurobiologic effects of hallucinogens is limited by the absence of a consistent model for evaluation of their complex effects on the human psyche and consciousness. There is always the temptation to make one or another a "mechanism," be it biochemical, receptor-mediated, or neurofunctional, responsible for their actions. In contrast to these more or less simple solutions, the brain represents a very complex system with different levels interlaced with each other not only anatomically but also functionally. What we know is that these substances work on a mix of different receptor systems in different ways at the same time to establish an altered matrix of brain (de)activation and functioning.

RELATIVE ADDICTION LIABILITY

Use of hallucinogens very rarely meets the ICD-10 or *DSM-V* criteria for a substance use disorder (abuse or dependence in *DSM-IV*). Community-based epidemiologic studies in the United States suggest that less than 3% of past-year hallucinogen users develop dependence, with another fifth developing abuse (270). The classical hallucinogens very rarely induce physical dependence or a withdrawal syndrome. There are no reports of a withdrawal syndrome from salvinorin A. Additionally, all classical hallucinogens (e.g., LSD, psilocybin, mescaline) induce tolerance relatively immediately, that is, after a few days. Therefore, more frequent, that is, daily, use will lead to little or no acute intoxication after a very short period of use (days), possibly discouraging extended periods of frequent use. This is different with the entactogens like MDMA. Entactogens lead to a massive depletion of intracellular serotonin, and therefore, the serotonin storage is emptied, and no entactogenic effects will occur after a very few daily ingestions. Meanwhile, the more amphetamine-like effects from entactogens (which are not dependent on serotonin but rather on norepinephrine and dopamine) still occur: psychophysical excitation, anorexia, overarousal, restlessness, and sleeplessness. Addiction resulting from the frequent use of entactogens is consistently reported, but psychological features play a more pronounced role than physical ones. Studies suggest that addiction to entactogens may have another structure than those related to alcohol, stimulants, or opiates (271).

The classical hallucinogens, as well as salvinorin A, have negative reinforcing properties in animal studies (158,272–275). Virtually all of the hallucinogenic drugs lack affinity either for DA receptors or for the DA uptake transporter and, therefore, do not directly affect DA neurotransmission (37). A recent survey (157) found that use of *S. divinorum* did not have the characteristics of a drug addiction, using the criteria of the Severity of Dependence Scale. This is congruent with preclinical data suggesting that kappa opioid receptor agonists are less reinforcing than other opioid receptor agonists (275).

MDMA shares some pharmacologic properties with the amphetamines and, therefore, has some reinforcing efficacy (276) but significantly less than methamphetamine and cocaine (276,277). In contrast, the prototype of the entactogens, MBDB, has no reinforcing properties (278),

which implies that the addictive potential of the entactogens can be dissociated from their entactogenic effect. In squirrel monkeys, the reinforcing effects of MDMA are not caused by stimulant- or dopamine transporter–mediated effects (279). 5-HT_{2B} knockout mice do not exhibit behavioral sensitization and place preference following MDMA (280), which suggests a role for this receptor subtype in reinforcing effects of MDMA. There is behavioral evidence that the endocannabinoid system is a modulator of the rewarding/reinforcing properties of MDMA. MDMA also alters the activity of the dynorphinergic and enkephalinergic systems in several brain structures (281).

CONCLUSIONS AND FUTURE RESEARCH

The hallucinogens represent a heterogeneous class of substances with individually different effects as well as diverse mechanisms of action. These substances are physiologically well tolerated in medium-range doses. Their main complications result from unsupervised use and may lead to serious psychological problems. Their dependence liability is not as high as with most other psychoactive drugs (31). If MDMA and PCP, as well as deliriants like atropine and nitrous oxide, are included in the category of hallucinogens, the spectrum of side effects and dependence potential is broader. In the future, newly synthesized substances with unknown psychophysical actions, designed to circumvent drug laws, may possess a greater potential for deleterious side effects.

Hallucinogenic substances stimulate receptors in a diverse and often quite nonselective fashion. Therefore, they were sometimes called "dirty ligands," that is, acting as agonists, partial agonists, or even antagonists on a vast range of receptors. Their "diffuse" mode of action may be due to their multiple receptor interactions. These multiple actions may imply a more "holistic" action, which leads to psychophysically useful and, in some cases, consciousness-expanding, enjoyable, and insightful states that may be useful in a therapeutic context (282).

Because research with these agents was interrupted in the mid-1960s (1,9,24), their potential was not thoroughly evaluated. Renewed research may open up new avenues for psychiatric and other therapies (31). Recently published studies used psilocybin and LSD or bromo-LSD for cluster headache (29,283), MDMA in the psychotherapy of PTSD (12,284), psilocybin in end-of-life anxiety (30), and ketamine in depression (285). Hallucinogens may also be used for research into experimentally induced psychotic states (286). Basic research may advance by the development of more specific agonists/antagonists and more refined brain imaging techniques, including connectivity analysis and receptor-related imaging.

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Queries

[Q1] Please check all the head levels.
[Q2] Please confirm whether "DSM-IV" and "DSM-V" should be italicized throughout the chapter.
[Q3] Please expand "C. purpurea."
[Q4] Please provide expansion of "ACTH," if appropriate.
[Q5] Please provide expansion of MAO, if appropriate.
[Q6] Refs. 45 and 50, and Refs. 73 and 100 (original) are found to be identical and duplicates have been deleted and renumbered. Please check.
[Q7] Please provide publisher location for Ref. (11).
[Q8] Please provide the year for Ref. (47).
[Q9] Please provide publishers location for ref. (140).
[Q10] Please provide complete source line for Figure 14-2.
[Q11] Please confirm if the formatting of Table 14.2 is okay as set.