INTRODUCTION

Drug addiction seriously affects public health and represents a social burden worldwide. The abuse of drugs has become a complex issue, mainly due to the development of synthesis and purification procedures that enable an increase in the effective quantities of the active compounds consumed and to the invention of the hypodermic syringe in the mid-nineteenth century, which allowed the direct injection of purified active compounds into the bloodstream. This also contributed to the increase of infections among drug addicts.

Among psychoactive drugs, alcohol (ethanol) is the most common in the world. Its harmful use is responsible for 3.8% of all global deaths. Besides alcohol, the most abused drugs in the world are cannabis (used annually by 2.9–4.3% of the world population aged 15–64), amphetamines (0.3–1.2%), cocaine (0.3–0.4%), and opiates (0.3–0.5%), as described in the World Drug Report 2010, from the United Nations Office on Drug and Crime. Although less consumed, opiates are illicit drugs that lead more people to seek treatment, due to the severe withdrawal effects and the increased risk for infections.

This chapter summarizes and compares the characteristics and toxicological properties of the main drugs of abuse, namely alcohol, amphetamines, cocaine, heroin, and cannabis.
CHARACTERISTICS OF PSYCHOACTIVE DRUGS

The term “drug of abuse” is usually applied to a psychotropic drug that is used in a manner that deviates from the approved medical or social patterns within a given culture at a given time.

Drugs with psychoactive effects can be divided into several groups, according to their specific actions. The most common illicit drugs of abuse are the psychostimulants (e.g. amphetamines and cocaine), depressants (e.g. alcohol (ethanol) and opiate narcotic analgesics), and hallucinogens (e.g. mescaline and lysergic acid – LSD). The properties of these groups of drugs are summarized in Table 17.1.

Some drugs of abuse induce effects that are common to more than one group. For example, ecstasy (or 3,4-methylenedioxymethamphetamine – MDMA) belongs to the class of amphetamine-type psychedelic drugs, which share stimulant and hallucinogenic effects. These drugs are also known by empathogens or entactogens, because they induce feelings of empathy and entactogeny. Another example is cannabinnoids, which share properties of all the groups described above.

Drug abuse is frequently associated with toxic effects that evolve under regular use, overdosage or the withdrawal syndrome that manifests during abstinence from the drug. It affects a number of body systems, leading to signals and symptoms of organ dysfunction, such as:

- Central nervous system (CNS) symptoms that may range from headaches and altered mental status to coma and seizures.
- Cardiovascular alterations that include changes in blood pressure, heart rate, as well as arrhythmias and organ ischemia.
- Respiratory changes that include respiratory arrest, pulmonary edema, and pneumothorax.
- Metabolic effects, including alterations in body temperature, electrolytes, and acid–base disturbances.
- Hepatic damage, from hepatitis to severe hepatoxicity and liver failure that may require liver transplantation.
- Renal damage, with symptoms derived from decreased filtration rate to acute kidney failure.
- Reproductive consequences that may range from impaired fertility to teratogenesis, intrauterine growth retardation, premature births and neonatal syndromes, and attention deficit hyperactivity disorder (ADHD).
- Infectious complications from intravenous drug use, including viral infections such as HIV and hepatitis B, and bacterial infections such as bacterial endocarditis, osteomyelitis, and abscesses.

The clinical toxicology of drugs of abuse depends on the administration pathway, which affects its bioavailability.

### Table 17.1 Classification and Principal Effects of the Main Drugs of Abuse

<table>
<thead>
<tr>
<th>Class</th>
<th>Acute</th>
<th>Chronic</th>
<th>Withdrawal</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative/hypnotics</td>
<td>Euphoria, relaxation, CNS depression, nausea, vomiting, impaired motor function, impaired sensory function, impaired cognition</td>
<td>Craving, tolerance, physical dependence</td>
<td>Severe shaking, sweating, weakness, agitation, headache, nausea, vomiting, tachycardia, seizures</td>
<td>Alcohol (ethanol)</td>
</tr>
<tr>
<td>Psychostimulants</td>
<td>Euphoria, tachycardia, hypertension, hyperthermia, increased mental alertness, seizures</td>
<td>Psychosis, paranoia, reduced appetite, weight loss, heart failure, nervousness, insomnia</td>
<td>Severe depression (sometimes), headache</td>
<td>Cocaine, amphetamine and derivatives (e.g. methamphetamine, ecstasy, cathinone, mephedrone)</td>
</tr>
<tr>
<td>Opioid-type depressants</td>
<td>Pain relief, euphoria, drowsiness/nausea, constipation, confusion, sedation, respiratory depression and arrest, hypothermia, unconsciousness, seizures, coma, death</td>
<td>Depressed sexual drive, lethargy, general physical debilitation, infections, hepatitis, tolerance, addiction</td>
<td>Anxiety, insomnia, nausea, vomiting, diarrhea, anorexia, tachycardia, lacrimation, sweating, severe back pain, stomach cramps, muscle spasms</td>
<td>Opium, morphine, heroin, desomorphine</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Altered states of perception and feeling</td>
<td>Persisting perception disorders (flashbacks)</td>
<td>No typical symptoms</td>
<td>Mescaline, LSD, psilocybin, ecstasy</td>
</tr>
</tbody>
</table>
ADULTERANTS AND CONTAMINANTS

A critical problem associated with drug abuse is the fact that the drugs available in the streets are illegally synthesized, usually under poor conditions. Deficient purification and low quality of the reagents used often leave some impurities in the final products. Frequently, adulterants are also intentionally added to the drugs to increase profit or to modulate the experienced effects.

Heroin is a semisynthetic drug, obtained from acetylation of morphine. *Street* heroin may contain different amounts of heroin and other components, depending on its origin and on the method of illicit synthesis. Usually, *street* heroin is illegally synthesized from morphine purified from opium extracts, which is often contaminated with other alkaloids. These alkaloids may also suffer synthetic acetylation during heroin manufacture. Depending on the purification procedure, *street* heroin may contain some impurities, such as morphine and 6-monooctyl morphine (6-MAM) (heroin metabolites) or codeine and acetylcodine. Heroin in seized samples often contains various inert diluents (starch, lactose, fructose, sucrose, mannitol, powdered milk) and active adulterants (caffeine, paracetamol, strychnine, acetylsalicylic acid, barbiturates, quinine, and amphetamines).

Street cocaine can be mixed with several diluents or adulterants, such as amphetamines, antihistamines, benzocaine, inositol, lactose, lidocaine, mannitol, opioids, phencyclidine, procaine, sugars, tetracaine, and sometimes arsenic, caffeine, quinidine, and even flour or talc.

MDMA is also frequently adulterated. Occasionally, tablets that are sold as “ecstasy” do contain drugs other than MDMA, or even none at all. Other psychoactive substances found in tablets sold as “ecstasy” included mostly other amphetamines, such as 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine, paramethoxyamphetamine, 2,5-dimethoxy-4-bromoamphetamine (DOB), and 4-methylthioamphetamine (4-MTA). Other compounds such as caffeine, cocaine, heroin, ketamine, LSD, aspirin, synthesis intermediaries, among other drugs, have been found in ecstasy tablets and may contribute to its toxicological outcome. The online project [http://www.ecstasydata.org/] receives ecstasy tablets sent by users for testing and publishes the results in their website with the aim of helping drug users with harm-reduction, medical personnel, and researchers.

### POLYDRUG USE

An important factor affecting drug toxicity and medical complications is polydrug abuse. A relatively common combination of drugs is the *speedball*, which consists in concurrent administration (by injection) of cocaine and heroin. *Speedball* has been reported to cause more rewarding effects in rats than cocaine or heroin alone. The popularity of this drug combination may be explained by the reduction of the unwanted side effects of one drug by the other, since they have different mechanisms of action, or by the enhancement of the desired effect at the reward system.

Ethanol is frequently combined with other drugs of abuse. When ethanol and cocaine are co-consumed, the euphoric effects of cocaine are enhanced. However, this combination also increases the toxic effects of both drugs, because the drugs are combined in vivo to form a very toxic metabolite – cocaethylene. This is a very lipophilic compound and is able to cross the blood–brain barrier. The effects of cocaethylene are similar to those of cocaine but the metabolite has a longer half-life, prolonging the acute effects of cocaine.

Consumption of ethanol also increases the toxic effects of MDMA, enhancing hyperthermia, hepatotoxicity, and neurotoxicity.

### TOXICOLOGICAL PROPERTIES OF SELECTED DRUGS

Characteristics of drugs of abuse such as induction of positive reinforcement, dependence, and withdrawal are generally associated with certain pharmacological properties. Psychoactive drugs with rapid absorption and delivery to the CNS, high bioavailability, low protein and peripheral tissue binding, small volume of distribution, short half-life, and high free drug clearance are generally predicted to produce positive reinforcement and lead to persistent self-administration. Drugs that induce physical dependence generally have a long half-life, low free drug clearance, and must achieve high enough concentrations for sufficient time to induce the development of compensatory homeostatic changes that permanently or temporarily change the organism’s...
response to the drug. These homeostatic changes are responsible for the development of tolerance and sensitization to the drug, and for the withdrawal syndrome that manifests in the absence of the drug. Withdrawal symptoms are most probably manifested for psychoactive drugs with a short half-life, high free drug clearance, and that rapidly exit the CNS.

The intensity and onset of a drug’s effects are determined by the rapidity of its delivery to the CNS. Drug users learn to optimize the delivery of the drug to the brain and to maximize the bioavailability of the drug by adapting the methods and routes of administration. The most rapid CNS delivery is achieved by inhalation, due to the direct access of pulmonary blood to the brain. Smoking is a very effective route of administration, but requires highly volatile forms of the drugs, to assure resistance to degradation at the temperatures produced by burning. Intravenous administration provides the highest bioavailability but is associated with severe health complications, whereas oral administration is generally more convenient, but is associated with lower bioavailability and slower delivery to the brain.

Central effects of drugs of abuse are due to the interference of these drugs with the molecular and cellular pathways involving neuronal active endogenous compounds, including monoamine and other types of neurotransmitters, endocannabinoids and endorphins, taking advantage of structural and bioisostere similarities (Fig. 17.1). The molecular targets of these xenobiotics are transporters or receptors that mediate the physiological actions of those endogenous compounds, activating specific intracellular signaling pathways. However, drugs of abuse do not completely mimic the action of the endogenous compounds because the molecular machinery involved in their removal from the synapse is frequently inefficient for these xenobiotics, which implies the interference with neuronal activity for longer periods of time.

In the next sections, we discuss the toxicological properties of the most common drugs of abuse, the main medical complications found in drug abusers and the biomarkers of abuse. The data presented are mainly based on literature referred at the Further Reading section.

Alcohol (Ethanol)

Alcohol (ethanol) has long been used by mankind for social, medical, cultural, and religious purposes. For most users, alcohol consumption does not impair physical or mental health. However, acute or chronic alcohol intoxication has negative individual and social consequences. Ethanol is a straight-chain alcohol (Fig. 17.1) produced by fermentation of sugars present in agricultural products. It is present in alcoholic drinks, namely in beer (3–6% w/v), wine (9–12%), spirits (32–40%), or cocktails (15–25%). Alcohol is generally used to obtain euphoria and relaxation. The effective dose in humans is around 22–40 g and the effects generally persist for 1.5–3 h. The harmful use of alcohol is generally associated with chronic or binge drinking.

Routes of Exposure

Alcohol is generally used by the oral route to obtain its psychoactive effects. However, it may be used as an antiseptic for medical purposes, applied topically in the skin.

Pharmacokinetics

- Absorption
  
  When taken orally, alcohol is rapidly absorbed in the small intestine into the bloodstream. The presence of food in the stomach may delay gastric emptying and slow absorption. The oral bioavailability of alcohol is generally higher than 80%. Peak blood concentrations typically occur between 30 and 90 min after ingestion.

- Biodistribution

  Alcohol has low molecular weight, mixes well with water and is only weakly charged, easily crossing biological membranes and the blood–brain barrier. It has low-protein binding and a volume of distribution around 0.55 l kg\(^{-1}\). On entering the bloodstream, alcohol is distributed throughout the body, mainly affecting the brain, liver, and kidneys.

- Plasma half-life

  At high alcohol concentrations, the plasma half-life is about 4–5 h, whereas at low alcohol concentrations the clearance is slower and the plasma half-life increases.

- Metabolism

  Alcohol is mainly metabolized in the liver by alcohol dehydrogenase into acetaldehyde. Alcohol dehydrogenase may also be present in the stomach and small intestine. Catalase and cytochrome P450 (CYP2E1) may also contribute to alcohol metabolism into acetaldehyde, and hepatic CYP2E1 expression is 5- to 10-fold increased in chronic alcohol users. Acetaldehyde is then converted into acetate by aldehyde dehydrogenases (these enzymes are found in many tissues of the body but are at the highest concentration in the liver). Acetate combines with coenzyme A, to generate acetyl-coenzyme A, which may enter metabolic pathways. A small percentage of ethanol is conjugated to give ethyl glucuronide and ethyl sulfate, which may be helpful as biomarkers of alcohol abuse.

- Excretion

  About 5–10% of ingested alcohol is excreted unchanged in urine, breath, and sweat. Alcohol or its
The chemical structures of some drugs of abuse and neuronal active endogenous compounds are shown in Figure 17.1. The structures of MDMA and LSD resemble the structure of serotonin and thus interfere with serotonergic systems. Amphetamine, methamphetamine, and cocaine are structurally similar to dopamine and norepinephrine, affecting primarily the systems involving these monoamines. Tetrahydrocannabinol has similarities with the endogenous cannabinoids anandamide and 2-arachidonylglycerol and interferes with the receptors for these compounds. Morphine and heroin present chemical similarities to the active sites of endogenous opioid polypeptides such as enkephalins and endorphins (polypeptidic structures not shown here for simplicity). Ethanol shares structural similarities with the neurotransmitters GABA and glutamate and interferes with receptors for these amino acids.
metabolites are generally detected in urine up to 96 h. Alcohol use is generally tested by breath analysis, which is well correlated with blood alcohol concentration.

**Pharmacology and Toxicology**

- **Pharmacodynamics/Mode of action**

  Although alcohol has long been believed to act nonspecifically by disordering lipids in cell membranes, it is now acknowledged that at physiologically relevant concentrations (5–20 mmol l\(^{-1}\)), alcohol interferes with neural activity by acting directly on neurotransmitter-gated ion channels. Ethanol enhances GABAergic neurotransmission by altering the conformation of inhibitory GABA\(_A\) receptors and inhibits the excitatory N-methyl-D-aspartate (NMDA) receptors, acutely depressing neural activity, thus explaining the sedative effect of alcohol.

  At the reward pathway, ethanol acts on GABA\(_A\) receptors present on inhibitory neurons in the ventral tegmental area, and induces the release of opioid neuropeptides, leading to the disinhibition of dopamine release in the nucleus accumbens. Ethanol may also act in the nucleus accumbens, possibly by inhibiting NMDA receptors in corticostriatal synapses.

  Long-term alcohol use leads to neuroadaptations at the ion channel sensitivity (subunit composition) or number. When alcohol is no longer present, the decrease in inhibitory and increase in excitatory receptor functions become unmasked, leading to the withdrawal syndrome, where neurons are in a hyperexcitable state.

- **Toxicity**

  Ethanol is a general CNS depressant, inducing a degree of sedation dependent on the blood concentration achieved. On drinking a moderate amount of ethanol, users may experience a stimulating phase, due to the depression of the brain mechanisms that control behavior. At low-blood alcohol concentrations (0.01–0.1% w/v), the main brain areas affected are at first the cerebral cortex and then the forebrain, associated with the feelings of relaxation, well-being, loss of inhibition, pleasure, and emotional arousal. From concentrations of 0.01–0.3%, the cerebellum and the brain stem also become affected, leading to mood swings, anger, sadness, aggression, and depression. From 0.31% to higher blood alcohol concentrations, the entire brain becomes affected, leading to unconsciousness, coma, and possibly death. Accordingly, the level of alcohol-induced impairment is also dependent on blood alcohol concentration. At first, alertness is affected, followed by judgment, motor coordination, visual tracking, balance, temperature regulation, bladder control, breathing, and heart rate.

  Chronic alcohol use induces liver damage, including fat accumulation, alcoholic hepatitis, and cirrhosis. Chronic alcohol intake also affects digestive functions, leading to gastritis and pancreatitis; cardiovascular function, by inducing cardiomyopathy, arrhythmias, and hypertension; brain damage, head, neck, and esophageal cancers; and also affects immune and endocrine systems. Undernutrition may also be observed in chronic alcohol users, particularly involving vitamin deficiencies.

  Tolerance to alcohol develops rapidly, due to neuroadaptations and induction of metabolic enzymes. These adaptations underlie the withdrawal syndrome, which highly contributes to the burden of alcoholism. Alcohol withdrawal is characterized by the symptoms of autonomic nervous system hyperactivity. The initial symptoms are usually mild and include anxiety, insomnia, and tremors, beginning within about 3–6 h of last alcohol intake and usually lasting about 1–3 days. In 5–10% of patients, severe convulsions may also occur in the first 2 days of abstinence. About 10% of alcoholics may develop more severe withdrawal symptoms involving autonomic nervous system hyperactivity, including increases in blood pressure, pulse, breathing and heart rates, and body temperature. Excessive sweating and tremors generally occur. In extreme cases, severe alcohol withdrawal may be complicated by the presence of delirium tremens,” which usually manifests within 48–72 h of abstinence. This condition involves agitation, confusion, disorientation, delusions, and vivid hallucinations, and may persist up to 96 h of drink cessation.

  Fetal alcohol syndrome (FAS) is an important complication of alcohol abuse by pregnant women. Children with FAS present developmental anomalies such as deficits in the formation of the CNS and restricted physical growth, which may lead to cognitive, behavioral, emotional, and social deficits.

  Blood concentrations found in ethanol-related deaths are in the range 2.2–5.0 g l\(^{-1}\) and a typical lethal dose varies between 276 and 455 g.

  The median lethal dose (LD50) in rats ranges between 5.6 and 10 g kg\(^{-1}\) when consumed orally. In mice, the LD50 (oral) was reported to be 3.45 g kg\(^{-1}\).

**Methamphetamine (and Other Amphetamines)**

Amphetamine was first synthesized in 1887 by Lazar Edeleanu at the University of Berlin. This drug is a synthetic derivative of the plant alkaloid ephedrine, extracted from plants in the genus *Ephedra*. *Ephedra sinica*, also known as Ma Huang, has been used in traditional Chinese medicine for 5000 years to treat several diseases, such as asthma and common cold. Amphetamines are illegally used to increase alertness, to relieve fatigue, control weight, and for their intense euphoric effects. Amphetamines are still used in medical practice.
to treat narcolepsy and ADHD and have been used as energy boosters by athletes, soldiers, fighter aircraft pilots, and long distance truck drivers.

Methamphetamine is a common amphetamine derivative, more potent than the parent compound. Methamphetamine hydrochloride is presented as a white to light-brown crystalline powder, or crystals that resemble ice, whereas methamphetamine base is a liquid. Methamphetamine is usually available in high purity forms, ranging from 60 to 90% purity. A typical dose ranges from 50 to 2000 mg day$^{-1}$, but in chronic binge users it may reach 5000 mg day$^{-1}$.

Another popular amphetamine derivative is MDMA, a ring-substituted amphetamine derivative with mild hallucinogenic properties. It was first synthesized and patented in 1912 by the German pharmaceutical company Merck under the name of “methylsafrylamin,” as a precursor for therapeutically active compounds. In 1976, MDMA was used for the first time in the clinics as an adjuvant to psychiatric treatment, to increase patient self-esteem and facilitate therapeutic communication, which continued until the early 1980s, when MDMA was classified as a schedule one drug due to its high abuse potential, lack of clinical application, lack of accepted safety for use under medical supervision, and evidence that it could be neurotoxic. Also at the early 1980s, it became popular in the streets as a recreational drug and is still highly used nowadays, especially in dance parties (raves). MDMA is a white, tan or brown powder, primarily available in tablet form. The typical content of MDMA per tablet has been reported to range from 2 to 130 mg, although the average is between 30 and 80 mg. The typical pattern of MDMA use ranges from 1 to 2 tablets in a single episode, though binge administration of ecstasy tablets is also frequent among users.

**Routes of Exposure**

Methamphetamine users generally begin with intranasal or oral use and may progress to intravenous use, and occasionally smoking. “Ecstasy” is almost exclusively sold and consumed orally in the form of tablets (rarely capsules), which frequently contain symbols (logos) and are colored.

**Pharmacokinetics**

- **Absorption**

  Amphetamines are rapidly absorbed after oral ingestion, with peak plasma levels occurring within 2.6–3.6 h. Peak plasma concentrations may range from 0.01 to 2.5 mg ml$^{-1}$ for methamphetamine or 0.02–0.44 mg ml$^{-1}$ for MDMA. The effects of methamphetamine usually persist for 4–8 h, but residual effects may last up to 12 h. MDMA effects may persist for 2–3 h.

- **Biodistribution**

  Amphetamines concentrate in the liver, kidney, lungs, cerebrospinal fluid, and brain. They are highly lipid soluble and readily cross the blood–brain barrier. Amphetamines are weak bases with high pKa values between 9.4 and 10.1, low molecular weight, low protein binding (around 20%), and high volume of distribution (3.5–71 kg).

- **Biological half-life**

  The biological half-life of orally administered methamphetamine is 10.1 h in average, ranging from 6.4 to 15 h, while that of MDMA is found to be in the range of 6–9 h, depending on the dose.

- **Metabolism**

  The phase I metabolism of methamphetamine by CYP2D6 generates two pharmacologically active metabolites, amphetamine and 4-hydroxymethamphetamine. The major metabolic pathway for amphetamine involves aromatic hydroxylation by CYP2D6 to 4-hydroxymethamphetamine, which is psychoactive, and deamination to phenylacetone. This compound is subsequently oxidized to benzoic acid and excreted as glucuronide or glycine (hippuric acid) conjugate. Smaller amounts of amphetamine are converted to norephedrine by oxidation. Hydroxylation of norephedrine produces an active metabolite, 4-hydroxynorephedrine, which is psychoactive.

  MDMA is also a substrate for CYP2D6. The major pathways of MDMA metabolism are N-demethylation, O-demethylation, and deamination. MDMA is converted to the catechol, 3,4-dihydroxymethamphetamine (DHMA) and the N-demethylated psychoactive product, 3,4-methylenedioxyamphetamine, MDA, by CYP2D6, but other enzymes may also contribute (e.g. 1A2, 2B6, and 3A4). MDA is further metabolized to the catechol intermediate, 3,4-dihydroxyamphetamine (DHA). DHMA and DHA can undergo oxidation to the corresponding ortho-quinones, which can form adducts with glutathione and other thiol-containing compounds.

- **Excretion**

  An oral dose of 30–54% of methamphetamine is excreted in urine as unchanged methamphetamine, and 10–23% as unchanged amphetamine. After intravenous use, 45% is excreted as methamphetamine and 7% as amphetamine. However, the amount of urinary excretion and metabolism is highly pH dependent, with alkaline urine significantly increasing the drug half-life. Detection time of amphetamine in urine is usually 1–4 days. Methamphetamine may be detected in urine 3–5 days after the last use. The urinary recovery of MDMA is approximately 60%, independently of the dose.

I. THE NATURE OF ADDICTION
administered. DHMA is the main metabolite found in urine (>20%), with less than 2% of the dose excreted as MDA. MDMA or its metabolites may be detected in urine 1–5 days after the last use.

**Pharmacology and Toxicology**

- Pharmacodynamics/Mode of action

  Methamphetamine increases synaptic levels of the monoamine neurotransmitters dopamine, serotonin (5-HT), and norepinephrine, and has α- and β-adrenergic agonist effects. Due to its structural similarity with dopamine (Fig. 17.1), amphetamine is a substrate for the dopamine transporter (DAT). Amphetamine also interferes with the vesicular monoamine transporter-2 (VMAT-2) function, impairing the active transport of the monoamines into synaptic vesicles, where they are stored. In addition, amphetamines can also deplete vesicular biogenic amine content by disrupting the pH gradient via a weak base effect that drives the transporter. Cytosolic dopamine is then released to the extracellular space via reverse transport through DAT. Amphetamine also inhibits dopamine synthesis by inhibiting tyrosine hydroxylase and may also slowdown catecholamine metabolism by acutely inhibiting monoamine oxidase.

  MDMA is similar in structure and effects to methamphetamine (Fig. 17.1), but has significantly less CNS stimulant properties. MDMA has a high affinity for 5-HT2 receptors and may cause acute depletion of presynaptic 5-HT, depression of 5-HT synthesis, and retrograde destruction of 5-HT neurons. MDMA easily diffuses across the cell membranes and lipid layers and may be specifically accumulated inside serotonergic neurons through the serotonin transporter (SERT). MDMA also increases the levels of norepinephrine and dopamine. MDMA hallucinogenic properties depend on the stimulation of 5-HT2A-receptors, mainly in the pyramidal neurons of the neocortex.

  Increase in synaptic dopamine in the brain reward pathway is associated with feelings of pleasure induced by amphetamines and other drugs of abuse.

- Toxicity

  The increase in dopamine levels induced by amphetamines leads to an increase in its oxidative metabolism, which generates free radicals that may induce cytotoxicity. Dopamine mediates locomotor stimulation, psychosis, and perception disturbances, whereas changes in norepinephrine levels are associated with alerting, anorectic, locomotor, and sympathomimetic effects and 5-HT is responsible for delusions and psychosis. Toxicity of methamphetamine may lead to renal and liver failure, hyperthermia, cardiac arrhythmias, heart attack, cerebrovascular hemorrhages, stroke, seizures, and death.

  The effects of methamphetamine are similar to those of cocaine, but start slower and last longer. In most methamphetamine-related deaths, blood concentrations found are in the range 1–43 mg l⁻¹.

  D-amphetamine has similar effects to methamphetamine, but is less potent. LD50 of amphetamine was reported as 55 mg kg⁻¹ (oral) and 180 mg kg⁻¹ (s.c) in rats and 24.2 mg kg⁻¹ (oral) in mice. LD50 for methamphetamine was reported as 70 mg kg⁻¹ (ip) in rats, 43 mg kg⁻¹ (ip) in mice, and 10 mg kg⁻¹ (oral) in dogs. The lethal dose of methamphetamine in humans is usually within 140–1650 mg.

  MDMA associated fatalities have been reported with blood levels of 0.04–8.5 mg l⁻¹. LD50 for MDMA was determined as 97 mg kg⁻¹ (ip) in mice, 49 mg kg⁻¹ (ip) and 160 mg kg⁻¹ (oral) in rats, and 26–98 mg kg⁻¹ (ip) in guinea pigs. The lethal dose of MDMA in humans is in the range of 150–1250 mg.

  MDMA neurotoxicity is the most widely studied toxic effect and potentially the most significant long-term effect of this drug. Other complications of acute MDMA use include hyperthermia, arrhythmias and cardiovascular collapse, liver failure, renal failure, and hyponatremia. Another severe consequence is rhabdomyolysis, which is characterized by the breakdown of muscle fibers that result in the release of their myoglobin contents into the bloodstream, contributing to kidney damage.

  The MDMA metabolite, MDA, induces higher levels of stereotypic behavior and is more neurotoxic than the parent drug. MDA destroys 5-HT-producing neurons, which regulate aggression, mood, sexual activity, sleep, and sensitivity to pain.

**Cocaine**

Cocaine was first isolated in 1855 by the German chemist Friedrich Gaedcke. This alkaloid is extracted from the plant Erythroxylum coca, which is cultivated in the South American countries Bolivia, Colombia, and Peru. The natives of these countries chew the coca leaves in magical ceremonies and initiation rites. Cocaine may be processed in water-soluble or -insoluble forms. Water-soluble forms include cocaine sulfate and cocaine hydrochloride. In medicine, cocaine is used as a topical local anesthetic for ear, nose, and throat surgery.

Cocaine hydrochloride is presented as a shiny white to light-brown crystalline powder, whereas cocaine base is generally a white to beige waxy solid. Cocaine is used recreationally to increase alertness, relief fatigue, and increase self-confidence, and is abused for its intense euphoric effects. Purity of cocaine hydrochloride ranges from 20 to 95%, and crack cocaine is generally 20–80% pure. Cocaine is often “cut” with sugars, other CNS stimulants, and local anesthetics. Common doses range from 10 to 120 mg.
**Routes of Exposure**

Cocaine sulfate and cocaine hydrochloride are used by oral, sublingual, intranasal, and intravenous routes, whereas coca leaves may be chewed. Drug smugglers, known as “mules” or “body packers,” may swallow packages of cocaine, which may leak or rupture and cause massive intoxication.

Water-insoluble forms such as free base cocaine or crack are usually smoked. Crack cocaine is abused by inhaling the vapor from cigarettes (usually mixed with tobacco or marijuana) or after heating the drug in a glass pipe. Most drug abusers use cocaine by the nasal route. Cocaine hydrochloride can be “sniffed” or “snorted” in “lines” on a flat surface. This route leads to pulmonary complications.

Some drug abusers inject cocaine hydrochloride subcutaneously, intramuscularly, or intravenously, alone or with heroin (“speedball”) or with other drugs. Cocaine can also be administered rectally, vaginally, and urethrally.

For clinical purposes, cocaine is used topically to take advantage of its local anesthetic effects.

**Pharmacokinetics**

- **Absorption**
  
  Cocaine is rapidly absorbed following smoking, snorting, and intravenous administration.

  Bioavailability is about 93.7% after intranasal use and 70% on smoking.

  Injecting cocaine produces an effect within 15–30 s. After smoking crack or snorting cocaine the effects are almost immediate. In fact, through this way, cocaine enters the pulmonary circulation and reaches the cerebral circulation within 6 s, eliciting a rapid, short, but very intense euphoric effect. The effects of crack typically last 5–15 min, whereas after snorting the effects may last 15–30 min.

  When orally ingested, the effects of cocaine begin to be observed in about 1 h and may persist for 1–2 h.

  Typical blood concentrations after a single use are in the range of 0.2–0.4 mg ml⁻¹, but tolerant individuals may present up to 5 mg l⁻¹.

- **Biodistribution**
  
  Cocaine is distributed within all body tissues, and crosses the blood–brain barrier. In large, repeated doses, it is probably accumulated in the CNS and in adipose tissue, due to its lipid solubility. Cocaine is found 91% bound to proteins and its volume of distribution varies between 1 and 3 l kg⁻¹. Cocaine crosses the placenta by simple diffusion and may accumulate in the fetus after repeated use.

- **Biological half-life**
  
  Cocaine half-life is about 1 h, varying from about 0.6 h on smoking, 0.8 h after oral administration, 1.25 h after nasal administration, and 0.7–0.9 h after parenteral administration.

- **Metabolism**

  Cocaine metabolism takes place mainly in the liver, within 2 h of administration. The rate of metabolism varies according to plasma concentration. There are three main routes of biotransformation: The major route is hydrolysis of cocaine by hepatic and plasma esterases, with loss of a benzoyl group originating eegonine methyl ester (EME). The secondary route is spontaneous hydrolysis, which leads to benzoylecgonine (BE) by demethylation. Both EME and BE are then converted into ecgonine. A minor route is N-demethylation of cocaine by CYP3A4, leading to the active metabolite nor-cocaine, which crosses the blood–brain barrier.

  Anhydroecgonine methyl ester can be produced when the drug is consumed in the free base form (as a result of thermal degradation of smoked “crack”). In the presence of alcohol another active metabolite, cocaethylene, is formed, which is more toxic than cocaine itself.

- **Excretion**

  Unchanged cocaine is recovered at less than 2% in urine, although higher proportions may be seen in acidic urine; 26–39% of cocaine is recovered as BE and 18–22% as EME. After 4 h of use, most of the drug is eliminated from plasma. Cocaine metabolites persist in urine at detectable concentrations from 2 to 4 days of abstinence, but after chronic use they may be present for up to 10 days after the last use.

**Pharmacology and Toxicology**

- **Pharmacodynamics (mode of action)**

  The main targets of cocaine are the CNS and cardiovascular system.

  Cocaine interferes with the reuptake of monoamine transmitters, particularly dopamine, a neurotransmitter associated with pleasure and movement. Cocaine binds to the DAT blocking its function, which leads to increased extracellular dopamine and results in chronic stimulation of postsynaptic dopamine receptors, resulting in the euphoric “rush.” Dopamine levels then fall, resulting in the dysphoric “crash.” Cocaine also interferes with the uptake of norepinephrine and 5-HT, leading to accumulation of these neurotransmitters at postsynaptic receptors. Cocaine also acts as a local anesthetic, because it reversibly blocks the initiation and conduction of the nerve impulse, by binding to voltage-gated sodium channels.
Cocaine also increases catecholamine concentrations in the blood, leading to excessive stimulation of peripheral \( \alpha - \) and \( \beta - \) adrenoreceptors.

**Toxicity**

The neurotoxic actions of cocaine involve several brain areas and different mechanisms of action. Euphoria, confusion, agitation, and hallucination result from an increase in dopamine activity in the limbic system. Cortical effects lead to pressure of speech, excitation, and a reduced feeling of fatigue. Stimulation of lower centers leads to tremor and tonic-clonic convulsions. Brain stem effects lead to stimulation and then depression of the respiratory vasomotor and vomiting centers. Cocaine may induce hyperthermia due to increased in muscular activity and by a direct effect on thermal regulatory centers.

At low doses, cocaine induces vagal stimulation with bradycardia, whereas at moderate doses, adrenergic stimulation leads to a rapid increase in cardiac output, myocardial oxygen consumption, and blood pressure, then followed by a decrease. This may result in increased risk of myocardial infarction and spontaneous cerebral hemorrhage. At very high doses, a direct toxic effect of cocaine on the myocardium may result in cardiac arrest.

Cocaine abusers may present rhabdomyolysis, probably due to a direct effect of cocaine on muscle and muscle metabolism, tissue ischemia, or due to the effects of other drugs taken with cocaine, such as alcohol and heroin.

Prenatal brain toxicity constitutes another serious negative effect of cocaine, leading to structural, metabolic, and functional brain abnormalities.

Lethal doses of cocaine in humans are estimated at 20–2000 mg. However, cocaine addicts can tolerate doses up to 5 g day\(^{-1}\). Toxic effects can be manifested with plasma concentrations of 0.50 mg l\(^{-1}\) or more and death has been reported with concentrations of 1–20 mg l\(^{-1}\).

The LD50 of cocaine was determined as 17.5 mg kg\(^{-1}\) (iv) in rats, 91 mg kg\(^{-1}\) (ip) in mice, and 21 mg kg\(^{-1}\) (iv) in dogs.

**Heroin and Morphine**

Morphine and heroin are derived from opium, which is extracted from the opium poppy *Papaver somniferum*. There are reports of cultivation of this plant in the Mesopotamia since 3400 BC. Opium contains about 40 alkaloids that make up 10–20% of total opium substances. The most abundant opium alkaloids are morphine (8–17%), codeine (0.7–5%), thebaine (0.1–1.5%), papaverine (0.5–1.5%), and noscapine (or narcotine, 1–10%). Morphine is purified from opium extracts and converted into heroin by acetylation. Heroin is more lipid soluble than morphine and is easily transported across the blood–brain barrier, being two to four times more potent than morphine. Heroin was first synthesized in 1874 by Charles Alder Wright in England, but it was only discovered by the medical community when it was independently resynthesized, 23 years later, by Felix Hoffmann, who worked for Bayer. The use of heroin was thought to be a potential cure for morphine addiction until it was found that heroin is converted into morphine, when metabolized in the liver.

Morphine and heroin are generally white, crystalline powders. Illicit heroin may vary in color from white to dark-brown due to impurities or may appear as a black tar-like material. Depending on the demographic region, the street purity of heroin can range from 20 to 90%. Heroin may be “cut” with inert or toxic adulterants such as sugar, starch, powdered milk, quinine, and ketamine.

Heroin is often mixed with stimulants, such as methamphetamine or cocaine (“speedball”), and injected. It may also be coadministered with MDMA or crack cocaine.

Daily heroin doses may range between 5 and 1500 mg, with an average daily dose of about 300–500 mg, which may be divided by two to four daily injections.

**Routes of Exposure**

Morphine may be used by oral, intramuscular, intravenous, subcutaneous, rectal, epidural, and intrathecal administration. Heroin may be smoked (referred to in street jargon as “chasing the dragon”), snorted or injected intravenously (“mainlining”), and subcutaneously (“skin popping”). Black tar heroin is typically dissolved, diluted, and injected, while higher purity heroin is often snorted or smoked.

**Pharmacokinetics**

- **Absorption**

  The absorption of heroin is 1.5 times higher than that of morphine, and it is 2–4 times more potent, and 200 times more soluble.

  Tolerance makes interpretation of blood or plasma morphine concentrations extremely difficult. Post-mortem analyses after heroin overdoses found blood morphine concentrations between 0.1 and 2.8 mg ml\(^{-1}\).

- **Biodistribution**

  The oral bioavailability of morphine is 20–40%, and 12–35% is bound in plasma, mainly to albumin, with approximately 5% bound to \( \gamma - \) globulin and 5% to \( \alpha 1 - \) acid-glycoprotein. The blood/plasma concentration ratio is about 1.02 in healthy individuals. The bioavailability of smoked heroin is about 44–61%.
Morphine is relatively hydrophilic and therefore distributes slowly into tissues. The volume of distribution of morphine is generally within 1–5 l kg\(^{-1}\). Heroin and 6-MAM cross the blood–brain barrier more easily than morphine. Morphine is transported into the brain by P-glycoprotein, present in brain capillary endothelium, and accumulates especially in the hippocampus where there is also a high concentration of opioid receptors.

- **Biological half-life**

  Heroin has an extremely short half-life of 2–6 min. The half-lives of 6-MAM and morphine are 6–25 min and 1.5–7 h, respectively.

- **Metabolism**

  Heroin is rapidly metabolized to 6-MAM and morphine. Heroin and 6-MAM are more lipid soluble than morphine and thus enter the brain more readily. Morphine is primarily glucuron conjugated at positions 3 and 6, to form morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), respectively. A small amount (5%) is demethylated to normorphine by CYP3A4 and to a lower extent by CYP2C8. M6G is an active metabolite with a higher potency than morphine. The half-life of M6G is 4 ± 1.5 h. About 90% of a single morphine dose is eliminated in urine in 72 h, 75% as M3G and less than 10% as unchanged morphine.

- **Excretion**

  Positive morphine results in urine generally indicate use within the last 2–3 days, or longer after prolonged use. Detection of 6-MAM in urine is indicative of heroin use. High concentrations may indicate chronic use of the drug.

**Pharmacology and Toxicity**

- **Pharmacodynamics (mode of action)**

  Morphine produces its major effects on the CNS primarily through \(\mu\)-Receptors, and also at \(\kappa\)- and \(\delta\)-receptors. \(\mu\)-Receptors are almost always located presynaptically. Interaction of opioids with \(\mu\)-opioid receptors located in inhibitory GABAergic interneurons in the reward pathway leads to inhibition of these neurons, resulting in disinhibition of dopaminergic neurons and increased synaptic dopamine concentrations associated with reward and repetitive drug use.

  The brain region that contains the greatest concentration of \(\mu\)-opioid receptors is the periaqueductal gray, but they are also found in the hippocampus, the superficial dorsal horn of the spinal cord, the external plexiform layer of the olfactory bulb, the nucleus accumbens (involved in reward and addiction), in some parts of the cerebral cortex, and in the amygdala.

  \(\mu_1\)-Receptors are involved in pain modulation, analgesia, respiratory depression, miosis, euphoria, and decreased gastrointestinal activity; \(\mu_2\)-receptors are involved in respiratory depression, drowsiness, nausea, and mental clouding; \(\kappa\)-receptors are involved in analgesia, diuresis, sedation, dysphoria, mild respiratory depression, and miosis; and \(\delta\)-receptors are involved in analgesia, dysphoria, delusions, and hallucinations.

  Heroin has little affinity for opiate receptors. It behaves as a highly lipophilic transporter of morphine and induces more rapid and more intense CNS effects. Most of its pharmacology resides in its metabolism to the active metabolites, 6-MAM, morphine, and M6G.

  Depending on morphine dose and the route of administration, effects begin within 5–60 min and may last 4–6 h. Following heroin use, the intense euphoria generally lasts from 45 s to several minutes. Peak effects may last 1–2 h, and the overall effects disappear in 3–5 h.

- **Toxicity**

  The toxic and lethal doses depend greatly on the individual’s tolerance to the drug, and thus the usual dose for an addict may be dangerous for the same individual after several days of abstinence, due to the rapid decrease in tolerance. A dose of 20 mg heroin may be lethal in non-tolerant subjects, whereas addicts may tolerate doses 10 times larger. Fatalities have been observed after a dose of 12 mg, resulting from respiratory depression.

  Plasma concentration of morphine after lethal overdosage of heroin is generally in the range 0.1–2.8 mg l\(^{-1}\), and the lethal dose is within 12–180 mg.

  LD50 of heroin is around 21.8 mg kg\(^{-1}\) (iv) in mice and 23 mg kg\(^{-1}\) in rats, whereas for morphine the LD50 in mice is 226–318 mg kg\(^{-1}\) (iv).

  Chronic heroin addicts frequently suffer from rhabdomyolysis, probably due to compression of muscle during prolonged immobilization, aggravated by the occlusion of vascular supply. Renal damage may progress to terminal renal insufficiency. Respiratory and cutaneous complications are also observed, probably due to immune deficiency, which may be related with a reduction in lymphocyte proliferation, spontaneous cytolytic activity, phagocytosis, and interferon production. Splenomegaly due to antigenic stimulation has been also described in heroin addicts.

**Cannabis**

Cannabis, also known as marijuana, is a term applied to preparations of the cannabis plant, especially of *Cannabis sativa*, intended for use as a psychoactive drug or for medicinal purposes. Cannabis is the most widely used illicit psychotropic drug in the world. The first descriptions of medical and toxic properties of the plant were part of the ancient Chinese herbal Pen-ts’ao, dating...
### TABLE 17.2  Characteristics and Pharmacokinetic Properties of Selected Drugs of Abuse

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ethanol</th>
<th>Amph</th>
<th>Meth</th>
<th>MDMA</th>
<th>COC</th>
<th>HER</th>
<th>MOR</th>
<th>THC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Sedative/hypnotic, CNS depressant</td>
<td>CNS stimulant, sympathomimetic, appetite suppressant</td>
<td>CNS stimulant, sympathomimetic, appetite suppressant</td>
<td>Mild CNS stimulant, empathogen, enactogen, mild hallucinogen and psychedelic, appetite suppressant</td>
<td>CNS stimulant, local anesthetic</td>
<td>Narcotic analgesic</td>
<td>Narcotic analgesic</td>
<td>Cannabis/marijuana</td>
</tr>
<tr>
<td>Main targets</td>
<td>GABA_A receptors, NMDA receptors</td>
<td>Monoamine terminals</td>
<td>Monoamine terminals</td>
<td>Monoamine terminals (5-HT)</td>
<td>Monoamine terminals DAT</td>
<td>Pro-drug (μ-opioid receptors)</td>
<td>μ-opioid receptors</td>
<td>Cannabinoid receptors, CB1 and CB2</td>
</tr>
<tr>
<td>Chemical formula</td>
<td>C₂H₅OH</td>
<td>C₁₀H₁₃N</td>
<td>C₁₁H₁₅NO₂</td>
<td>C₂₁H₃₀O₂</td>
<td>C₁₇H₂₁NO₄</td>
<td>C₁₇H₂₃NO₅</td>
<td>C₁₇H₂₅N₃O₂</td>
<td>C₂₀H₂₅N₃O</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>46.07</td>
<td>135.21</td>
<td>149.24</td>
<td>193.25</td>
<td>303.35</td>
<td>369.42</td>
<td>285.54</td>
<td>314.5</td>
</tr>
<tr>
<td>Routes of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Intranasal; oral; intravenous; smoked</td>
<td>Oral</td>
<td>Topically; chewed (leaves); smoked (crack); intranasal</td>
<td>Smoked, snorted, intravenous, subcutaneous (skin popping)</td>
<td>Oral; intramuscular; IV; rectal; epidural, intrathecal</td>
<td>Smoked, oral</td>
</tr>
<tr>
<td>Common dose (mg)</td>
<td>22 000–40 000 (10–15 g/serving)</td>
<td>10–100</td>
<td>50–2000</td>
<td>50–2500 (average 30–80)</td>
<td>10–120</td>
<td>5–1500 (average 300–500)</td>
<td>60–120</td>
<td>5–25</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>80%</td>
<td>Oral: 67.2% Smoked: 90.3%</td>
<td>Oral: 67.2% Smoked: 90.3%</td>
<td>–</td>
<td>Intranasal: 93.7% Smoked: 70%</td>
<td>Smoked: 44–61%</td>
<td>Oral: 20–40%</td>
<td>Smoked: 8–50% Oral: 4–12%</td>
</tr>
<tr>
<td>Usual blood levels (mg l⁻¹)</td>
<td>100–4000</td>
<td>–</td>
<td>0.01–2.5; (average 0.6)</td>
<td>0.02–0.44</td>
<td>Single dose: 0.2–0.4; repeated: up to 5</td>
<td>n.d.</td>
<td>0.20–2.3</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>Peak</td>
<td>30–90 min</td>
<td>–</td>
<td>Oral: 2.6–3.6 h; shortly after injection; few minutes after smoking</td>
<td>20–30 min</td>
<td>15–30 s</td>
<td>&lt;10 min</td>
<td>Oral: 60 min IV: 5 min</td>
<td>10–30 min</td>
</tr>
<tr>
<td>Duration (h)</td>
<td>1.5–3</td>
<td>4–8</td>
<td>2–3</td>
<td>1–2</td>
<td>1–2</td>
<td>4–6</td>
<td>3–5</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>Low (~20%)</td>
<td>~20%</td>
<td>~20%</td>
<td>91%</td>
<td>0%</td>
<td>12–35%</td>
<td>95–99%</td>
<td></td>
</tr>
<tr>
<td><strong>Vd (l kg⁻¹)</strong></td>
<td>0.55</td>
<td>3.5–6.1</td>
<td>5–6</td>
<td>6–7</td>
<td>1–3</td>
<td>1–5</td>
<td>4–14</td>
<td></td>
</tr>
<tr>
<td><strong>T₁/₂</strong></td>
<td>4–30 h</td>
<td>6.4–15 h (average 10.1 h)</td>
<td>6–9 h</td>
<td>Smoked: 0.6 h Oral: 0.8 h; intranasal 1.25 h; parenteral 0.7–0.9 h</td>
<td>4.5 h BE 3.1 h EME</td>
<td>1.5–7 h; M6G: 4 ± 1.5 h</td>
<td>1–5 days</td>
<td></td>
</tr>
</tbody>
</table>

**Metabolizing enzymes (metabolite formed)**
- Alcohol dehydrogenases: CYP2E1
- Catalase (Acetaldehyde)
- CYP2D6 (4-OH-Amph)
- CYP2D6 (amph, 4-OH-meth, norephedrine)
- CYP2D6 (MDA, DHMA)
- CYP1A2 (MDA, DHMA)
- CYP3A4 (DHMA)
- Plasma and liver esterases (EME)
- Carboxylesterase 1 (Mor)
- UGT 287 (M3G, M6G)
- UGT1A1, 1A3, 1A6, 1A9, 1A10 (M3G only)
- CYP3A4 and CYP2C8 (norpseudine)
- CYP2C9 and CYP2C19 (11-OH-THC)
- CYP3A4 (8-OH-THC)

**Main metabolite or biomarker**
- Acetaldehyde, Ethyl glucuronide
- Amph
- Amph (10%)
- DHMA and MDA
- BE; EME
- Mor; 6-MAM; M6G
- M6G
- 11-nor-9-carboxy-THC
- 4-OH-Amph
- 4-OH-norpseudine
- Amph
- 4-OH-Meth
- MDA
- Norcocaine, Cocaethylene
- Mor, 6-MAM, M6G
- M6G
- 11-OH-THC, 8-OH-THC

**Active metabolites**
- 4–96 h
- 1–4 days
- 3–5 days
- 1–5 days
- BE 2–4 days. Up to 10 days (chronic)
- 2–3 days
- 2–3 days
- 2–3 days
- 4–5 weeks (chronic)

**Detection time in urine**
- 24–96 h
- 1–4 days
- 3–5 days
- 1–5 days
- 2–4 days. Up to 10 days (chronic)
- 2–3 days
- 2–3 days
- 4–5 weeks (chronic)

**LD₅₀ (mg kg⁻¹)**
- Rats (oral) 5628–10300
- Mice (oral) 3450
- Rats (sc) 180
- Mice (oral) 24.2
- Rats (ip) 70
- Mice (ip) 97
- Rats (ip) 49
- Guinea pigs (ip) 98
- Rats (iv) 17.5
- Mice (iv) 21.8
- Mice (iv) 226–318
- Rats (oral) 730–1270
- (iv) 40 (inhalation) 105.7

Note: For details see text.
from the first to second centuries AD. The popularity of cannabis recreational use by young people on both sides of the Atlantic was closely linked to the protest and rebellion associated with the 1960s generation. Cannabis contains more than 400 different chemical compounds, but the main psychoactive chemical compound is the delta-9-tetrahydrocannabinol (THC). Cannabis is used recreationally as a psychoactive drug under unprocessed or processed forms. In the streets, cannabis may be found in the form of leaves or small stems (known as marijuana, bhang, dagga, or kif), female flower heads (sensimilla), as resin (known as hashish, hash, charas, or polm), or oil (alcoholic resin extract). These forms have different levels of purity, ranging from 1 to 60% THC. In recent years, there has been a large increase in the consumption of home-grown cannabis – often using modern strains of plants yielding a high THC content. Cannabis is consumed in many different ways, most of which involve inhaling vaporized cannabinoids (smoke) from small pipes, paper-wrapped joints, or tobacco leaf-wrapped blunts. Cannabis may also be ingested orally in foods and drinks.

Clinically, cannabis may be used in the treatment of anorexia associated with weight loss in patients with AIDS, and to treat mild to moderate nausea and vomiting associated with cancer chemotherapy. Recreationally, marijuana is used for its mood altering effects, euphoria, and relaxation.

**Routes of Exposure**

The most common way of consuming marijuana and hashish is through inhalation. The inhaled smoke of one cigarette (joint) may contain 0.5–0.7 g of delta-9-THC, but a common dose generally contains 5–25 mg THC. Marijuana can be smoked directly or through small pipes or ‘bongs.’ The oral route is the usual route of administration for medical purposes. Cannabis may also be ingested orally in foods and drinks for recreational purposes.

**Pharmacokinetics**

- **Absorption**

  Absorption by the oral route of administration is slow, with low, delayed peak THC levels. Bioavailability is reduced following oral ingestion (4–12%) due to extensive first pass metabolism.

  Smoking marijuana results in rapid absorption, with a bioavailability of 8–50%. Peak THC plasma concentrations generally occur during the act of smoking. Typical peak plasma concentrations range from 100 to 200 ng ml⁻¹ and drop below 5 ng ml⁻¹ less than 3 h after smoking. The minimum plasma concentration of THC, which produces psychotropic effects, was reported as 25 ng ml⁻¹.

- **Biodistribution**

  THC is highly lipophilic and thus widely distributed throughout the organism, with high concentrations accumulating in fatty tissues that are then slowly released into the circulation. The volume of distribution is about 4–14 l kg⁻¹.

- **Biological half-life**

  The half-life of THC is about 3 days. Plasma concentrations of THC and its metabolite 11-hydroxy-THC decline in a few minutes, due to their redistribution to fatty tissues. After that the decline is slow, with a half-life of 30 h. The half-life may be increased in chronic users, from 2.9 to 5.0 days.

- **Metabolism**

  THC is primarily metabolized by CYP2C9 and CYP2C19 to 11-hydroxy-THC, which has equipotent psychoactivity. The 11-hydroxy-THC is then rapidly metabolized to the 11-nor-9-carboxy-THC (THC-COOH), which is not psychoactive, and then to non-cannabinoid metabolites such as terpenes and alkenes. CYP3A4 in human liver catalyzes the oxidation of the 7- or 8-position of THC.

  THC and its metabolites persist in human plasma for several days or weeks. Chronic marijuana smokers metabolize THC more rapidly than nonsmokers.

- **Excretion**

  THC is rapidly and extensively metabolized with very little THC being excreted unchanged from the body. A majority of THC is excreted in the feces (~65%), with approximately 30% of the THC being eliminated in the urine, as conjugated glucuronic acids and free THC hydroxylated metabolites.

  Metabolites can be detected in urine even 2–3 days after one exposure and, in cases of chronic use, after 4–5 weeks of abstinence.

**Pharmacology and Toxicology**

- **Pharmacodynamics (mode of action)**

  THC binds to the cannabinoid receptors CB1 and CB2, and interferes with important endogenous cannabinoid neurotransmitter systems. CB1 exists mainly in the brain and in the nerve terminals innervating the gastrointestinal system, whereas CB2 is expressed mostly in immune cells.

  Cannabis affects the CNS by activating CB1 receptors located on excitatory and inhibitory nerve terminals. Receptor distribution correlates with brain areas involved in physiological, psychomotor, and cognitive effects.

  Repetitive use of cannabis is explained by the interaction of THC with presynaptic CB1 receptors located at
inhibitory GABAergic interneurons in the reward pathway, leading to decreased gamma-aminobutyric acid (GABA) release. This causes disinhibition of dopaminergic neurons and leads to an increase in synaptic dopamine concentrations, similarly to what happens with opioid drugs of abuse.

*Toxicity*

THC produces alterations in motor behavior, perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature. Long-term use of cannabis has been associated with the occurrence of psychotic episodes.
Activation of CB1 receptors causes profound coronary and cerebral vasodilation and hypotension. An increase in heart rate, usually accompanied by a mild increase in systolic pressure, is generally observed after THC use. Lethal blood concentration of THC is within 0.180–0.315 mg l$^{-1}$, and the lethal dose is over 15 g.

In rats, LD$_{50}$ (oral) of cannabis is within 730–1270 mg kg$^{-1}$, LD$_{50}$ (iv) is about 40 mg kg$^{-1}$, and LD$_{50}$ (inhalation) is 105.7 mg kg$^{-1}$. The LD$_{50}$ in mice is 22 mg kg$^{-1}$ (oral) and in monkeys is 130 mg kg$^{-1}$ (iv).

**CONCLUSIONS**

Drugs of abuse, such as alcohol, amphetamines, cocaine, heroin, and cannabis have distinct toxicological properties and cause severe medical complications. Table 17.2 summarizes and compares the main chemical, pharmacological, and toxicological properties of these drugs, which share chemical similarities with neuronal active endogenous compounds and are thus psychoactive. All drugs of abuse affect neurotransmission, by interfering with neurotransmitter receptors and transporters. The molecular targets of these drugs of abuse in nerve terminals are represented in Fig. 17.2.

**SEE ALSO**

Alcohol Use Disorders, Heroin Addiction, Cocaine Addiction, Marijuana Use and Abuse, Methamphetamine Addiction, Hallucinogens, Ecstasy/MDMA

**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>BE</td>
<td>benzoylecgonine</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DAT</td>
<td>dopamine transporter</td>
</tr>
<tr>
<td>DHA</td>
<td>3,4-dihydroxymethamphetamine</td>
</tr>
<tr>
<td>DHMA</td>
<td>3,4-dihydroxyamphetamine</td>
</tr>
<tr>
<td>DOB</td>
<td>2,5-dimethoxy-4-bromoamphetamine</td>
</tr>
<tr>
<td>EME</td>
<td>ecgonine methyl ester</td>
</tr>
<tr>
<td>FAS</td>
<td>fetal alcohol syndrome</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>5-HT</td>
<td>serotonin</td>
</tr>
<tr>
<td>LD50</td>
<td>median lethal dose</td>
</tr>
<tr>
<td>LSD</td>
<td>lysergic acid</td>
</tr>
<tr>
<td>M3G</td>
<td>morphine-3-glucuronide</td>
</tr>
<tr>
<td>M6G</td>
<td>morphine-6-glucuronide</td>
</tr>
<tr>
<td>6-MAM</td>
<td>6-monooacetyl morphine</td>
</tr>
<tr>
<td>MDA</td>
<td>3,4-methylenedioxyamphetamine</td>
</tr>
<tr>
<td>MDMA</td>
<td>methylenedioxyamphetamine</td>
</tr>
<tr>
<td>4-MTA</td>
<td>4-methylthioamphetamine</td>
</tr>
<tr>
<td>SERT</td>
<td>serotonin transporter</td>
</tr>
<tr>
<td>THC</td>
<td>9-tetrahydrocannabinol</td>
</tr>
<tr>
<td>VMAT-2</td>
<td>vesicular monoamine transporter-2</td>
</tr>
</tbody>
</table>

**Glossary**

**Bioavailability** the proportion of drug absorbed into the systemic circulation.

**Biodistribution** the extent of distribution of a drug throughout the body.

**Biotransformation** chemical modification(s) made by an organism on a chemical compound.

**First pass effect** the loss of drug, following oral administration, due to hepatic metabolism, before it reaches systemic circulation.

**Hyponatremia** an electrolyte disturbance in which the sodium concentration in the plasma is lower than normal.

**Median lethal dose (LD$_{50}$)** dose of a drug that kills half (50%) of the population tested (LD = lethal dose).

**Plasma half-life** a measure of the elimination rate, indicating the time it takes for the plasma concentration of a drug to reach half of its original concentration.

**Parenteral** route of administration independent of the gastrointestinal system.

**Pharmacodynamics** biochemical and physiological effects of drugs on the organism, including the mechanisms of drug action and the structure–activity relationship.

**Pharmacokinetics** study of the fate of substances administered externally to a living organism.

**Rhabdomyolysis** the destruction or degeneration of skeletal muscle tissue that is accompanied by the release of muscle cell contents (such as myoglobin and potassium) into the bloodstream.

**Volume of distribution** a measure of the volume in which the total amount of drug used would need to be uniformly distributed to produce the observed blood concentration.

**Xenobiotic** a chemical compound that is foreign to a living organism.

**Further Reading**


Couper, F.J., Logan, B.K., Drugs and Human Performance Fact Sheets (http://www.nhtsa.gov/people/injury/research/job185drugs/technical-page.htm).


Relevant Websites

http://www.ecstasydata.org/ – Ecstasy Data