Chapter 1
Psychopharmacology of Drugs of Abuse

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Introduction

How do drugs act in the human body? Why do they affect the human brain? This chapter aims to help you answer these questions while reading the next pages. However, it is necessary for you to remember (or learn from today) some basic facts of biology and pharmacology.

Remember the following:

- Human tissues are different because they are composed of distinct cell populations.
- Distinct cellular morphology and function are basically due to the presence of different sets of proteins.
- Drugs are exogenous substances (produced outside the body) that exert effects on our organism by binding into different cellular and molecular targets present in one or more tissues (i.e., they find "fittings" in molecules that form the body).
- Psychoactive drugs alter an individual's behavior because their target molecules are present in the brain.
- Drugs of abuse are a group of psychoactive substances that favor their repeated use and can lead to substance use disorders (abuse and addiction).

In this chapter, you will read about the pharmacokinetic and pharmacodynamic aspects of different drugs of abuse. Pharmacokinetics refers to "what the human body does with a drug," in other words, how a drug is absorbed, distributed,

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metabolized, and eliminated. Meanwhile, pharmacodynamics refers to "what the drug does with the human body," that is, what are the receptors stimulated or inhibited by a drug, their localization, and what happens when a drug acts on them.

Brain function is based on *communication* between different groups of neurons. For this to happen, neurons send messages in the form of chemical substances called neurotransmitters (serotonin, dopamine, noradrenaline, glutamate, γ-aminobutyric acid, or GABA, among others), which will bind to specific receptors found in the cell that should receive the message. There are, then, a variety of receptors in the human brain: serotoninergic, dopaminergic, glutamatergic, and so on. Besides the receptors, other families of proteins involved in neurotransmission are also targets of drugs of abuse. As an example, we can mention transporters (responsible for the reuptake of neurotransmitters), synthetic or metabolic enzymes, and proteins involved in the storage and release of neurotransmitters.

By acting on one or more types of synapses, different drugs of abuse will cause *stimulation, depression, or disturbance in general brain function.* Based on this, different drugs of abuse can be grouped into specific categories as follows (SENAD, 2020):

Stimulants: cocaine/crack, amphetamines, caffeine, nicotine.
Depressants: ethanol, benzodiazepines, opioids, γ-hydroxybutyric acid (GHB), inhalants (glue, poppers, solvents, aerosol sprays).
Hallucinogens or psychedelics: lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), psilocybin, mescaline, marijuana, methylenedioxymethamphetamine (MDMA).

Most of the drugs mentioned above, besides acting more or less intensely in specific regions of the brain, activate the so-called reward system, which is a set of brain structures that interconnect the midbrain with cortical and limbic regions and use dopamine as the main neurotransmitter – the mesocorticolimbic dopaminergic system. It is a primitive system that functions to reinforce behaviors that are needed for survival by providing pleasure and a drive toward the target behavior. The overstimulation of the reward circuit induces dopaminergic neurons in the mesencephalic ventral tegmental area to increase dopamine release in structures such as the nucleus accumbens, which plays a key role in establishing addictive behaviors. This system also sends projections to the prefrontal cortex, influencing executive functions, such as risk assessment, outcome evaluation, critical judgment and, therefore, decision-making. The drug-induced increase in dopamine transmission in the reward system triggers the pleasure that many users report during early use. The involvement of the mesocorticolimbic dopaminergic system in the development of substance use disorders is well-documented in scientific literature (Di Chiara & Imperato, 1988; Volkow & Morales, 2015).

Stimulants

Excitatory synapses are crucial for the various functions of the nervous system, such as maintenance of wakefulness, feeling of well-being and pleasure, cognitive function, and body movement. These functions are triggered by the activation of different neurotransmitter systems that include glutamatergic, dopaminergic, noradrenergic, and serotoninergic pathways. The neurotransmitters involved in these pathways generally increase the activity of the CNS by binding to receptors present on the postsynaptic neuron.

The increased CNS activity induced by the stimulation of excitatory neurotransmission can lead to acceleration of motor behavior, speech, and thought, besides increasing the risk of seizures and, rarely, causing death. Depending on the drug, CNS excitation that follows stimulant use may be triggered by different mechanisms. This chapter will then focus on the psychopharmacological aspects of cocaine/crack and amphetamines.

Cocaine/Crack

Cocaine is an alkaloid extracted from coca (*Erythroxylum coca*) leaves, a native plant of South America. The chemical processing of macerated leaves originates cocaine base, which may be transformed into cocaine hydrochloride (powder), crack, and *merla.*

The intensity and duration of cocaine effects will depend on the way it is administered and absorption routes, which may vary. When taken orally (chewed leaf or tea) and snorted (hydrochloride powder), cocaine is absorbed by the gastrointestinal and nasopharyngeal mucosa, respectively. The onset of effects with intranasal use – which is the preferred route – occurs within 5 minutes and persists between 60 and 90 minutes (Zimmerman, 2012).

Some people choose injecting cocaine and, in this case, its actions start within the first 60 seconds and remains about 20 to 30 minutes. When crack is used, the time is even shorter since its action starts from 3 to 5 seconds after smoking. Due to the extensive surface area and vascularization of the lung, crack is rapidly absorbed, and its effects only persist between 5 and 15 minutes. This, in turn, may lead to repeated use when the user wants to maintain the desired effects, also referred as "high" (Zimmerman, 2012). Long-lasting action is associated with smaller peak plasma concentration, which takes longer to be reached, as well as it takes longer to decay. In general, routes of administration that cause short-term effects are more addictive than those which elicit prolonged action (Swift & Lewis, 2009).

Following absorption, cocaine is widely distributed throughout the body and rapidly metabolized by plasma and liver cholinesterases via cytochrome P450, giving it a short half-life of 0.7 to 1.5 hours (Zimmerman, 2012). The main cocaine metabolites are benzoylecgonine and ecgonine (Coe, Phipps, Cone, & Walsh, 2018; Drake

& Scott, 2018), which are excreted in urine. Benzoylecgonine can be found in urine 2 to 5 days after cocaine use (O'Brien, 2018) and, due to its greatest amount, its detection in urine and blood is targeted by toxicological tests (Jones, 2019). At the same time, cocaine itself appears in varying quantities from 5% to 20% in its unchanged form in the urine (Freye, 2010).

Cocaine and ethanol are simultaneously used by some people and lead to the formation of the active metabolite called cocaethylene, in the liver. The longer half-life of cocaethylene, which is about 2.5 hours, may lengthen the euphoric effects of cocaine (Zimmerman, 2012). It is worth noting that this association is considered the most common cause of death in cocaine users (Swift & Lewis, 2009).

Cocaine has complex effects on the brain. In general, the main mechanism of action is the increase in monoaminergic transmission, such as those mediated by dopamine, noradrenaline, and serotonin. By blocking monoamine reuptake, cocaine increases neurotransmitter concentration in the synaptic cleft, thereby potentiating its actions on postsynaptic neurons. It is suggested that cocaine acts more selectively on dopamine reuptake, increasing its availability in the synaptic cleft and leading to enhanced signaling through dopaminergic receptors 1 and 2 (D1 and D2), which activate intracellular signaling pathways with short- and long-term impact on neural function (Frazer, Richards, & Keith, 2018).

The main action of cocaine targets the dopaminergic neurons of the mesocorticolimbic pathway, mentioned before. Reward system stimulation through nucleus accumbens plays a central role in reinforcing drug-seeking behavior, and this stimulation is even more pronounced when effects are short-lasting, such as when cocaine is injected, or crack is used. Besides that, prefrontal cortex may be hypofunctional in drug addicts or people with other psychiatric comorbidities, thereby affecting decision-making (Frazer, Richards, & Keith, 2018).

Initially, the use of cocaine can cause euphoria and pleasure due to the potentiation of monoamine transmission. Other effects include increased alertness, thought acceleration, impaired judgment, agitation, tachycardia, nausea or vomiting, and appetite inhibition. Dose variation and psychological factors may induce mood fluctuation (euphoria/bad feelings), deliriums, hallucinations, and paranoia.

In long term, repeated blockage of the reuptake system caused by chronic abuse of cocaine leads to monoamine depletion, which can result in various psychiatric symptoms and disorders, such as insomnia, impulsivity, depression, anxiety, aggressiveness, addiction, and withdrawal symptoms (Oliveira & Dinis-Oliveira, 2018). In high doses, cocaine may cause seizures, cardiac arrhythmias, and respiratory arrest and may even lead to death.

Amphetamines

Amphetamines and related compounds (structural analogues) are synthetic drugs with a wide variety. Some of them have therapeutic properties and may be prescribed for attention deficit hyperactivity disorder (ADHD), obesity, and

narcolepsy, while others are illegally produced and sold. Methamphetamine, also known as "ice" or "crystal", is a prohibited amphetamine which offers great risk of drug use disorders that is considered a public health problem in the United States, but not widespread in Brazil.

Due to the substantial increase in medical prescriptions and indiscriminate use of therapeutic amphetamines in Brazil, these drugs were prohibited by the Brazilian Health Regulatory Agency (ANVISA) in 2011 with the only exception to lisdexamfetamine (LDX) and methylphenidate, which are used in the treatment of ADHD. More recently, in 2017, Brazilian Congress approved the production, marketing, and consumption of the anorexigenic drugs amfepramone, fenproporex, mazindol, and sibutramine.

Amphetamines and related compounds (except mazindol) are classified as β-phenylethylamines and are usually taken orally by tablets, although they can be inhaled, smoked, or injected in cases of recreational use. Amphetamines of medical use are well-absorbed in the gastrointestinal tract, metabolized in the liver, and eliminated mostly in urine. Due to the variety of amphetamines and their specificities regarding biotransformation, we have chosen LDX (Venvanse®), methylphenidate (Ritalin®), and fenproporex (Desobesi®) to be described in this chapter.

Lisdexamfetamine (LDX) is a prodrug *d*-amphetamine, absorbed in its inactive form mainly by the peptide transporter-1 in the small intestine into systemic and portal circulation. LDX biotransformation depends on red blood cells peptidases, which hydrolyze it to *l*-lysine and active *d*-amphetamine in the portal circulation (Hutson, Pennick, & Secker, 2014; Pennick, 2010). After ingestion, the conversion of LDX into *d*-amphetamine occurs gradually, in approximately 1.5 hours. Thus, *d*-amphetamine effects on CNS only begin after the molecules have crossed the blood-brain barrier and last from 1.5 to 13 hours in children and 2 to 14 hours in adults. Due to its prolonged action, no more than a daily dose of LDX is indicated in the treatment of ADHD. The excretion occurs predominantly in urine and about 40 to 45% in the form of *d*-amphetamine (Krishnan, Pennick, & Stark, 2008).

Unlike LDX, methylphenidate has less prolonged action. It is a racemic compound of the enantiomers *d*-amphetamine and *l*-amphetamine, which is absorbed in its active form in the gastrointestinal tract. Methylphenidate is primarily transported to the portal circulation but also to nonspecific regions and, after increasing its serum levels, it binds mainly to brain tissue (Yang, Duan, & Fisher, 2016). Drug metabolism occurs via hepatic de-esterification by carboxylesterase 1A1 to form ritalinic acid, and between 60% and 80% of the dose is excreted as this metabolite. The peak concentration of methylphenidate is reached at about 2 hours after administration, and its effects are shorter when compared to other amphetamines, lasting up to 4 hours in the case of Ritalin® (Wenthur, 2016).

Fenproporex, which is structurally similar to amphetamine, is one of the first pharmacological agents used as an anorectic drug (Paumgartten, Pereira, & Oliveira, 2016). From absorption into the gastrointestinal tract, biotransformation occurs presystemically, through metabolism by intestinal microbiota, first pass effect, or a combination of both processes (Kraemer, Theis, & Weber, 2000). Fenproporex metabolism occurs by N-dealkylation by cytochrome P450 in the liver, and it yields

14 metabolites, with amphetamine being the one in greater amounts. Peak concentrations are reached in 1 to 2 hours, and it is hypothesized that its action on hypothalamus is related to the inhibition of appetite. The half-life of fenproporex is 4 to 6 hours, and it is excreted in urine, largely as amphetamine. Since amphetamines lead to increased aerobic muscle capacity (Mariz, 2004; Nikolopoulos, Spiliopoulou, & Theocharis, 2011), alertness, and decreased fatigue (Docherty, 2008), which could be a competitive advantage to athletes, fenproporex, LDX, and methylphenidate have been prohibited in official competitions and are controlled by the World Anti-Doping Agency (WADA).

Amphetamines increase the level of brain excitability through complex interaction with monoamine systems. In general, these drugs act by blocking the reuptake of monoamines and inducing efflux of monoamines by reverse transport. This leads to an increase in monoamines availability in the synapse, thereby potentiating dopaminergic, noradrenergic, and serotonergic neurotransmission. It should be noted that methylphenidate, LXD and fenproporex have less effect in serotonergic pathways (Sitte & Freissmuth, 2015).

As other psychostimulants, amphetamines can increase attention, wakefulness, and energy, as well as they decrease fatigue and appetite. Therefore, these drugs are abused by different professional classes who seek to extend working hours and spend more time awake. An example is the consumption of fenproporex, popularly known as *rebite*, by professional drivers in Brazil.

Amphetamines intensify the central release of noradrenaline with consequent sympathomimetic action, such as increase in blood pressure, mydriasis, tremor, sweating, and restlessness, which are classical signs of stimulant intoxication. When the effects vanish, the user may present signs of fatigue and anxiety, and the abuse of high doses of amphetamine can cause stereotypic movements, seizures, and psychosis (De La Torre et al., 2004).

Depressants

Both excitatory and inhibitory pathways are needed for the proper functioning of the brain. Since the neurons are never "switched off" or "disconnected," the balance between excitatory and inhibitory neurotransmitters is essential to adjust the degree of activity of different brain regions. Different areas of the brain are more or less active according to the type of behavior we are performing. For example, neurons of the primary motor cortex will increase their activity when we are moving, as well as hippocampal neurons will fire when we need to locate ourselves spatially. In this context, GABA is the main inhibitory neurotransmitter in our brain, and it acts by decreasing the excitability of postsynaptic neurons that contain GABAergic receptors.

The mechanism by which the depressants discussed here reduce general functioning of the CNS is based on their binding to GABAergic receptors. $GABA_A$ receptors are proteins that have a channel shape and form a pore in the neuronal

membrane. When GABA binds to $GABA_A$ receptors, these channels open and allow chloride to enter and hyperpolarize the postsynaptic neuron and thus decrease the excitability of the target cell (i.e., inhibiting it). Both ethanol and benzodiazepines will then reduce CNS activity by potentiating the inhibitory action of GABA when it binds to its receptor.

Ethanol

Ethanol – the alcohol which is found in alcoholic beverages – is a small, water-soluble molecule that is rapidly absorbed by the mucosa of the stomach and duodenum, allowing its maximum blood concentrations to be reached, in general, between 20 minutes and 1 hour after ingestion. The absorption rate can, however, be influenced by several factors, such as the alcohol concentration of the beverage and aeration (e.g., used in sparkling wines). The presence of food in the stomach, especially carbohydrates, slows down gastric emptying and, therefore, slows absorption (Mitchell, Teigen, & Ramchandani, 2014; Paton, 2005).

Ethanol is rapidly and widely distributed in the body, mainly in fat-free body mass (brain, muscles, liver), where it is delivered proportionally to the water content of the tissues. Women may have a higher peak concentration when compared to men after ingesting an equivalent dose due to a lower total body water content, less lean mass, and also differences in first-pass metabolism. Blood alcohol concentration (BAC) also varies with menstrual cycle and concomitant use of other drugs such as antihistamine medications (Paton, 2005).

Since ethanol easily crosses biological membranes and the brain receives a large proportion of total blood flow, the concentration of ethanol in the CNS increases rapidly. More than 90% of the alcohol consumed is metabolized in the liver, and almost all the rest is eliminated in its unchanged form through urine and lungs (this is why it is detected by the breathalyzer). A typical adult can metabolize 7 to 10 g of alcohol per hour, the equivalent of approximately a standard drink (350 mL of beer with 5% alcohol content, 140 mL of wine with 12% of alcohol content, or 40 mL of distilled spirits with 40% alcohol content) (Cederbaum, 2012; NIH, 2020).

The metabolism of ethanol consists of its conversion into acetaldehyde through enzymatic reactions that occur mainly, but not exclusively, in the liver. Alcohol dehydrogenase (ADH) produces acetaldehyde, which in turn is converted to acetate by acetaldehyde dehydrogenase (ALDH), and both reactions result in a second product, reduced nicotinamide adenine dinucleotide whose excess modifies the speed of other metabolic pathways. This metabolic imbalance contributes both to lactic acidosis and hypoglycemia, which often accompany acute alcohol intoxication, and to metabolic disorders resulting from chronic ethanol consumption (Paton, 2005).

The acute changes induced by ethanol are rapid and reversible and cease when concentrations of ethanol, acetaldehyde, and acetate decrease. The concentrations of these metabolites and the time they remain in the body may vary according to

polymorphisms in genes encoding ethanol metabolic enzymes. Genetic variations in these enzymes are then associated with the risk of developing alcohol use disorders (Ramoz & Gorwood, 2018). Specific variations in ADH and ALDH genes, for example, may slow the removal of acetaldehyde, which is a toxic compound. These variations are most frequent in Chinese, Japanese, and Korean and are associated with lower rates of alcoholism in these populations (Edenberg & McClintick, 2018; Li, Zhao, & Gelernter, 2012; Luczak, Glatt, & Wall, 2006).

The second major pathway for alcohol metabolism is the microsomal ethanol oxidizing system (MEOS). This system is also involved in metabolizing other drugs, and when its activity is induced by chronic ethanol consumption, there is an elevated generation of toxic by-products from cytochrome P450 reactions (a MEOS component) since the metabolism of those other substrates is also increased.

Once in the brain, ethanol exerts its effects on different neurotransmitter systems (Costardi et al., 2015), affecting cortical and subcortical areas (such as the striatum) as well as the hippocampus, amygdala, and cerebellum (Harrison et al., 2017). However, its action on $GABA_A$ receptors, which potentiates GABA synapses, is the most studied mechanism of action. Ethanol also slows down CNS activity, reducing glutamate actions on NMDA-type receptors, and it affects adrenergic, cholinergic, serotonergic, opioidergic, and peptidergic neurotransmission (Anderson & Becker, 2017; Förstera, Castro, Moraga-Cid, & Aguayo, 2016; Rao, Bell, Engleman, & Sari, 2015).

Ethanol effects on the CNS are proportional to the BAC, and that is why their manifestations vary from "inhibiting inhibition" (something like "losing the brake") with initial doses to a general depression at high blood concentration that can result in coma and respiratory failure. The ingestion of moderate amounts of ethanol (BAC of 50 mg/dL) can lead to anxiety symptoms and loss of inhibitory control. At 150 mg/dL, signs of moderate drunkenness already appear. From 250 mg/dL on, important intoxication is observed and manifested as motor incoordination, slurred speech, labile humor, and uncontrollable emotionality. Changes in memory and inappropriate behavior may occur, in addition to nausea and vomiting as a result of gastric irritation. In cases of more severe intoxication, the function of the CNS becomes progressively depressed and finally reaches sedation. Blood levels above 350 mg/dL can lead to coma and, as a result of respiratory depression, the safety margin between ethanol concentrations producing anesthetic or fatal effects is difficult to be determined (Masters, Trevor, & Katzung, 2017; Mihic, Koob, Mayfield, & Harris, 2018). It is worth noting that the relationship between BAC and ethanol effects is influenced by previous experience with alcohol and can be quite different in chronic alcoholics due to their tolerance to ethanol (Paton, 2005).

Benzodiazepines

Benzodiazepines (BZD) are a group of more than 20 drugs that act on the CNS and are named after their molecular chemistry. Because of their depressant actions, BZD have wide clinical utility, being prescribed to treat anxiety, insomnia, sleep disorders, epilepsy, and neural induced spasticity. They are also used as muscle relaxants and preoperative drugs due to their amnesic and anxiolytic actions. Among the best-known examples are diazepam (Valium®), midazolam (Dormonid®), clonazepam (Rivotril®), and alprazolam (Frontal®). Despite the scarcity of data, the abuse of BZD in Brazil has been documented and seems to be associated with specific populations, such as women and adolescents (Fegadolli, Varela, & Carlini, 2019; Kapczinski et al., 2001; Opaleye, Ferri, Locatelli, Amato, & Noto, 2014; Souza, Opaleye, & Noto, 2013).

Most BZD are administered orally and are completely absorbed into the gastrointestinal tract without undergoing biotransformation (clorazepate is an exception). The absorption rates of these drugs differ because they depend on several factors, including lipophilicity of the substance. In the case of diazepam, it is rapidly absorbed, reaching its peak concentration in 1 hour after oral administration in adults. Alprazolam, chlordiazepoxide, and lorazepam have intermediate rates of absorption, reaching peak plasma concentration in 2–4 hours after oral administration (Wishart et al., 2006).

BZD and its metabolites bind to proteins and are distributed in the body, accumulating preferably in fat-rich tissues, such as the nervous system and adipose tissue. The speed of different BZD excretion depends on the rate of their metabolism, which is in turn determined by the hepatic microsomal systems. Most of them are extensively metabolized by cytochrome P450 in the liver, but the speed can vary according to specific compounds, and different pathways may be needed. BZD excretion occurs almost entirely through the urine, and some of them, such as diazepam, produce active metabolites that can lengthen the effects (Griffin, Kaye, Bueno, & Kaye, 2013).

Considering the half-life (t1/2), BZD can be grouped as follows:

- Ultrashort-acting agents, remimazolam (t1/2 ~ 1 h*)[1] (Whizar-Lugo, Garnica-Camacho, & Gastelum-Dagnino, 2016).
- Short-acting agents (t1/2 < 6 h), including midazolam, triazolam (t1/2 ~ 2 h), and eszopiclone (t1/2 ~ 5–6 h).
- Intermediate action agents (t1/2 ~ 6–24 h), including estazolam and temazepam.
- Long-acting agents (t1/2 > 24 h), including flurazepam, diazepam, and quazepam.

Like ethanol, BZD have a high-affinity binding site on $GABA_A$ receptors, increasing the binding and action of GABA on its receptor. The $GABA_A$ receptor is

[1] Because it is a new drug, several studies are still being conducted using remimazolam, whose half-life depends on several factors but is much shorter than that of midazolam, for example (Rex et al., 2018).

a pentameric complex, whose glycoproteic subunits may vary, and, in addition to the GABA binding site, it has a binding pocket for BZD. The heterogeneity of $GABA_A$ receptors resulting from the combinations of different subunits generates, at least in part, the pharmacological diversity of BZD effects (Mihic, Mayfield, & Harris, 2018). Different effects profiles will also be determined by the affinity of BZD for receptors that are more or less concentrated in specific regions of the CNS. Those receptors concentrated in the cortex, thalamus, and cerebellum, for example, will mediate sedation, anterograde amnesia, and anticonvulsant effects of those drugs that bind to them. Meanwhile, receptors that mediate anxiolytic and myorelaxant effects are located in the limbic system, motor neurons, and dorsal horn of the spinal cord (Griffin et al., 2013).

Regarding sedative and hypnotic effects of BZD, increasing doses of these drugs lead to sedation that progresses to hypnosis and to stupor. The abuse of BZD alone will unlikely lead to death or some serious pathology. However, these drugs are often used concomitantly with ethanol or other substances (Schmitz, 2016), and the combination of alcohol and BZD may cause respiratory failure and death due to the synergistic effect of these drugs.

High doses of BZD can cause daytime sleepiness, dizziness, increased reaction time, deficit of motor coordination, impaired mental and motor functions, and confusion (Mihic, Mayfield, & Harris, 2018). Therefore, they can impair activities that require attention and quick reactions when used without prescription.

People who use high doses of BZD usually need hospital detoxification. In general, the abuse of BZD is part of a combined addiction that often involves alcohol, opioids, and cocaine (Mihic, Mayfield, & Harris, 2018). As it was said before, when alcohol and BZD are used together, they have stronger depressant effects due to the synergistic action of their combination.

Hallucinogens

Hallucinogenic drugs are so-called because they qualitatively alter (disturb) the functioning of the CNS, modifying the way we perceive reality, our thoughts, and emotions. Throughout the twentieth century, these substances were called psychotomimetic and hallucinogenic because of their psychotic and hallucinogen effects. However, these terms have been criticized for carrying strong social stigma and because they refer to the less frequent symptoms caused by the usual doses. Nowadays, these drugs are commonly called psychedelics, once they bring mind-manifesting capability and/or entheogens, because they favor spiritual experiences. These terms have recently been applied to *classic psychedelics* with stronger effects on altering consciousness, such as LSD, DMT (component of the ayahuasca brew), psilocybin (found in magic mushrooms such as *Psilocybe cubensis)*, and mescaline (present in cacti such as Peyote and San Pedro) (Nichols, 2016). Other hallucinogenic substances have been called *atypical psychedelics* and include marijuana, MDMA, dissociative drugs such as ketamine and phencyclidine, muscarine (present

in the *Amanita muscaria* mushroom), ibogaine, and salvinorin (Calvey & Howells, 2018).

Because their molecules resemble serotonin, classic psychedelics activate 5-HT_2 serotonergic receptors (5-HT_{2A} subtype has been the most cited) causing psychedelic effects. The brainstem raphe nuclei are the main source of serotonin in the CNS, and they send neuronal projections to the different brain regions, such as the thalamus, cerebral cortex (prefrontal, visual, somatosensory association), amygdala, hippocampus, cerebellum, and others. This system is involved in sensory perception, mood, and emotional regulation and in cognitive and motor functions. Unlike other drugs of abuse, *classic psychedelics* do not directly activate the reward dopamine system (Nichols, 2016).

Having in mind the particularities of each of those drugs, the alteration of consciousness involves important changes in sensory perception (seeing kaleidoscopic images, distortion of auditory stimuli), synesthesia (overlapping of sensory modalities such as hearing colors), mood alterations, thinking, emotional processing, and memories. These alterations result in a different perception of reality, including the notion of self, and can both cause confusion and favor insights. Anxiety and paranoia are common effects, and psychotic symptoms (usually transient) may appear, all of them under modulation by the context of use (the environment and interaction with other people, for example). Although they are known as "heavy drugs" when considering the risks they offer, there is little evidence that *classic psychedelics* – LSD, psilocybin, mescaline, and ayahuasca/DMT – are addictive because they are not compulsively used and do not induce withdrawal syndrome (Canal & Murnane, 2016; Rucker, Iliff, & Nutt, 2018). Moreover, psychedelic drugs have gained attention in recent years due to their therapeutic potential. Stigmatized substances such as marijuana and its components (THC and cannabidiol), MDMA, ketamine, psilocybin, and ibogaine, have been the target of research to treat epilepsy, chronic pain, post-traumatic stress disorder, depression, and drug addiction, among other medical and psychiatric conditions (Nutt, Erritzoe, & Carhart-Harris, 2020).

Atypical psychedelics act mainly in other neurotransmission systems. As an example, the dissociative substance ketamine, known as special k and used for depression, inactivates NMDA-type glutamate receptors. Plant-derived substances salvinorin A and ibogaine, which are found in *Salvia divinorum* and the African plant Iboga, respectively, act on multiple targets, including opioid receptors (Litjens & Brunt, 2016; Sellers, Romach, & Leiderman, 2018). Marijuana and MDMA will be addressed in more detail in the sequence.

Marijuana

Marijuana or *cannabis* is a plant that has more than 100 phytocannabinoids, with delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) being the best known and studied. While THC induces the psychoactive effects following *cannabis* use, CBD has the greatest therapeutic potential, and of particular interest is the fact it has

no reinforcing effects. Medical properties of CBD include analgesia, neuroprotection, anticonvulsant, antiemetic, and antispasmodic effects (Lucas, Galettis, & Schneider, 2018). Because of varying species, strains, and cultivation methods, different proportions and concentrations of THC and CBD may be found in the drug, therefore causing different effect profiles.

Although c*annabis* is usually smoked or inhaled through vaporizers, it can also be eaten. The pharmacokinetic profile is similar when it is smoked or inhaled, and THC and CBD are rapidly absorbed by the lungs. Both compounds are primarily distributed to vascularized tissues, such as the brain, which is responsible for the reinforcing properties of marijuana and its abuse and addictive potential. Because of its lipophilicity, most THC is combined to plasma proteins in order to be distributed throughout the body. When smoked, both cannabinoids reach their peak plasma concentration between 3 and 10 minutes, allowing the user to regulate its consumption according to the effects. When *cannabis* is orally consumed, the plasma peak of THC and CBD is much longer (around 120 minutes), and their bioavailability is shorter when compared to smoking (first pass metabolism; Grotenhermen, 2003).

The metabolism of THC occurs predominantly in the liver, via cytochrome P450, which produces the active metabolite 11-hydroxy-THC and later 11-nor-9-carboxi-THC, which is inactive. Extrahepatic metabolism occurs in the small intestine and brain, also by cytochrome P450, and excretion occurs in feces and urine. Due to its lipid structure, THC can accumulate in the adipose tissue of chronic users and can be gradually released into the bloodstream for several weeks after consumption (Amin & Ali, 2019). For similar reasons, THC crosses the placenta and is available in breast milk, and its use during pregnancy and breastfeeding is discouraged, since changes have been shown in the offspring of women who used *cannabis* during pregnancy and also because animal models provides clear evidence of developmental abnormalities (Roncero et al., 2020). The metabolism of CBD is similar to THC, since it depends on hepatic cytochrome P450 and generates metabolites that are excreted in feces and urine.

Reward system stimulation by acute THC use is controversial in human neuroimaging studies, which point to milder effect of marijuana when compared to stimulant drugs (Bloomfield, Ashok, Volkow, & Howes, 2016). THC is a partial agonist of cannabinoid type 1 and 2 receptors (CB1 and CB2) with its psychoactive and pain regulatory actions been mediated by CB1. CBD acts on the same receptors, although with less affinity for CB1, and acts as a negative allosteric modulator reducing THC effects on this receptor (Lucas et al., 2018). In other words, the presence of CBD in marijuana counterbalances some effects of THC, and it has been proposed that higher concentrations of CBD may offset some of the acute and long-term side effects of THC, such as anxiety, psychotic symptoms, potential for abuse, and cognitive impairment (Bloomfield et al., 2019; Ferland & Hurd, 2020). CB1 are inhibitory presynaptic receptors and are present mainly in CNS areas involved with executive and cognitive functions, emotional and appetite regulation, reward detection, and motor behaviors, such as the prefrontal cortex, hippocampus, amygdala, hypothalamus, nucleus accumbens, basal ganglia, and cerebellum. When a presynaptic neuron is hyperactivated, the postsynaptic neuron responds to the

overstimulation releasing endocannabinoids that act retrogradely on CB1, thereby reducing the activity of the presynaptic cell. CB1 is found in glutamatergic and GABAergic neurons present in the different brain regions, and therefore the endocannabinoid system finely regulates the excitatory/inhibitory balance of a large part of the brain. CB2 receptors are mainly found in the peripheral tissues and immune cells, although they are also present in neurons but in small amounts.

The common acute effects of marijuana and its derivatives are red eyes, dry mouth, increased appetite, and enhanced libido. In addition, there are changes in time perception, thoughts, emotional processing, impaired attention, and memory consolidation, besides confusion. Marijuana alters the sense of reality and can cause anxiety and paranoia and induce psychotic symptoms in healthy people. These effects are usually transient and more frequent in those with schizoid personality traits. Using marijuana is a risk factor for people who are predisposed to schizophrenia, since the drug can trigger the onset of the disorder (Bloomfield et al., 2019). Chronic use can cause addiction, attention deficits, as well as learning and memory impairments, which seem to be reversible within a few months of abstinence (Broyd, Van Hell, Beale, Yücel, & Solowij, 2016). Cannabis use among adolescents is inadvisable because the prefrontal cortex, which is involved in risk assessment and decision-making, is still maturing, and early use is associated with the development of *cannabis* use disorders (Ferland & Hurd, 2020). Marijuana potentiates the depressant effects of sedative hypnotics, and concomitant alcohol use increases plasma THC levels and perceived subjective symptoms (Lucas et al., 2018).

MDMA

Like amphetamines, MDMA is a β-phenylethylamine. It was first synthesized in 1912 and became popular at electronic music festivals from the 1980s (Karch, 2011). Its therapeutic potential in the treatment of post-traumatic stress disorder (PTSD) has been studied in clinical trials, where it was combined with psychotherapy in a controlled setting. The MDMA-assisted psychotherapy is expected to be regulated by the Food and Drug Administration (FDA) in the United States by 2022 (Thal & Lommen, 2018).

MDMA is commonly called ecstasy or molly. It is usually taken as colored tablets or capsules with different patterns (like brands and logos) and can also be found in the form of crystal, which is usually left on the mouth or diluted in water. Some people prefer to snort it and rarely inject it. It is important to keep in mind that is not rare to find other substances instead of MDMA and that this is true to every drug. Sometimes there is no MDMA on the ecstasy pill, or it has adulterants such as methylenedioxyethylamphetamine (MDEA) and methylenedioxyamphetamine (MDA), amphetamines, methamphetamine, ephedrine, and pseudoephedrine, which can be even more dangerous than MDMA itself.

After absorption into the gastrointestinal tract, MDMA effects start to be noticed between 20 and 60 minutes, and the peak plasma concentration is reached in

approximately 2 hours. It is metabolized mainly in the liver by isoenzymes of P450 cytochrome (Kalant, 2001), and the catechol-O-methyltransferase (COMT) breaks down the by-products of this drug. MDMA is metabolized into methylenedioxyamphetamine (MDA), which in turn is broken down into dihydroxyamphetamine (HHA). In parallel, MDMA can also be converted to dihydroxymethamphetamine (HHMA), and this turns into hydroxymethoxymethamphetamine (HMMA). The by-products HHA and HMMA can finally be biotransformed into hydroxymethoxyamphetamine (HMA; Xavier et al., 2008). MDMA is a substrate and, at the same time, an inhibitor of an isoenzyme of cytochrome P450, even at relatively low doses. In other words, the metabolism of MDMA at higher doses is slower, and drug peaks are more rapidly reached in the brain and blood (Papaseit, Torrens, Pérez-Mañá, Muga, & Farré, 2018). As its half-life is approximately 8–9 hours, the excretion of 95% of the substance will only be reached about 40 hours after its consumption. This may be an explanation for the adverse effects that remain within 2 days of use (Kalant, 2001). In addition, since the metabolite MDA is also psychoactive, it causes the effects to remain longer than the MDMA itself in the body. The excretion is mainly by urine, and the metabolites may undergo glucuronidation and sulfation (Xavier et al., 2008).

MDMA is considered a psychedelic amphetamine because it has stimulating and psychedelic (hallucinogenic) effects. It acts by increasing the availability of serotonin, noradrenaline and, to a lesser extent, dopamine, which resembles the stimulant effects of amphetamines, while it also activates 5-HT_{2A} receptors like classical psychedelics, inducing subtle visual and auditory distortions. The increase in serotonin, which is the main responsible for the effects of MDMA, occurs by two distinct mechanisms: (1) by increasing serotonin release and (2) by blocking serotonin transporters, inhibiting its reuptake. The increase in noradrenaline and dopamine occurs due to similar mechanisms, but dopamine is released in smaller amounts (White, 2014). Studies indicate that depending on the MDMA isomer, subjective effects may be more stimulant-like or more related to psychedelics (Kalant, 2001).

Doses usually range from 50 to 150 mg (Kalant, 2001). The desired subjective effects commonly include relaxation or higher energy and agitation; positive emotions such as euphoria, well-being, and pleasure; increased propensity to touch, not necessarily sexual; enhanced libido; and prosocial behaviors, such as increased levels of empathy, a sense of closeness, and openness to talk with other people. These prosocial effects seem to be mediated by increased oxytocin hormone release, while increased energy and resistance to fatigue are related to an increase in circulating cortisol, which is released in stressful situations (White, 2014). Studies indicate that MDMA reduces the feeling of fear and anxiety, which is consistent with reduced activity in the amygdala (Papaseit et al., 2018). The reduction in fear/anxiety levels combined with prosocial behaviors has been proposed to explain the effects of using MDMA-assisted psychotherapy to treat PTSD, in order to favor the bond with the therapist and the confrontation of trauma, allowing a rereading of the experience that caused it (Thal & Lommen, 2018).

The sympathomimetic effect of MDMA produces quite dangerous physiological effects including tachycardia, increased blood pressure, and a significant increment

in body temperature (hyperthermia/hyperpyrexia). Along with hyperthermia, the electrolyte imbalance due to the drop in blood sodium levels (hyponatremia) is another risk factor related with this drug, which may be worsened by excessive water intake and urinary retention that are associated with the context in which MDMA is used. These effects are more pronounced in women, when high doses are consumed, and when it is combined with other substances or intense physical activity, such as in parties. In extreme cases, complications can lead to cerebral edema, seizures, renal and hepatic failure, as well as rhabdomyolysis, leading to death (Papaseit et al., 2018).

Other milder but unwanted effects such as bruxism and trismus – due to jaw clenching – muscle stiffness, loss of appetite, and insomnia are common. The adverse effects on mood emerging days after the use of MDMA, such as depressed mood, result mainly from neuronal serotonin depletion and inhibition of its synthetic enzyme, tryptophan hydroxylase, for a prolonged time (White, 2014). Chronic MDMA-induced neurotoxicity has been documented, and it points to long-term losses in serotonergic neurotransmission in different parts of the brain, especially cortical regions (Benningfield & Cowan, 2013).

Final Considerations

This chapter has shown that drugs of abuse act in various brain neurotransmission systems, thereby altering perception, emotion, cognition, and behavior. Pharmacokinetic and pharmacodynamic profiles of each drug are determinant in understanding how body and substance interact, whether in recreational or therapeutic use. Although drugs of abuse, particularly illicit ones, are sometimes exclusively related to individual and social harm, we cannot ignore the therapeutic potential of some of those substances. If on the one hand their chronic consumption can lead to substance use disorders in vulnerable/susceptible individuals, on the other hand they can help treating psychiatric disorders or diseases such as in the case of benzodiazepines, amphetamines, MDMA, and cannabinoids. A question then arises: are they drugs of abuse or medication? More than the isolated pharmacological properties, the pattern of use and the reasoning toward rational/therapeutic use, based on scientific evidence, seem to make a better distinction between these concepts.

In this circumstance, it may be interesting for professionals to be aware of some particularities associated to some of those drugs, such as the fact that cocaine and crack overstimulate the reward system, which is associated with the addictive potential of these drugs, while the classic psychedelics do not directly activate this system and do not generate addiction. In this context, detailed information has been provided regarding psychedelic drugs for two reasons: (1) they have been receiving increasing attention from users, professionals, and researchers; and (2) the available literature on psychedelics is more scarce compared to stimulants and depressants. Thus, we have tried to offer the least necessary, so the reader will be able to keep

reading this book and to build his or her own reasoning and positioning in relation to a topic of great social relevance.

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