Pathophysiology, Molecular Interaction Mechanism, Metabolism, Pharmacotherapy and New Perspectives in the Pharmacological Treatment of Chemical Dependence on the Main Illicit Drugs Consumed in the World

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Abstract Since the early days of mankind, humans have used chemicals from a wide range of origins for psychic changes, whether for religious, occupational or recreational purposes. Among the most widely used illicit substances on the planet, according to the United Nations Office on Drugs and Crime (UNODC), are Cannabis sativa, amphetamines, cocaine, opiates, ecstasy and heroin. These are responsible for the dependence of millions of people. Thus, this review is about chemical dependence with a focus on the mechanism of molecular interaction, metabolism and its consequent symptomatology manifested during drug withdrawal, as well as the current pharmacological treatments used during its manifestation and the search to increase pharmacotherapeutic arsenal against this pathology.

Keywords Amphetamine · *Cannabis sativa* · Lysergic Acid Diethylamide · Cocaine · Chemical dependency · Withdrawal syndrome

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1 Introduction

Since the dawn of mankind, chemicals that alter behavior and cognition were already employed for the most diverse purposes, from recreational use to religious rituals [1]. Many of these substances today are called 'drugs of abuse' which are those that, when used legally or illegally, cause psychological, mental, emotional or social damages [2].

The most commonly used drugs of abuse in the world are cocaine, marijuana, amphetamines, which has its most expressive agent Ecstasy (methylenedioxymethamphetamine) and hallucinogenic substances such as lysergic acid diethylamide (LSD) [3]. Due to the increased use of such substances, in the last 50 years there has been a significant advance in the understanding of the processes by which drug abuse causes dependence, especially with respect to its biomolecular targets [4]. Illicit use of these substances has been increasing in underdeveloped countries, data from the United Nations Office on Drugs and Crime (UNODC) reports large-scale apprehensions of cocaine, *Cannabis sativa*, amphetamines and other proscribed substances worldwide, among which the most commonly found is marijuana. Still according to UNODC data, there are around 200 million users of some drug abuse worldwide [5].

Misuse and consequent chemical dependence are complex disorders regulated by a wide range of biochemical interaction networks and changes in gene expression in the mesolimbic dopaminergic system [6]. Understanding drug-induced changes in molecular and cellular interactions processes help to reveal a better understanding of these specific behavioral changes in chemical dependence [7]. This review introduces the pathophysiology, molecular drug interaction mechanisms and their reference biological targets, the drugs used and the perspectives in the treatments in case of chemical dependence of the main illicit drugs currently used.

2 Method

A bibliographical review was carried out in several electronic databases such as PubMed, Scielo, Web of Science, Science Direct and Nature, in order to investigate the publications that refer to the topic of *Cannabis,* LSD, Amphetamines and Cocaine. The descriptors used to capture the relevant articles were: *marijuana*, *cannabis*, Lysergic Acid Diethylamide, cocaine, Physiopathology, symptomatology, chemical dependency, treatment. Among the scientific works used in this research, more than 80% were published in the period from 2013 to 2019.

3 *Cannabis sativa*

3.1 Cannabis

The *Cannabis sativa* plant, commonly known as marijuana belongs to the Moráceas family, known as "hemp" in India, and grows spontaneously in regions of tropical and temperate climate [8]. The use of Cannabis is predominantly smoked and can also be found in the form of resin in the form of plaques or rods, called hashish. The Leaf can be mixed with crack, or as skunk—a polymorphic form of marijuana [9] that is cultivated in a special way and with psychotropic power 7 to 25 times stronger than common marijuana, with content of the main psychoactive substance, Δ [9]-Tetrahydrocannabinol (Δ [9]-THC), estimated at 0.2–0.3% of the plant [10]. Figure 1 represents the chemical structure of Δ [9]-THC.

3.1.1 Action Mechanism of Cannabis

Two cannabinoid receptor subtypes, CB1 and CB2, have been identified and are responsible for many biochemical and pharmacological effects produced by most cannabinoid compounds [11]. Psychotropic activity is caused by interaction with the Δ [9]-THC (Fig. 1) and the cannabinoid receptor CB1 [12], being the activation trigger for this process of conformational changes of this receptor, the interaction of the cannabinoid with the amino acid residue Ser383 and its surroundings (Fig. 2). Despite the differences between cannabinoid receptor CB1 and CB2, most cannabinoid compounds interact similarly in the presence of both receptors [13].

With the conformational change of the cannabinoid receptor CB1 a series of reactions occurs, including inhibition of Adenylate Cyclase, which decreases the production of cAMP (cellular activities depend on the enzyme cyclic adenosine monophosphate—cAMP); opening of the potassium channels (K^+), reduction of signal transmission and closure of calcium channels (Ca^+ [2]), leading to a decrease

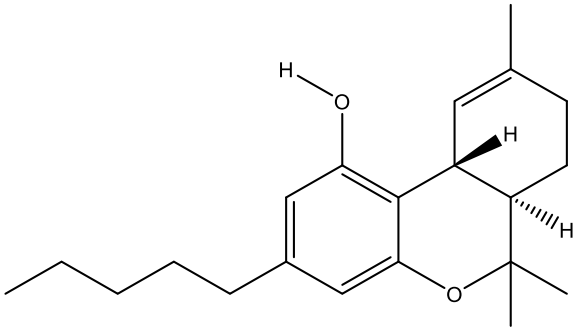


Fig. 1 Structural formula of Δ [9]-THC

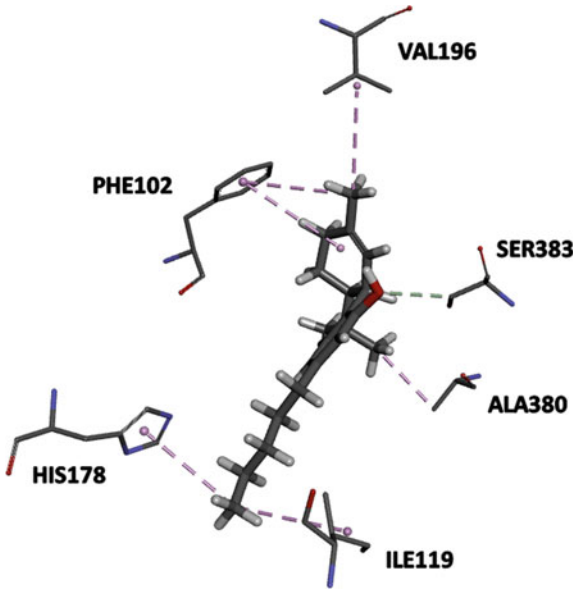


Fig. 2 Amino acid residues of the cannabinoid receptor CB1 interacting with Δ [9]-THC

in the release of neurotransmitters. Whose decreased concentration is related to the psychotropic effects of *C. sativa* [14].

The location of cannabinoid receptor CB1 in the central nervous system (CNS) is directly associated with the behavioral effects produced by cannabinoids. The higher density of these receptors is found in (a) cells of the basal ganglia, involved in the coordination movements of the body [15], (b) in the cerebellum, a region responsible for the coordination of body movements and cognition [16], (c) hippocampus, responsible for learning, memory, fear, and response to stress and (d) cerebral cortex, responsible for cognitive functions [17]. Regions with lower concentrations of cannabinoid receptor CB1 are also involved with reactions derived from the use of *C. sativa*, and these are (a) region of the hypothalamus, related to temperature regulation, hydroelectrolytic balance, and reproductive function, (b) Amygdala responsible for emotional response, (c) column vertebral body responsible for peripheral sensation and (d) brain stem responsible for sleep regulation and motor control [15, 16].

3.1.2 Metabolism of *Cannabis Sativa*

Δ [9]-THC is a very lipophilic molecule and, not by chance, easily crosses the blood–brain barrier (BBB). In addition, it is rapidly distributed to more vascularized organs and tissues, such as the lungs, kidneys, liver, heart salivary glands, pituitary, and thyroid [17]. The decrease in blood pressure of the molecule is mainly due to its first-pass metabolism, although its main metabolite, 11-OH-THC, also has psychoactive power, high liposolubility and acts promptly in the CNS [18].

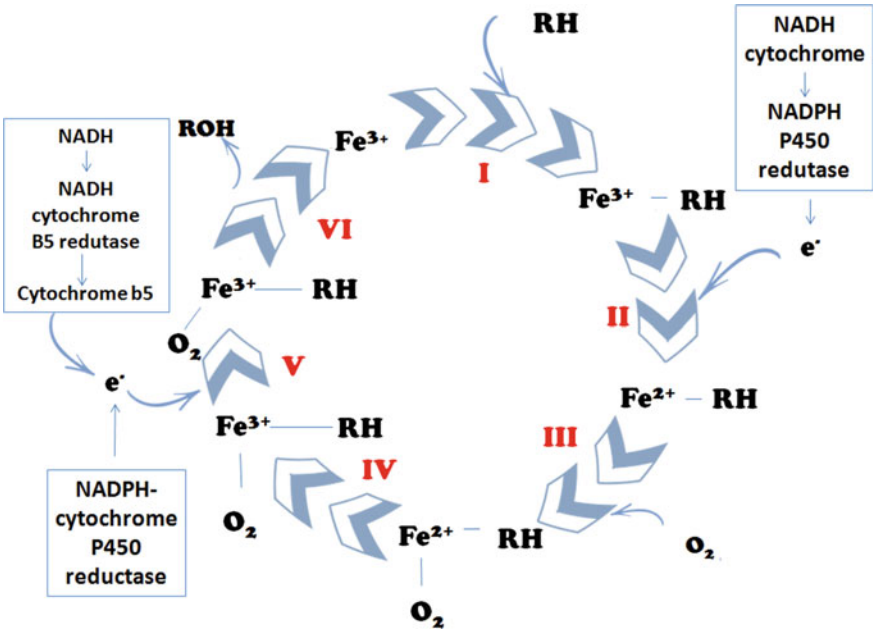


Fig. 3 Catalytic cycle of cytochrome P450. RH represents the substrate of the drug and ROH is the corresponding hydroxylate metabolite [20]

Δ [9]-THC is rapidly converted to 11-hydroxy-THC (11-OH-THC) in the liver by microsomal hydroxylation, mainly by the isoenzymes CYP2C9, CYP2C19 and CYP2D63 [19]. These enzymes belong to the cytochrome P450 family and are responsible for the aromatic hydroxylation that occurs in the conversion of the compounds mentioned above. This reaction is very common for drugs and xenobiotics that have an aromatic ring, and its mechanism is shown (Fig. 3). Cytochrome has a prosthetic group with iron protoporphyrin (Fig. 4), which is extremely important for the electronic transfer system [20].

The Δ [9]-THC substrate is oxidized by the isoenzymes according to the mechanism of action of the cytochrome P450, below is a schematic of the chemical reaction in a simplified way (Fig. 5).

In Fig. 6, the hydroxylation mechanism catalyzed by cytochrome P450 is shown. A radical reaction is observed, and the compound is released after the reaction with water. This step can be repeated, yielding the compound 11-hydroxy-THC (11-OH-THC) [21].

After step 6 present in the catalytic cycle (Fig. 4), the 11-hydroxy-THC (11-OH-THC) can be oxidized again. It would return to the cycle and after all reactions would convert to the 11-N-9-carboxy-9-THC (THC-COOH) (Fig. 7) [23, 24].

Thereafter, cytochrome P450 is involved in oxidation where the inactive metabolite 11 -Nor-9-carboxy-9-THC (THC-COOH) is excreted in conjunction with

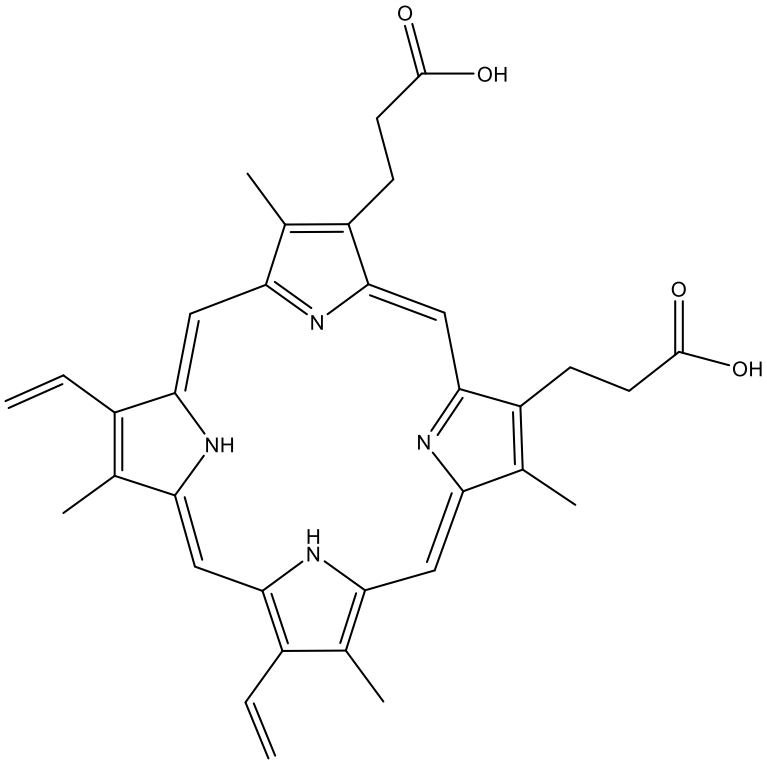


Fig. 4 Structure of iron protoporphyrin IX, the prosthetic group of cytochrome P450 [20]

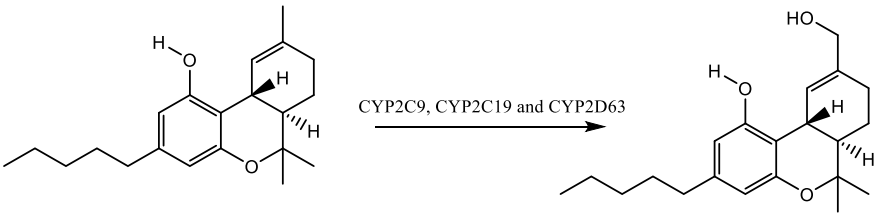


Fig. 5 Aromatic hydroxylation reaction of Δ 9 -THC being converted to 11-hydroxy-THC (11-OH-THC) by the isoenzymes CYP2C9, CYP2C19 and CYP2D63

glucuronic acid [25]. The complete reaction of Δ [9]-THC metabolism is shown below (Fig. 8):

About 100 THC metabolites were identified. In addition to the liver, there are other organs capable of metabolizing cannabinoids, such as the lungs, heart, and intestines, although to a lesser extent (Fig. 9) [26].

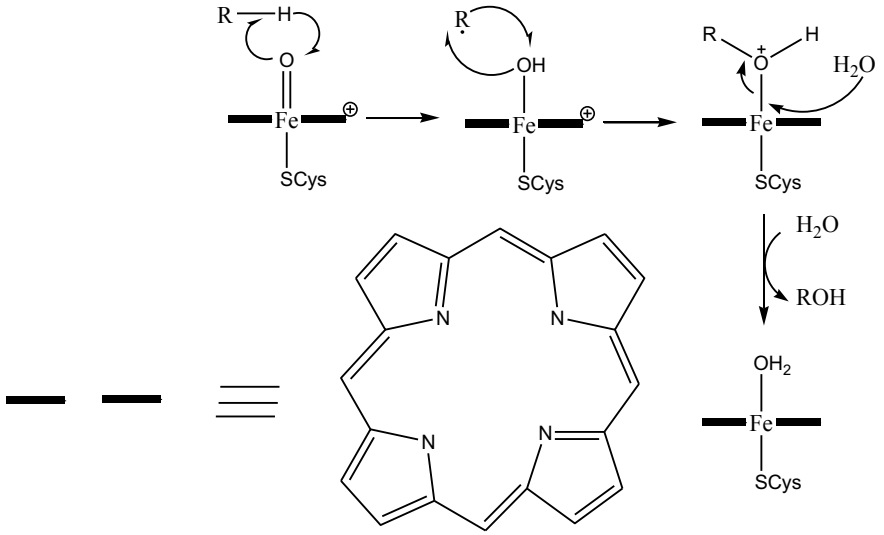


Fig. 6 Cytochrome P450 catalyzed hydroxylation mechanism [22]

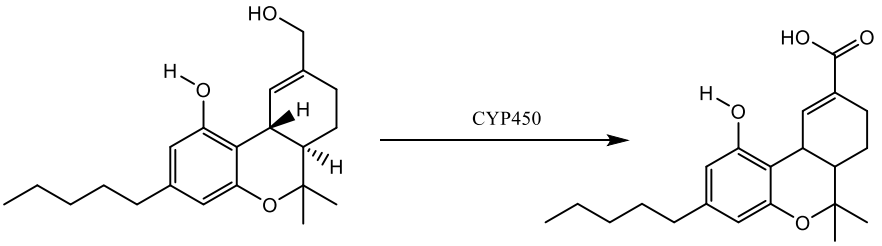


Fig. 7. 11-Hydroxy-THC (11-OH-THC) oxidation reaction being converted to 11-Nor-9-carboxy-THC (THC-COOH) by the cytochrome P450

3.2 Lysergic Acid Diethylamide (LSD)

Lysergic Acid Diethylamide (LSD) (Fig. 10) was first synthetized from ergot in 1938 and banned by FDA in 1966. At the beginning of their popularization the products contained 0.25 LSD per sugar cube or dose, currently the circulating products contain about 0.4–0.06 mg per dose [27]. Although also found in liquid form (drops), capsules, tablets, gelatin cubes or microdots, is mainly consumed orally in the form of illustrated seals (blotters) [28]. Variations in standard consumption include: swallowed by themselves, wrapped in cigarette paper, mixed with a drink, impregnated with a candy, a biscuit or a drop of sugar. It can also be left on or under the tongue or between the cheek and gum. Other more marginal routes of administration are known: in the smoke, injected or instilled in the eye in liquid form [29].

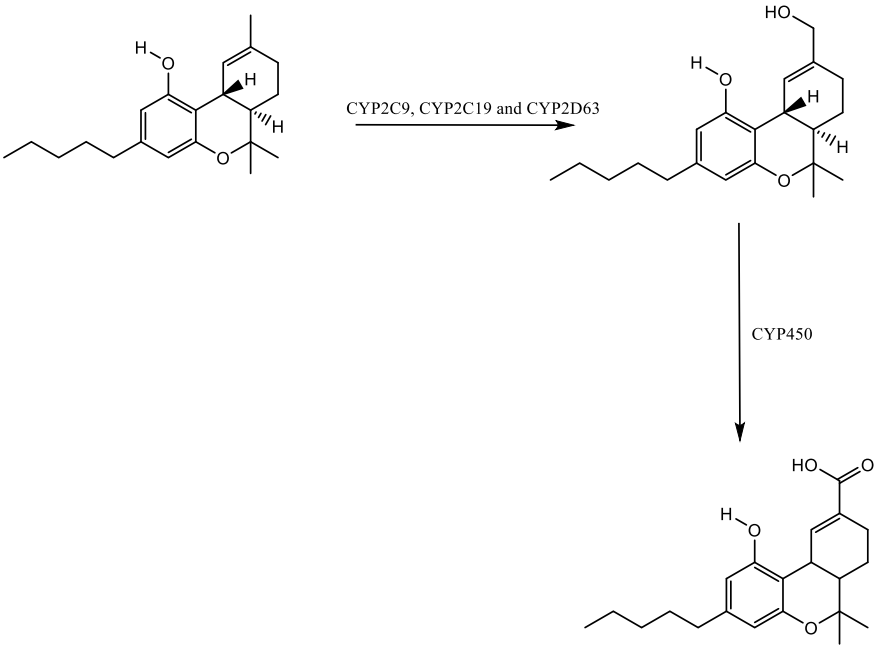


Fig. 8 Complete reaction of Δ [9]-THC metabolism and subsequent formations of 11-hydroxy-THC (11-OH-THC) and 11-N-9-carboxy-THC (THC-COOH)

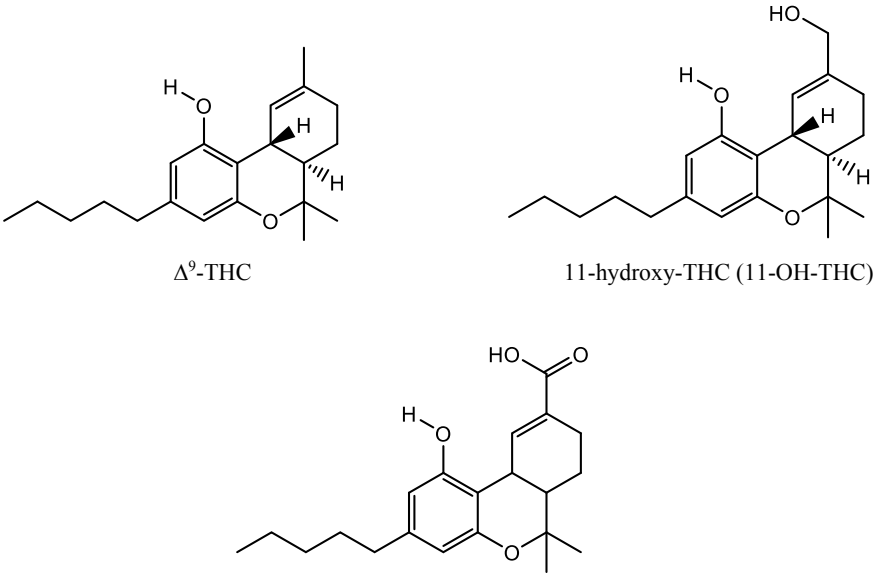


Fig. 9 Δ [9]—THC and some of its major metabolites

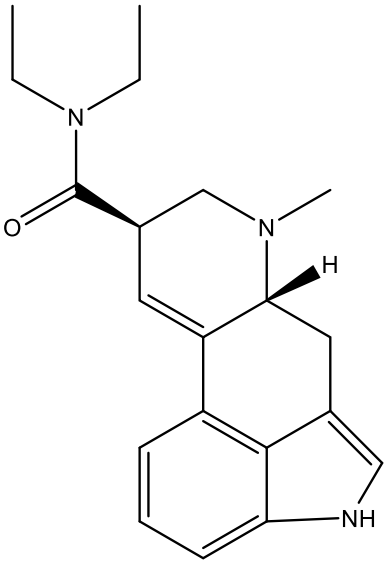


Fig. 10 Structural formula of lysergic acid diethylamide

3.2.1 Action Mechanism of LSD

The hallucinogenic and psychotic effects of LSD are related to the interaction of this drug in the serotoninergic, dopaminergic and adrenergic systems.

The Serotonergic System

Serotonin syndrome is characterized by hyperstimulation of postsynaptic serotonergic receptors, presenting symptoms frequently associated with the use of LSD such as tremors, hyperreflexia, muscle spasms, tachycardia, hyperthermia, and delirium [30, 31].

LSD activates different signaling cascades of serotonin (5-HT) receptors, and the interaction with the 5-HT2A receptor, coupled to G protein, is the main factor responsible for the hallucinogenic action related to the serotoninergic receptor [32]. At this receptor, LSD acts as an agonist increasing the rate in the brain or preventing abstinence from 5-HT. Consequently, when 5-HT binds to 5-HT2C receptors, a strong response of inositol triphosphate occurs, a secondary messenger involved in the transduction of the biological signal with or without increased intracellular levels and phosphorylation of calcium [13].

Dopaminergic System

LSD can directly activate the two major categories of dopaminergic receptor subtypes, D1 and D2 [33]. It is known that the ventral tegmental area receives afferent serotonergic neurons from the raphe nucleus, so that activation of 5-HT2A may affect the local dendritic release of dopamine in the mesolimbic and mesocortical pathways [34]. The release of dopamine into the cortical and limbic structures characterizes the first phase (with an estimated duration of 60 min in rats) of the effects of LSD. The second phase (approximately 60–100 min occurs in rats after LSD administration) is mediated by stimulation of D 2 receptors, which is also consistent with the idea that excess dopaminergic activity may be the cause of drug-induced psychosis [35].

Adrenergic System

LSD has little affinity for α2 adrenergic receptors and may also increase glutamatergic transmission in the cortex by the presynaptic activation of the 5-HT2A receptor and subsequent activation of α-amino-3-hydroxy-5-methyl-isoxazole (AMPA) receptors. This fact contributes to the rapid onset of the tolerance effect on the mental responsiveness to the use of LSD in humans (around 4 days) [36].

3.2.2 Docking

The simulation of the coupling of the LSD structure bound to one of the molecular targets allowed to clarify the relation of the chemical structure of this drug with its activity, kinetics, and signaling. Although lysergamides are relatively rigid, they are found to have conformational flexibility [37] generating stereochemical differences, mainly related to the amide substitution of these that adopt a restricted conformation in the binding site, a fact that has influence in the hallucinogenic activity, so that these conformations are crucial for the hallucinogenic effects of LSD [38].

The positioning and interactions of diethylamide contribute to the long residence time of LSD in 5-HT2B and 5-HT2A targets [32]. In the active site of these targets, the ergoline system of LSD forms a narrow slit lined with hydrophobic side chains that comprise aromatic interactions with the phenylalanines of residues Phe340 and Phe341 and bonds of H with residue Gly221. In relation to the diethylamide group of LSD, one ethyl group forms non-polar interactions with residues Leu132 and Trp131, while the other group extends to Leu362 acetate (Fig. 11) [39].

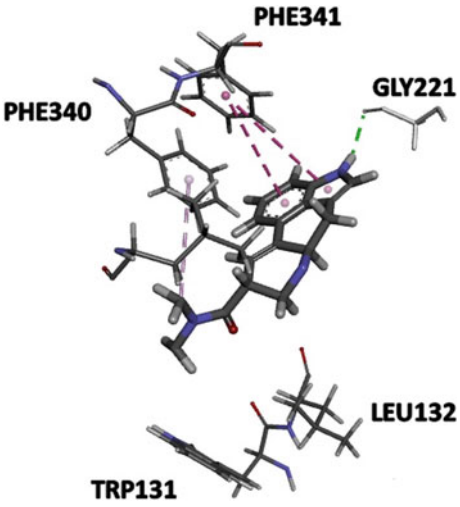


Fig. 11 Residues of Serotonin Receptor amino acid interacting with lysergic acid diethylamide

3.2.3 Metabolism of LSD

At the beginning of this century, studies indicated that LSD metabolism would be converted into phase I biotransformation into hepatic microsomes and human hepatocytes for 2-oxo-3-hydroxysilergic acid diethylamide (OH-LSD) and N-desmethyl—LSD) [40] metabolite present in human urine at concentrations 16–43 times greater than LSD [18].

The LSD is oxidized in OH-LSD by the cytochrome P450 according to the scheme shown in Fig. 12.

Another reaction that occurs also in LSD is dealkylation, which occurs in drugs containing secondary or tertiary amines, an alkoxy or substituted alkyl thiol group. The lost alkyl group becomes its corresponding aldehyde. In the case of dealkylation occurring in LSD for conversion to nor-LSD N-Desmethyl-LSD, the corresponding aldehyde is the methanal [20].

The reaction occurs in two steps, the first being hydroxylation in the methyl group bound to the nitrogen, forming an unstable intermediate. The second step is the decomposition of this intermediate, shown in the figures below:

Due to the extensive metabolism of LSD, research is advancing in the discovery of new metabolites, and the most recent ones conclude that myeloformidases (MPO), abundantly expressed in neutrophils and monocytes and also in neurons and microglia, may also be involved in the metabolism of this substance. This pathway of formation of metabolites would occur concomitantly with the cytochrome P450 system giving rise to another important metabolite, N, N-diethyl-7-formamido-4-methyl-6-oxo-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carboxamide (FOMBK), which is an open indolic ring compound. Hydrolysis of the FOMBK metabolite leads

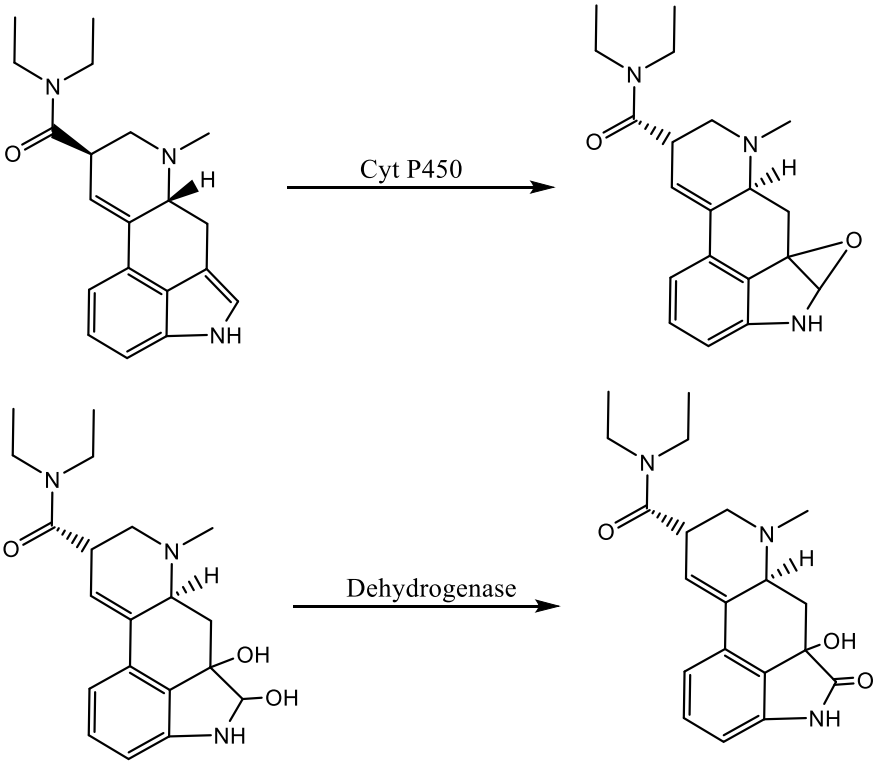


Fig. 12 LSD metabolic pathway and 2-oxo-3-hydroxy lysergic acid [40]

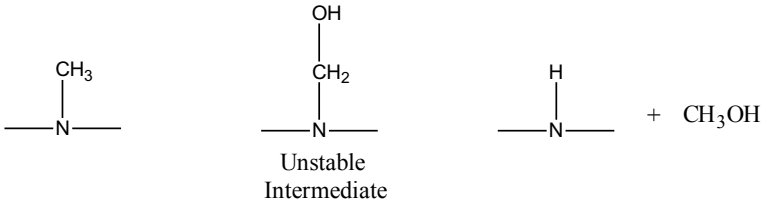


Fig. 13 Formation of the unstable intermediate in the dealkylation step [20]

to 7-amino-N, N-diethyl-4-methyl-6-oxo-2,3,4,4a, 5,6-hexahydrobenzo [quinoline-2-carboxamide (AOMBK) [41]. The formation of these two products is shown in Fig. 17.

The above scheme first shows the formation of a radical, followed by the reaction with an oxygen molecule. The loss of an oxygen will form the compound O–H-LSD while another alternative would be the formation of an unstable intermediate, which will give rise to OH-LSD and FOMBK. With the exit of a molecule of H_2CO, AOMBK is formed (Fig. 18).

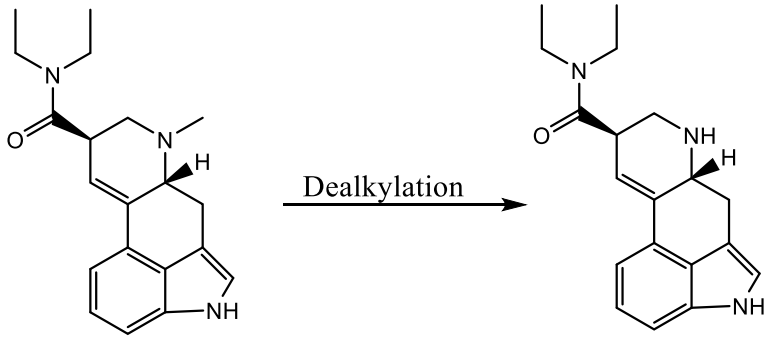


Fig. 14 LSD dealkylation reaction in nor-LSD N-Desmethyl-LSD

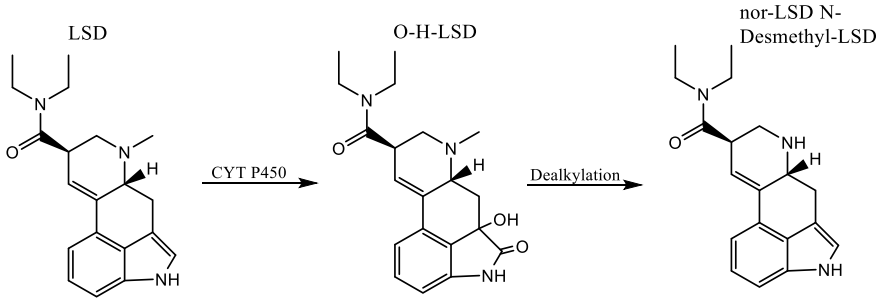


Fig. 15 Complete reaction of LSD metabolism

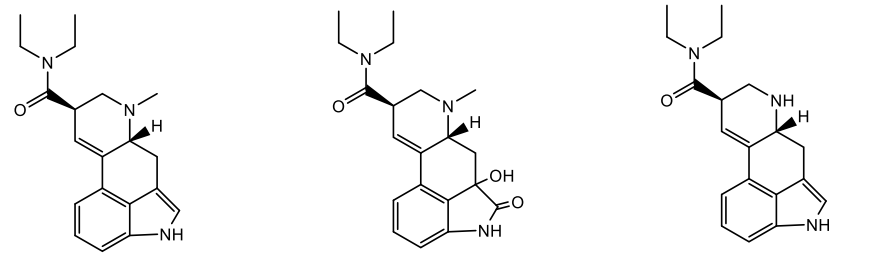


Fig. 16 LSD and its metabolites

3.3 Amphetamine

Amphetamines are substances that have a very complex system that implies several consequences due to inappropriate use. These include a diverse class of synthetic chemicals and naturally occurring alkaloids, e.g. ephedrine and cathinone, which

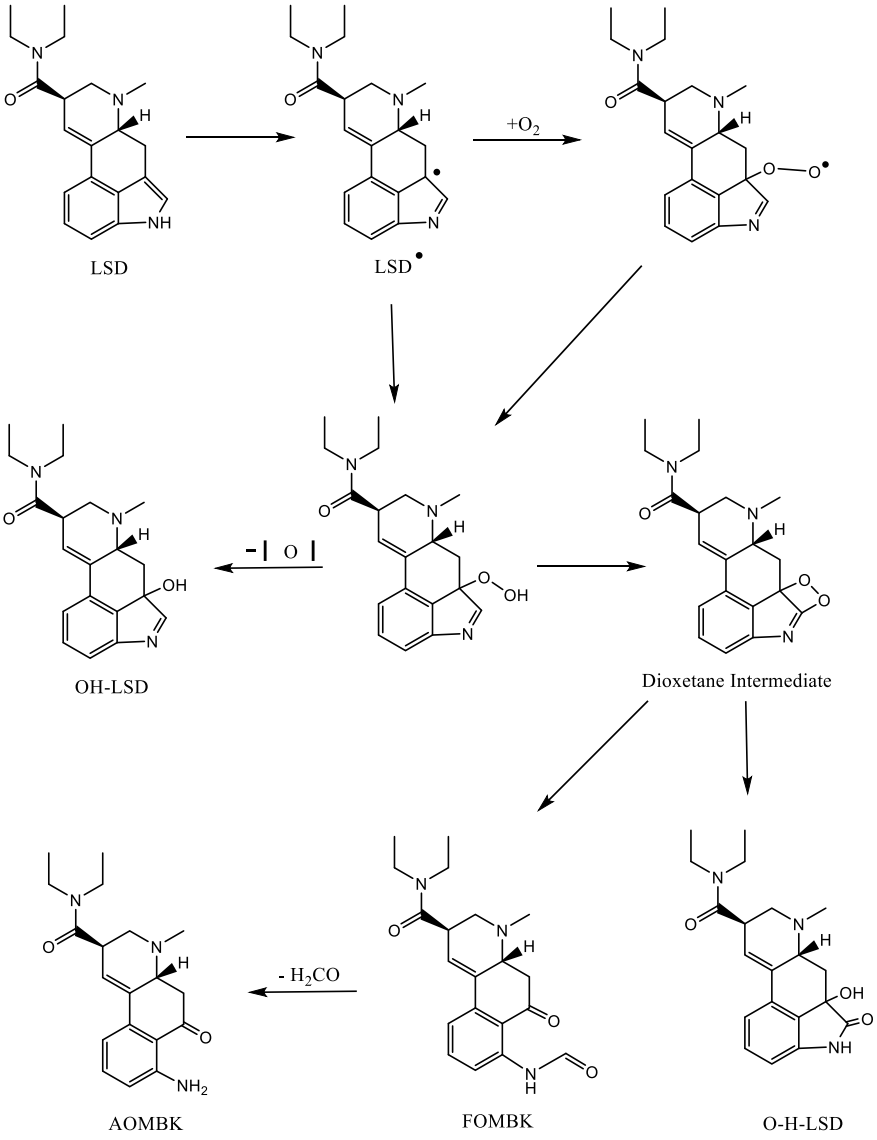


Fig. 17 Proposed reaction for the formation of AOMBK and FOMBK using MPO [42]

are synthesized in the plant species *Ephedra sinica* and *Catha edulis*, respectively [43, 44].

The complexity to explain the mode of action of these substances is due to the mechanisms of action ranging from the central and peripheral stimulation of the

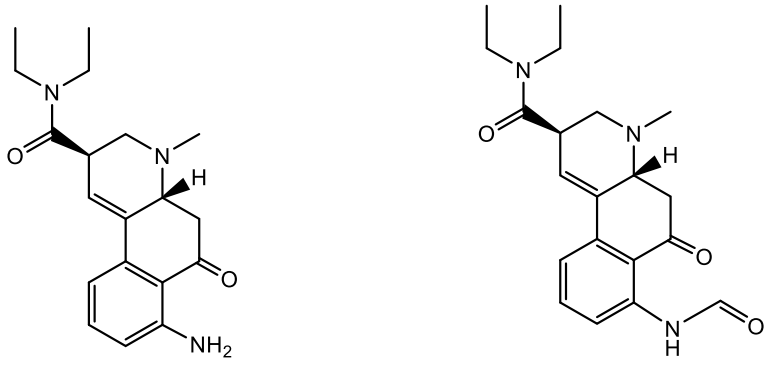


Fig. 18 LSD and its metabolites

release of endogenous biogenic amines by the binding to the monoamine transporters, which are already difficult to define chemical structures until the blockade of absorption induced by methylphenidate [45].

Amphetamine (Fig. 19) is produced in the laboratory and belongs to the class of phenylethylamines, which are sympathomimetic substances with a predominant action in the CNS, whose induction causes hyperactivity of brain activity. In general, amphetamines and illicit derivatives are used for feelings of euphoria, relaxation, anxiety decline, whose response is dependent on the organism [46]. Due to stimulation of the CNS, the most common users of amphetamines are those whose activities related to this activation, such as the academics that although the intention is the improvement in cognitive performance, present greater difficulties and lower average score in relation to the non-users [47]; the drivers, in relation to the alert state [48]; young people to produce or intensify pleasurable effects or attenuate negative effects; individuals who seek the anorexic effect in search of improvement in self-esteem and the professionals of the arts in search of greater creativity [49].

Methylenedioxymethamphetamine commonly called Ecstasy or "Love Pill" and 4-Bromo-2,5-dimethoxy-amphetamine, the "Wind Capsule" [50], are derived from amphetamines and are easily produced illicit drugs in clandestine laboratories and,

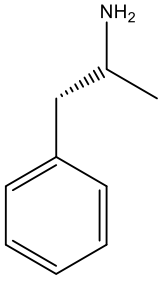


Fig. 19 Structural formula of amphetamine

for this reason, there is a very rapid dispersion of these drugs by society, having influence in the most varied family contexts [51].

3.3.1 Action Mechanism of Amphetamine

Amphetamine acts predominantly in the CNS, being an agonist of indirect action of the amines, mainly the dopamine and other neurotransmitters like serotonin and noradrenaline [52]. These competitively inhibit the transport of norepinephrine and dopamine and at high doses also inhibit the reuptake of serotonin [53]; releases dopamine and norepinephrine independent of Ca $[2]^{+}$, that is, the effect does not depend on the depolarization of the nervous terminal [54]. Similar amphetamine drugs, in addition to acting as agonists in the indirect action of noradrenergic, dopaminergic and serotonergic synapses, also inhibit the enzyme monoamine oxidase (MAO), a flavoenzyme that catalyzes the oxidation of biogenic amines [45].

There is a widespread mechanism to explain the action of amphetamines on dopamine levels, which is related to neurotransmitter uptake, a fact that was found due to the administration of dopamine uptake inhibitors to attenuate the effects of amphetamine on the cytoplasmic transporter. This model is known as exchange diffusion, where amphetamine acts directly and/or indirectly on the dopamine transporter. Amphetamine can increase the presence of this transporter on the inside of the cell and this leads to a reverse dopamine transport, decreasing its cytoplasmic concentrations and blocking the reuptake of this neurotransmitter that will be present in the synaptic cleft [55]. This abundant neurotransmitter will interact with various receptors on postsynaptic neurons, specified as type D1-like (D1 and D5) and type D2-like (D2, D3 and D4), these proteins differ in their molecular capacities and pharmacological responses when interconnected with dopamine [56].

The interaction between amphetamine and dopamine occurs through the interaction of the amine group with the carboxylate of Asp46 and is crucial for the hallucinogenic effect, considering that this residue is conserved between neurotransmitters of biogenic amines. In addition to this interaction, the catechol group occupies the cavity in which residues Phe325 and Phe319 [57] (Fig. 20).

3.3.2 Metabolism of Amphetamine

In recent years, numerous compounds derived from amphetamines with modified ring systems have reached the market constituting a new class of psychoactive substances (NPS) [58]. Of course, metabolic variation exists in each case, but metabolic O-demethylation is mediated by CYP2D6 (catalyzes the hydroxylation of many amine rings) in man and by CYP2B and CYP2D enzymes in relation to methoxy-amphetamine metabolism in the case of species related to amphetamine. Metabolism continues with the formation of hydroxylated metabolites, p-hydroxyamphetamine (POHA), p-hydroxynorephedrine (POHNOR), and p-hydroxyamphetamine glucuronide (POHAG) [59].

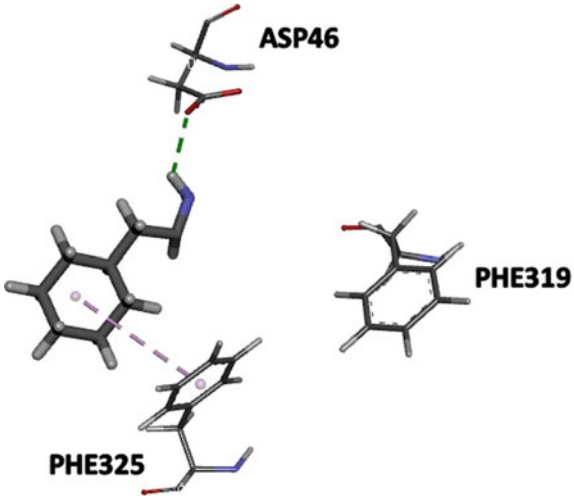


Fig. 20 Amino acid residues from the dopamine transporter interacting with amphetamine

In the conversion of amphetamine to 4-hydroxyamphetamine, a β-hydroxylation, performed by CYP2D6, occurs. This cytochrome belongs to the P450 family, so it will perform reactions similar to this. To obtain the POHA, the mechanism will be the same as that shown in Fig. 21.

4-hydroxynethephedrine is obtained from 4-hydroamfetamine by the action of the enzyme Dopamine-ß-hydroxylase (DBH), which catalyzes the conversion of dopamine to norepinephrine using ascorbic acid, as can be observed in the following reaction (Fig. 22).

DBH catalyzes the hydroxylation not only of dopamine, but also of other phenylethylamine derivatives, when available (Fig. 23). The minimum requirement appears to be a benzene ring having a two carbon side chain terminating at an amino group [61].

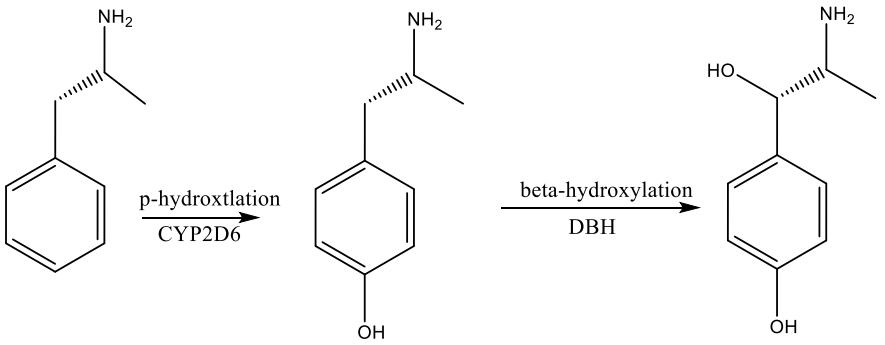


Fig. 21 Metabolic pathways of amphetamine [60]

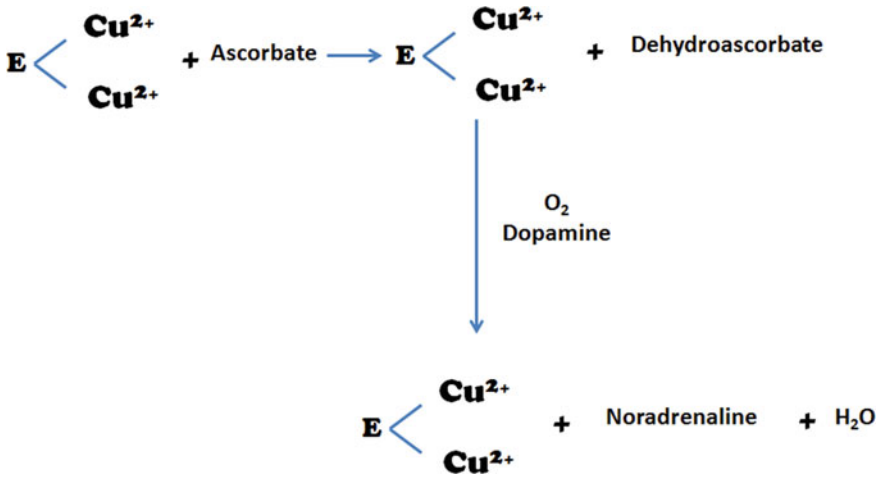
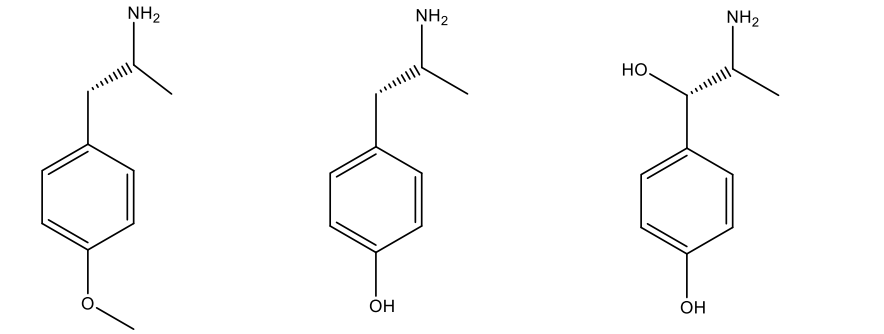


Fig. 22 Mechanism of dopamine ß-hydroxylase reaction (DBH) [61]



4 Metoxyamphetamine p-hydroxyamphetamine (POHA) p-hydroxynorephedrine (POHNOR)

Fig. 23 Amphetamine metabolites

3.4 Cocaine

The cocaine alkaloid (COC) (Fig. 24), commonly known as coca, is a drug of abuse that has a relatively short history compared to the *Erythroxylum* plant from which it derives. There are several species of this plant originating in the tropical zone of the South American Andes, of which the most outstanding are *Erythroxylum novogranatense*, *Erythroxylum novogranatense Truxillense* and *Erythroxylum coca* [62], the latter being the most prominent in the illicit use of COC [63].

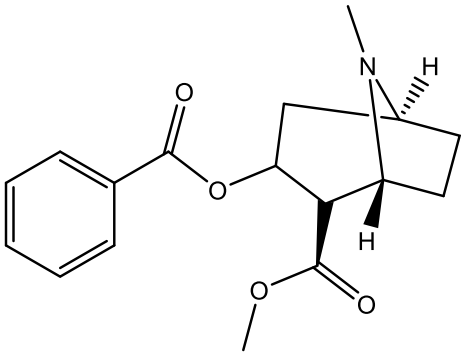


Fig. 24 Structural formula of cocaine

3.4.1 Action Mechanism of Cocaine

The psychotropic effect of cocaine is caused by stimulation of the CNS due to sodium channel block and neuronal inhibition by catecholamine uptake, changes in synaptic transmissions of noradrenaline, serotonin and dopamine [64], with the last inhibition of neuronal reuptake being the most important involved in the process of dependence [65]. It is important to mention that the amount of norepinephrine and 5-HT in the synaptic cleft is also increased during the cocaine effect, but with less significance [66].

Cocaine has similar actions to catecholamines, not acting directly on adrenergic or dopaminergic receptors, because it is known as an indirectly acting sympathomimetic amine. It can act by blocking the norepinephrine and dopamine reuptake carrier protein in the presynaptic terminal, increasing the levels and effects of these neurotransmitters in the synaptic cleft [67]. The difference between cocaine and amphetamine in relation dopamine reuptake inhibition is related to the inhibition site where these molecules act, while amphetamines occupy the same site as dopamine in the carrier protein, cocaine acts elsewhere, specifically at an allosteric site, causing carrier deformation that prevents interaction with dopamine [68].

Studies on cocaine docking with the neurotransmitter acetylcholine indicate that this interaction occurs mainly by the tryptophan maintained at the center of the active site and, to a lesser extent, by the Tyr195 residue. Thus, this binding occurs competitive and non-competitive, depending on the concentration of the compound [69] (Fig. 25).

3.4.2 Metabolism of Cocaine

The first step in the biotransformation of cocaine is catalyzed by CYP3A, where it occurs with oxidative N-demethylation of the substance in its biologically active hepatic metabolite, norcocaine. This conversion occurs by two alternative routes, one involving only the cytochrome P450 and the other requiring the monooxygenase containing the cytochrome P450 and (Flavin Adenine Dinucleotide (FAD) [70].

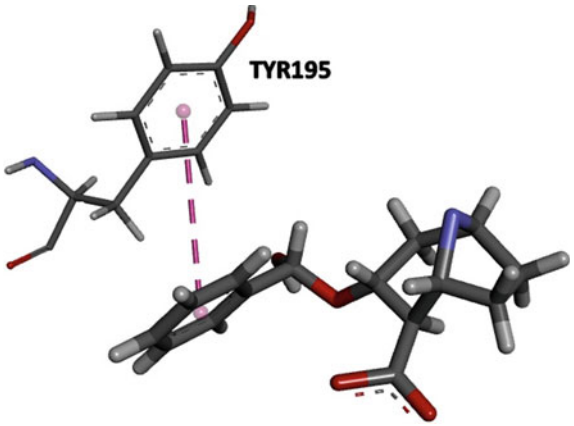


Fig. 25 Amino acid residues of acetylcholine interacting with cocaine

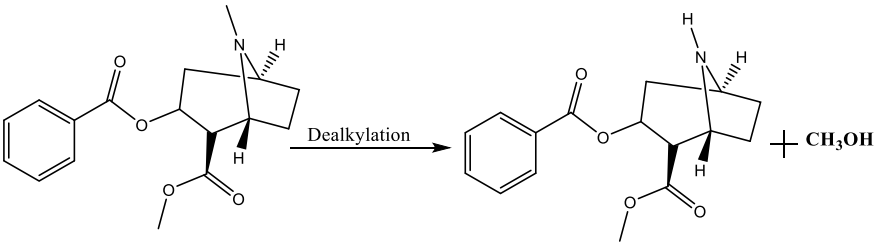


Fig. 26 Dealkylation reaction of cocaine

In the first route, cocaine is directly N-demethylated in norcocaine by cytochrome P450. In this case the presence of a dealkylation reaction is again present, as can also be seen in LSD (Fig. 26).

The second pathway was found to be a two-step reaction involving cocaine N-oxide as an intermediate, the first step being made by a monooxygenase enzyme containing FAD [20]. The reaction mechanism of this monooxygenase containing FAD is shown in the figure below. This mechanism can be simplified in the following global reaction:

$$\mathrm{NAD(PH)H^{+}O_2 + RN \xrightarrow{FMO} NAD(P)^{+}H_2O + RN - O}$$

In this route, cocaine is first oxidized to cocaine N-oxide by FMO, followed by N-demethylation catalyzed by cytochrome P450 to norcocaine (Fig. 28).

The major excreted metabolites of cocaine are benzoylecgonine (formed by non-enzymatic hydrolysis), methyl ester of ecgonine (both representing 75–90% of cocaine metabolism) and ecgonine (formed in smaller amounts). Ecgonine

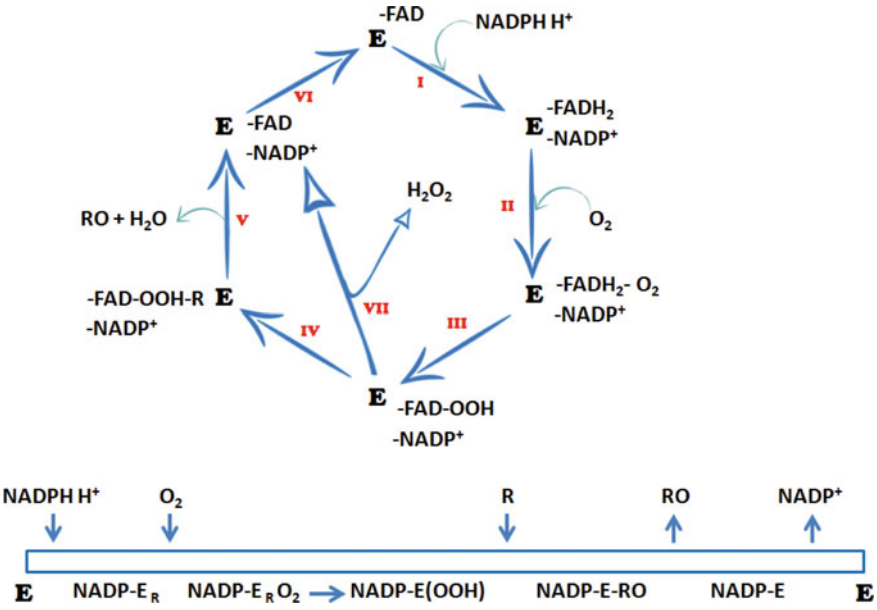


Fig. 27 Oxidation of compounds by microsomal flavin-containing monooxygenase (FMO) [20]

methyl ester undergoes cholinesterase activity (liver and serum enzymes) while benzoylecgonine is formed by non-enzymatic hydrolysis [71, 72].

For the conversion of cocaine to methyl ester of ecgonine, enzymes are used cholinesterase (ChE). In this case, the substrate (cocaine) binds to the amino acid Asn70, and then binds to the active site of choline (cation π site). In the next step, cocaine rotates to the horizontal position for hydrolysis to occur and approaches Ser198 (Fig. 29). After all these steps are completed the final product is obtained, the methyl ester of ecgonine [73] (Fig. 30).

In the case of benzoylecgonine and ecgonine, these compounds are formed by deesterification (hydrolysis) in the liver. In a reaction with water, a bond in the compound is broken, resulting in two compounds. At the same time, a water molecule divides into two, with one hydrogen being transferred to one compound and one hydroxyl to another compound. The hydrogen atom is transferred to the cocaine substrate, giving benzoylecgonine and hydroxyl to the alkyl methyl forming methanol. Methanol, in turn, reacts with cocaine, originating ecgonine methylester and a molecule of water [75] (Figs. 31, 32 and 33).

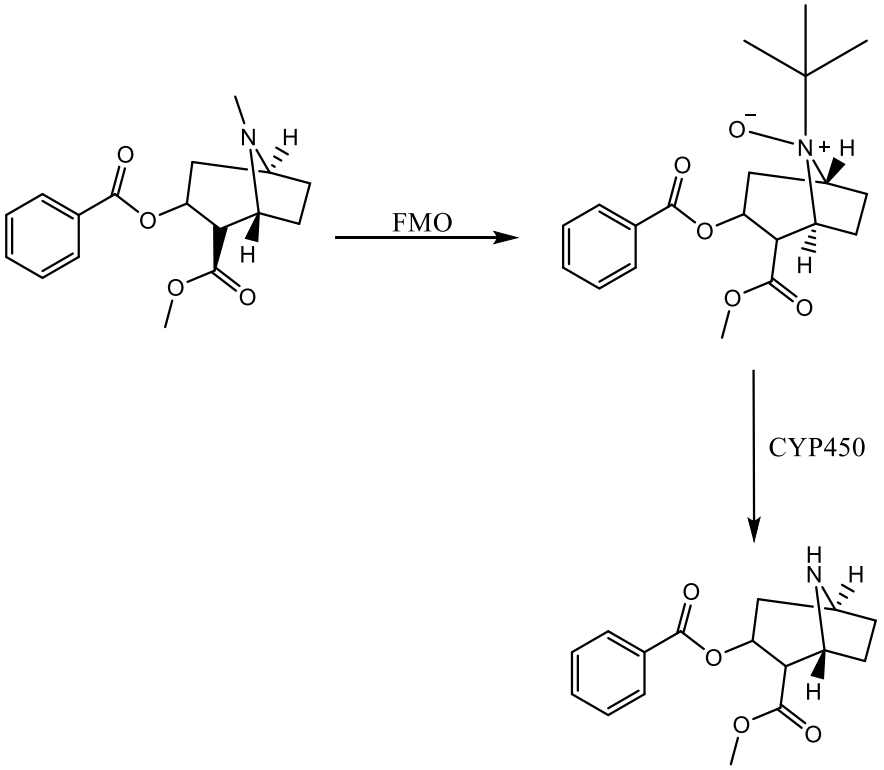


Fig. 28 N-oxide cocaine oxidation by FMO, followed by cytochrome P450 catalyzed N-demethylation to form norcocaine

4 Physiopathology of Chemical Dependence

Drug dependence is increasingly recognized as one of the leading causes of death, morbidity, and loss of productivity in developed countries. Due to the urgent clinical and social need to do something about addiction, neuroscience has advanced in the past 50 years favoring extraordinary progress in global efforts to combat addiction [76].

Drug dependence is defined by the 10th Revision of the International Classification of Diseases (ICD-10) with the presence of three or more dependency indicators. These indicators consist of: (a) a strong desire to use the substance, (b) poor use control, (c) withdrawal syndrome by stopping or reducing use, (d) tolerance to the effects of drugs, (e) need for larger doses to achieve the desired psychological effect, (f) a disproportionate amount of time spent by users obtaining, using and recovering from drug use, g) drug persistence, despite problems [77].

To create selective therapies with action on receptors and neurons altered by drugs and thus inhibit drug abuse, it is necessary to understand the neuronal changes

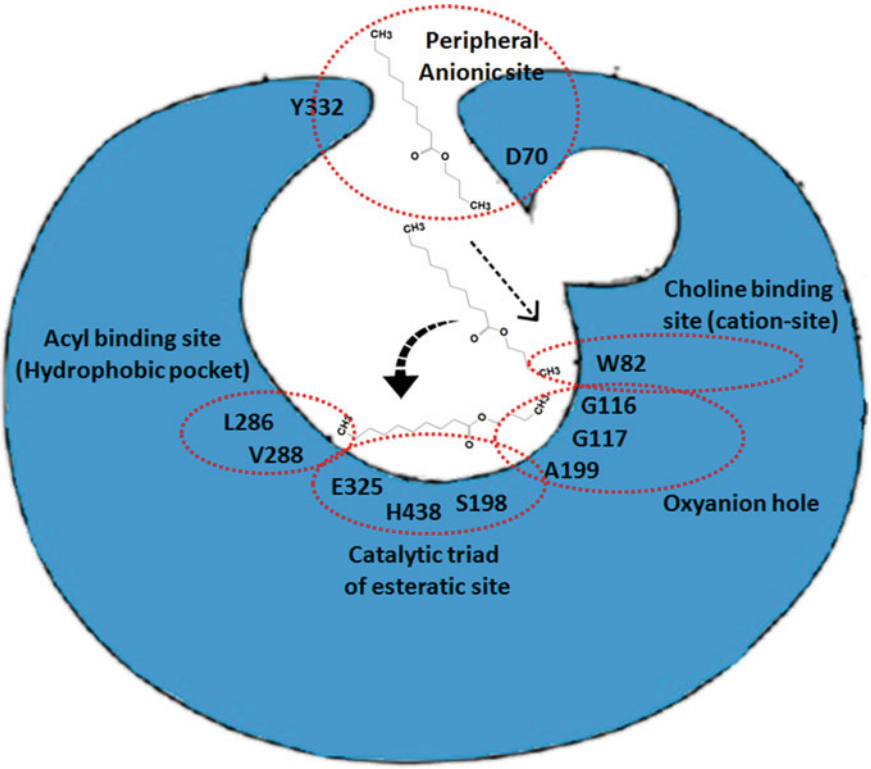


Fig. 29 Amino acids from cholinesterase involved in the conversion of cocaine into ecgonine [73]

associated with chemical dependence [78]. Since the beginning of research on chemical dependence, the causative behavior of these has been seen as a consequence of alterations in the dopaminergic and GABAergic neurotransmission system, linked to the ability of psychoactive substances to interfere in the release and reuptake of dopamine in the neural circuit complex linked to the reward the brain, specifically the striatum [79]

In this understanding, studies are needed to better understand how each substance causes these dopaminergic changes—which may be implicated in greater direct or indirect release of dopamine, modulation of reuptake into synaptic clefts, availability of receptors, or combination of variables presented at different levels [80].

4.1 Cannabis

Cannabis consists mainly of three species: *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. *C. sativa* presents serrated and green leaves, unisex flowers,

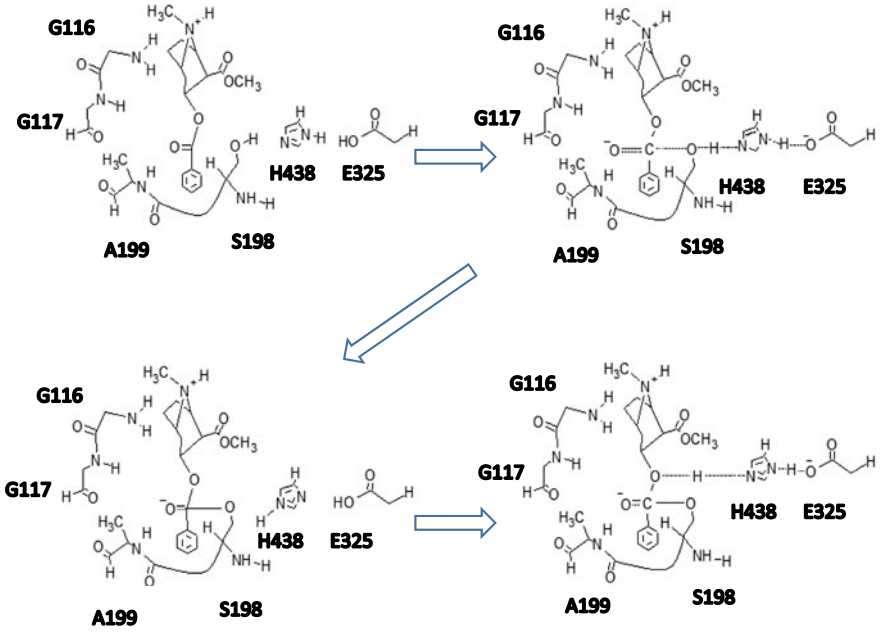


Fig. 30 Schematic representation of the pathway of BChE catalytic hydrolysis with cocaine [74]

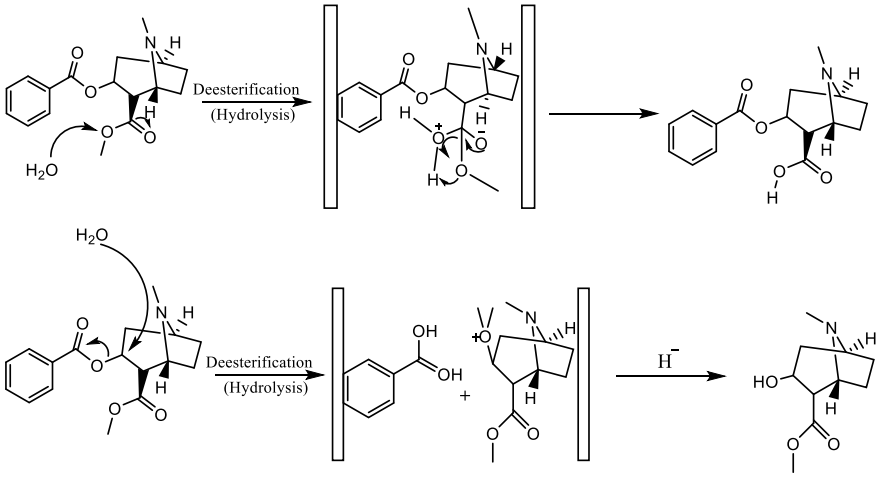


Fig. 31 Formation reaction of benzoylecgonine and ecgonine methylester

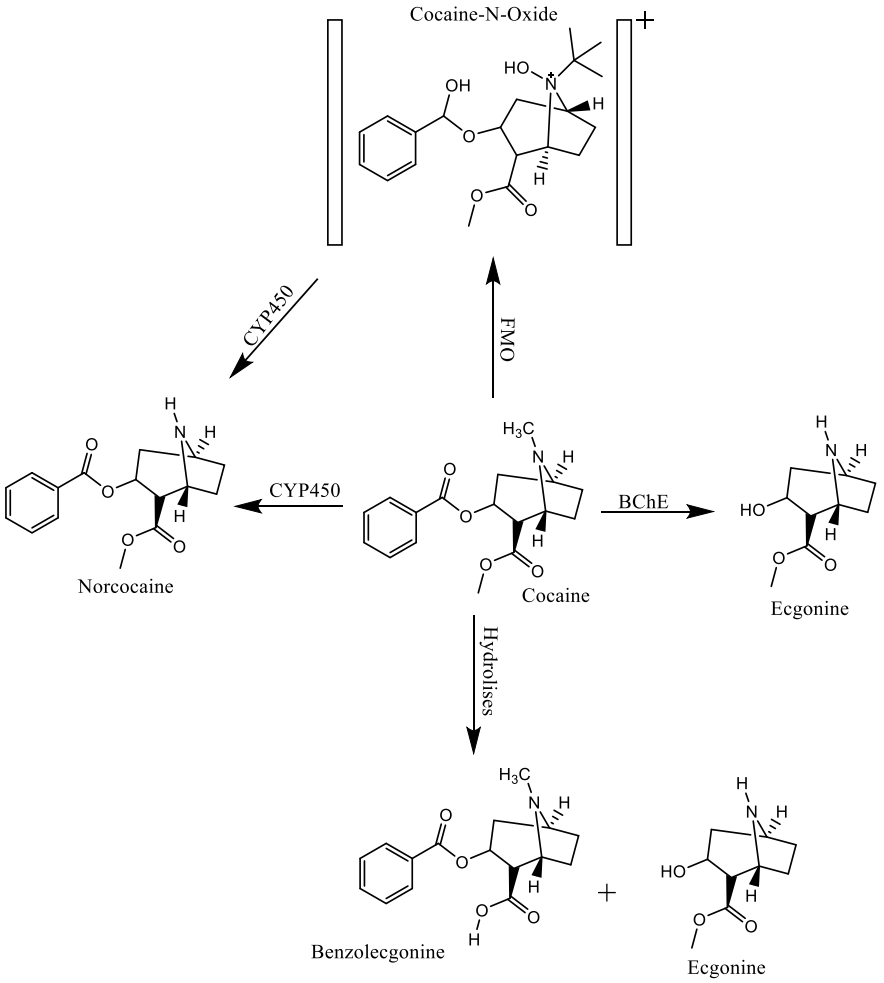


Fig. 32 Pathways to obtaining Cocaine metabolites

granular and composed of fibers arranged on the stem [81]. The biosynthesis of *C. sativa* is concentrating on more than 600 chemical substances, including over 60 different cannabinoids that are recognized for their toxic effects and potential therapeutic [82].

The main component responsible for the psychoactive activity of the plant was identified in the 1960s, known as Δ [9]-THC, (Fig. 1). In addition to Δ [9]-THC, cannabinol (CBN), carboxylated THC, canabidivarine, Tetrahydrocannabivarin, Δ [8]-THC, canabigerol (CBG), cannabicromene (CBC) and Canabidiol (CBD), the latter constituting about 40% of the active substances of the plant [83, 84].

Cannabinoid receptor CB1, identified as molecular targets of exogenous and endogenous cannabinoids, are present in different tissues, such as liver, skeletal

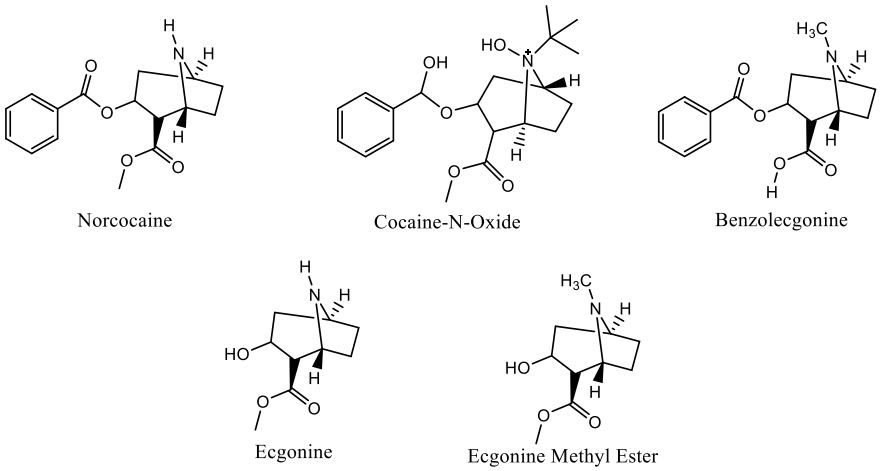


Fig. 33 Cocaine metabolites

muscle, pancreas and fat [85]. These receptors are found in greater abundance in the ganglia of the base, in the hippocampus and in the cerebellum, mainly in the cerebral mitochondria [86]. CB2 cannabinoid receptors for many decades were thought to be distributed only in peripheral organs related to the immune system, but it is now known that they maintain a wide distribution in the CNS, mainly microglial cells, granular cells of the cerebellum, mast cells and in astrocytes humans [84, 87].

Cannabinoid receptor CB1, responsible for most of the psychotropic effects of cannabinoids, are present in areas associated with motor control, emotional response, learning and memory, targeted behaviors and goals, energy homeostasis and higher cognitive functions [88]. This is a membrane receptor coupled to a G protein that, when activated, inhibits the enzyme Adenylate Cyclase and the activity of the calcium channels, increasing the activity of the potassium channels and modulating the release of other neurotransmitters. In peripheral organs and tissues, cannabinoid receptor CB1 are expressed in lower density [89].

Interactions between Δ [9]-THC and cannabinoid receptor CB1 produce acute physical effects such as: dry mouth, dilated conjunctival vessels and accelerated heart rate [90]. This chronic interaction can also cause chronic obstructive pulmonary disease (COPD) and lung cancer, as well as containing levels of benzopyrenes similar to those of tobacco, also reduce the body's immune defenses [91].

4.2 LSD

Hallucinogenic drugs are substances capable of inducing perceptual, affective and judgment sensorial changes [92]. There is evidence that the characteristic effects

of LSD and other hallucinogens, for example, psilocybin and mescaline, are mediated by the serotonergic system and the dorsal raphe nucleus acting as agonist or partial agonist connected to 5-HT2A receptors. At higher doses, LSD also modulates the ventral tegmentar area by stimulating D2 dopaminergic receptors, the Trace Amine Associate 1 receptor (TAAR1), and the 5-HT2A receptor [35]. The interaction between serotonin-glutamate systems and serotonin-dopamine signaling mediate synaptic activity in specific regions of the brain, such as the frontal cortex, cause hallucinogenic action with distortion of reality and altered senses, perception, cognition, mood, and psychosis [93]. LSD also acts on the locus coeruleus, which receives sensory stimuli from the body and produces sympathomimetic mechanisms [94].

About one hour after ingestion LSD is fully absorbed and reaches a higher plasma concentration in 3 h. Distribution throughout the body easily affects the CNS including being absolved by the placenta in pregnant women. The effects can last from 6 to 12 h, depending on the dose ingested [95].

Functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) research have reported that the use of LSD causes increased blood flow from the visual cortex, increased whole brain functional integration (reduced modulatory organization) and decreased oscillatory power over a wide frequency range [96, 97]. Recent research conducted during rest conditions used complementary neuroimaging techniques that revealed marked changes in brain activity correlated with hallucinogenic effects of LSD such as: (a) increased cerebral blood flow from the visual cortex; (b) the alpha power of the diminished visual cortex; and (c) a functional connectivity profile of the greatly expanded primary visual cortex strongly correlated with visual hallucination classifications, implying that intrinsic brain activity exerts greater influence on visual processing in the brain [98].

4.3 Cocaine

The effect of cocaine (Fig. 24) occurs through the competitive inhibition of dopamine transporters, inhibiting the removal of this neurotransmitter from the synaptic and postsynaptic spaces, thus increasing the extracellular concentrations of dopamine [99]. This inhibition prevents the conduction of electrical impulses inside the nerve cells, avoiding the rapid increase of the cellular membrane permeability to the sodium ions during depolarization [100]. Thus, there is an increase in the amount of other neurotransmitters such as norepinephrine, dopamine, serotonin and acetylcholine, involved in motivation, pleasure, cognition, learning, memory, fine motor control and modulation of neuroendocrine signaling [101].

Recent research suggests that cocaine serves as a negative allosteric modulator, altering the function of the dopamine reuptake transporter (DAT), and reversing its transport direction in a co-transport that depends on the burning of dopamine in the synaptic cleft, functioning as an analog of an inverse agonist. Activation of the sympathetic nervous system produces an acute increase in blood pressure, tachycardia, a

predisposition for ventricular arrhythmias and seizures, in addition to mydriasis, hyperglycemia, and hyperthermia [102].

Dopamine is essential as a drug reward mediator [103]. In the short term, cocaine stimulates dopamine neurotransmission by blocking dopamine uptake at D1 and D2 receptors [104], but in the long term the nerve endings mainly in the region of the ventral and dorsal striatum are depleted of this neurotransmitter [105]. This depletion contributes to the dysphoria that develops during cocaine withdrawal and the subsequent desire for more consumption, and this mechanism is responsible for the development of tolerance and dependence patterns [106]. At higher and more regular doses, the involvement of the serotonergic system may occur, directly or indirectly, in mediation of the CNS toxicity [107].

4.4 Amphetamines

Amphetamines (Fig. 19) are a diverse group of compounds that resemble monoamine neurotransmitter transporters. In addition, the structural differences between the various amphetamines highlight the specificity with the carriers [108]. However, amphetamines also bind to targets of non-monoamine transporters such as, for example, adrenergic receptors or traced amine receptors [109, 110].

Human striatum is functionally organized into subdivisions, such as mesolimbic and mesostriated, which have the function of producing pleasure in response to positive events in the individual's life, rewarding the learning process [111].

Amphetamine transporters coupled to the Na^{+}/Cl^{-99}, channels are responsible for the removal of the synaptic and postsynaptic spaces of dopamine and norepinephrine [112].

Amphetamine blocks dopamine reabsorption, thereby increasing the concentration of this neurotransmitter at synapses [113]. This fact causes inhibition of appetite [114], euphoria [115], insomnia, accelerated speech, feeling of power [116], irritability [117], impairment of judgment, perspiration, and chills [118]. The resulting mydriasis is harmful and dangerous, especially for drivers because of the increased sensitivity to the presence of car headlamps [48].

The use of amphetamine is also a reason for hypertension and tachycardia that can lead to acute myocardial infarction or cardiac arrhythmias whose concomitance is usually fatal [119]. Vascular and ischemic attacks, which cause decreased attention, concentration and memory problems may occur at the CNS level, in addition to hyperthermia which may lead to seizures [120, 121].

Ecstasy is the common name for MDMA (3,4-methylenedioxyamphetamine) (Fig. 34), a derivative of methamphetamine substituted on the aromatic ring [122]. This is a powerful CNS stimulant, which increases activity in various neurotransmitters and neurohormonal systems. This powerful neurobiological activation can be strongly euphoric, encompassing feelings of intimacy and closeness, and this state of humor is the main motivation of use by recreational users [123] Ecstasy causes dependence, although research suggests that this may be a less potent booster

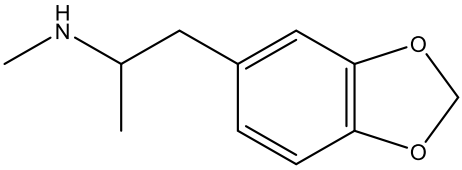


Fig. 34 Structural formula of 3,4 methylene-dioxymethamphetamine

than other drugs. Although less frequent the phenomenon of tolerance in chronic users may occur [124, 125], being the main withdrawal symptoms such as increased appetite, tiredness and drowsiness, bad mood, paranoia and irritability [126].

5 Symptomatology of Withdrawal Syndrome

Abstinence syndrome is the set of signs and symptoms that generate feelings of discomfort and varying degrees of mental and physical suffering [127] that occurs when there is a voluntary or non-voluntary removal of drug use [128]. In general terms, the withdrawal syndrome presents symptoms such as dysphoria, insomnia, anxiety, irritability, nausea, agitation, tachycardia and hypertension. In correct treatment, the initial identification of the type of drug used is important because the complications differ according to the substance [129].

5.1 Cannabis

The effects of acute *Cannabis* intoxication appear after a few minutes of use with motor and cognitive deficits, such as short-term memory loss, impulsivity, and difficulty remembering events that occurred immediately after use [130]. There are also loss of activities that require coordination and attention, such as driving, as well as reducing the ability to solve problems [131, 132].

In recent years a steady increase in epidemiological studies on the use of *Cannabis* and psychosis (or schizophrenia) has suggested that chronic use of *Cannabis* probably precipitates or worsens schizophrenia in individuals susceptible to this pathology [133], and may trigger anxiety attacks, with panic and depression reactions [134]. Some examples of psychic effects are: depersonalization; altered state of consciouness; lethargy; depression; psychomotor excitation; hallucinations and illusions; panic attacks; somnolence; self-referral and paranoia; anxiety; prejudice of the judgment; irritability and concentration problems [132, 135].

The chronic use of marijuana is capable of causing cognitive impairment in the organization and integration of complex information, so that chronic users have lower verbal memory, reduced processing speed, and executive functioning [136]. Physically, chronic use may cause symptoms of chronic bronchitis induced by respiratory

infections [137] while immunohistotopathological and epidemiological evidences suggest the influence of *Cannabis* on the risk of developing lung cancer [91, 138]; reduction in the number of spermatozoa [139], besides influencing the induction of genes linked to the onset of breast cancer [139]. Recent research suggests the influence of *Cannabis* in triggering intracranial arterial stenoses mainly in young users [140].

It is important to mention that the use of *Cannabis* during adolescence can cause lasting effects on brain functions that can compromise the performance of users in adult life in different sectors, whether personal or professional [141].

5.2 Cocaine

Cocaine abuse is related to many physical, psychiatric, and social problems [142]. Although some neurological complications may occur in association with cocaine use, there appears to be no consensus among researchers about cognitive deficits arising from drug use [143].

The chronic use of cocaine is related to the vasoactive effects of the substance. There is evidence that abnormalities of cerebral blood flow frequently occur in users even in the absence of evidence of neurological symptoms [144]. Multiple episodes of substance abuse produce a cumulative effect and there is an increased incidence of stroke even in relatively young individuals, so it is suggested that cocaine use should be classified as a risk factor for cardiovascular and cerebrovascular diseases [145].

Among the classic physiological responses to cocaine use are increased blood pressure, heart and respiratory rates, body temperature, pupil dilation, high alertness and increased motor activity [146]. There are numerous and serious cardiovascular consequences for cocaine users with exclusive mechanisms of cardiotoxicity that include sympathomimetic effects, sodium and potassium channel blockade, oxidative stress, mitochondrial damage and consequent rupture of the excitation–contraction coupling [64], in addition to hypertension, tachycardia, seizures and persecutory delirium, characterized by severe cardiopulmonary dysfunction, hyperthermia and acute neurological alterations that frequently lead the user to death [147].

Some cases, probably caused by lack of dopaminergic control, extreme psychomotor agitation, hyperthermia, aggressiveness and hostility, have been described after cocaine use and require intensive care [148].

5.3 Amphetamines

Amphetamines activate the reward system of the brain producing highly reinforcing effects, which can lead to abuse and dependence. The recreational use of these lipophilic compounds generates acute and chronic effects through the release of noradrenaline, mainly in the lateral hypothalamic area (LHA) [149], thus activating parts

of the sympathetic nervous system and also decreasing the gastrointestinal activity with the consequent inhibition of appetite [150, 151]. Amphetamines and derivatives also cause chills, a climate of confidence and presumption, mydriasis, xerostomia, wheezing, frantic pulsation, hyperexcitation, feeling of power and euphoria [58, 152]**.** Consequently the body is agitated with high energy release and increased sexual desire, also occurring the feeling of well-being, joy and reduced fatigue [153].

Some amphetamines are able to act on the serotonergic system, increasing the release of the neurotransmitter at the synapse, responsible for the hallucinogenic effects, so that in removing the drug this system increases anxiety and reduces the ability to cope with stress, a fact that contributes to relapse of use [154].

The psychiatric impairment associated with the use of amphetamines may be cognitive, intellectual or affective [155]. These consequences are correlated with the duration of use as well as the amounts used. Memory, language and attention deficits are also reported among users [156]. Neurological failure may persist for 9 months or more after cessation of amphetamine use, but recovery in attention activity and improvement in cognitive functioning are possible with sustained abstinence [153].

About 40% of chronic users, in addition to developing the phenomenon of tolerance, may develop a toxic reaction, known as "Amphetamine Psychosis" [157] characterized by symptoms such as agitation, irritability, insomnia, hallucinations and delirium. This may require a psychiatric hospitalization because this problem can lead the user to death [158].

Prolonged or intense use of amphetamines may trigger an abstinence syndrome characterized by a sudden change in dysphoric disorder, decreased libido, fatigue, increased appetite, deceleration and sleep disturbances, or accelerated psychomotor activity [159]. The severity of these symptoms is related to the duration and intensity of drug use and symptoms last up to 3 weeks [160, 161].

5.4 LSD

The mental changes produced by LSD are variable and abnormal (although the sensory changes resulting from the use are not relevant), however, some consequences are considered terror and panic. At low doses it causes hallucinations, delusions, altered perception of time and space, mental confusion, memory lapses and generalized distortion [162], similar to schizophrenia [163], in addition to undesirable physical effects related to autonomic disorders such as nausea, increased blood pressure and frequency heart failure, body weakness, drowsiness, and increased body temperature [164].

Psychic effects vary depending on the user's emotional state, context, quality and quantity of the product, ranging from extremely pleasant to very unpleasant [165]. Illusions, auditory and visual hallucinations, great sensory sensitivity with the glimpse of brighter colors and perception of imperceptible sounds, synesthesia, mystical experiences, feelings of well-being, ecstatic experiences, and euphoria are

the most common effects [166]. The less common use of intranasal LSD can cause coma, hyperthermia, vomiting, mild gastric bleeding, and respiratory problems [167].

6 Pharmacological Treatment for Withdrawal Syndrome

Drug damage can be acute, leading to intoxication or sudden changes called "overdose" and chronic, producing longer lasting changes, such as chemical dependency, and even irreversible changes [168].

One of the first reports on pharmacological treatment for chemical dependence and symptoms related to withdrawal syndrome was carried out by Sigmund Freud in his book Über Coca, where he described the use of cocaine to treat psychic disorders and dependence on morphine [169]. In the following months, Freud witnessed the "deep despair" of cocaine-treated patients who had symptoms such as fainting, convulsions, severe insomnia, and unusual patterns of behavior [170]. At that time, delirium tremens were reported—a state of temporary confusion leading to dangerous changes in the regulation of circulation and breathing, leading to the risk of heart attack, stroke or death [171].

The symptoms of cocaine withdrawal are eminently psychic, with depressive and anxious disorders being the most common. They usually appear more intense in the first seven days and appear less intense when the patient is in protected environments [172]. Currently, cocaine users with agitation and withdrawal syndrome can be treated with benzodiazepine [173], GABAergic agonists [174], and antipsychotics or with the combination of drugs [175]. The use of these drugs intramuscular (IM) or intravenous (IV) is recommended if the patient has intense psychomotor agitation and heteroaggressivity and should not accept oral medications [176].

More recently, disulfiram (a substance well known in the treatment of alcohol dependence) [177] and modafinil are used to control withdrawal symptoms in stabilizing clinical and psychiatric conditions resulting from sympathomimetic and neural dysregulation caused by cocaine [178]. Disulfiram, at a dose of 250–500 mg daily, acts in the dopaminergic system, blocking the enzymes DβH [179], MAO inhibits the conversion of dopamine to noradrenaline and thus causing a reduction of dopamine in the nucleus accumbens, an integral part of the reward system [180]. Studies with selective DβH inhibitors are being conducted for use in minimizing the cardiovascular effects produced by cocaine [181, 182].

Modafinil blocks the reuptake of dopamine and noradrelin, increasing the concentration in the brain, and increases the activity of the glutamate system, which is generally deficient due to chronic use of cocaine [183]. The dose used is 200 to 400 mg per day, although it does not offer statistically significant benefits, demonstrates the tendency of maintenance in the state of abstinence [184].

Cannabinoids are used as therapeutic agents against nausea and vomiting in terminal patients with cancer and AIDS. *Cannabis* decreases the intensity of spasms and tremors in the case of multiple sclerosis and epilepsy [185]. The main problem

is that chronic use can cause serious side effects on cognitive functions, coordination, learning disabilities and impairment of memory, dependence, and induction of suicide attempts [186].

Research is advancing in the search for pharmacological approaches in *Cannabis* use disorders, obtaining more substantial data on the clinical efficacy of any specific drug to be used in the treatment of chronic users of the plant [187]. Buporpione, a noradrenaline and dopamine reuptake inhibitor, partial serotonin 5HT receptor agonists such as buspirone, are being studied but have reduced effects on *Cannabis* removal [188]. The use of cannabinoid receptor CB1 agonists seems to be the most promising, such as Dronabinol, which is associated with lofexedine, α2 adrenergic agonist [189]. Naltrexone, an opioid receptor antagonist, may moderate effects and reduce self-administration, whereas cannabinoid receptor CB1 antagonist, such as Rimonabant, has a small reduction in use but causes considerable side effects to psychic changes [190]. In the use of *Cannabis* derivatives, for example, nabiximol showed a reduction in most of the symptoms but was not effective in the long term of abstinence [191].

Initially amphetamines were used for narcolepsy [192] and are currently used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and restricted obesity [193, 194] with its main mechanism of action being the blockade of neurotransmitter transporters that mediate the reuptake of monoamines potentiating dopaminergic, adrenergic and serotonergic neurotransmission [195]. The first step in treating amphetamine dependence is detoxification that aims to lower blood levels of the drug, but requires prolonged drug treatment. The main symptoms presented at this stage are anxiety and agitation, energy reduction and depressive mood, so in these cases benzodiazepines such as diazepam 5 mg are used orally and neuroleptics such as haloperidol 2 to 5 mg, oral or injectable [196]. It is very important to mention that psychosocial counseling is a factor that should accompany treatment from the beginning of detoxification [197].

LSD has analgesic effects in patients with terminal cancer [198], mainly with improvement of mood and reduction of anxiety [199]. In the mid-last century, LSD-based drugs indicated mental relaxation, anxiety in psychotic nature studies and treatment of alcoholism, with 100 ml ampoules of 100 μg, orally or subcutaneously / intravenously. These were allowed and made available for free to psychiatric clinics, however, the abuse of products prompted manufacturers to remove supplies of medicines [150]. LSD acts on several neurotransmitters, but action on serotonin seems to be the most important, due to the clinical presentation of delusions and hallucinations [200]. Benzodiazepine medicinal products such as diazepam 10 mg orally or midazolam 15 mg intramuscularly may be used to control the agitation and symptoms of schizophrenia caused by drug withdrawal [201]. Research advances in the use of isoxazol-9 during the removal of methamphetamine, since this molecule presents preliminary results that contribute directly inhibiting the search behavior of the drug [202].

7 Conclusion

This review concludes that drugs, in addition to being included in humanity from the earliest stages, are also present in society, following their own scientific evolution. With the development of new synthetic routes, the appearance of new drugs is not a rare occurrence, which exposes a considerable part of society to chemical dependence. In general, the treatments developed currently have little efficacy and act to combat the symptoms triggered by the withdrawal syndrome in users intensely dependent on *Cannabis*, cocaine, amphetamines, and LSD. Therefore, it is concluded that it is necessary to develop drugs that act selectively on biological targets involved in the process of chemical dependency, as well as those directly involved in the onset of withdrawal symptoms initiated by each drug of abuse.

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References

1. Ree, E.V.: Drugs, the democratic civilising process and the consumer society. Int. J. Drug Policy **13**, 349–353 (2002)
2. Caddy, B.: Drugs of Abuse. Science. Pharmaceutical Press, pp. 119–119 (2003). https://doi.org/10.1016/S1355-0306(03)71753-5.
3. Degenhardt, L., Hall, W.: Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet **379**(9810), 55–70 (2012). https://doi.org/10.1016/S0140-6736(11)61138-0
4. Nutt, D.J., Lingford-Hughes, A., Erritzoe, D., Stokes, P.R.A.: The dopamine theory of addiction: 40 years of highs and lows. Nat. Rev. Neurosci. **16**(5), 305–312 (2015). https://doi.org/10.1038/nrn3939
5. World Health Organization (WHO): Neurociências: consumo e dependência de substâncias psicoativas RESUMO Organizaç a ˜ o Mundial da Saú de Genebra
6. Walker, D.M., Nestler, E.J.: Neuroepigenetics and addiction. In: Handbook of Clinical Neurology; Elsevier, vol. 148, pp. 747–765 (2018). https://doi.org/10.1016/B978-0-444-64076-5.00048-X
7. Degenhardt, L., Chiu, W.T., Sampson, N., Kessler, R.C., Anthony, J.C., Angermeyer, M., Bruffaerts, R., De Girolamo, G., Gureje, O., Huang, Y., et al.: Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS Med. **5**(7), 1053–1067 (2008). https://doi.org/10.1371/journal.pmed.0050141
8. Clarke, R.C., Merlin, M.D.: Cannabis: Evolution and Ethnobotany, vol. 53 (2013). https://doi.org/10.1525/j.ctt3fh2f8
9. Datwyler, S.L., Weiblen, G.D.: Genetic variation in hemp and marijuana (Cannabis Sativa L.) according to amplified fragment length polymorphisms. J. Forensic Sci. *51*(2), 371–375 (2006). https://doi.org/10.1111/j.1556-4029.2006.00061.x
10. Di Forti, M., Murray, R.M.: Cannabis, skunk and spice: the evolving risk of psychosis. Schizophr. Res. **153**, S31 (2014). https://doi.org/10.1016/S0920-9964(14)70104-5

11. Mallipeddi, S., Janero, D.R., Zvonok, N., Makriyannis, A.: Functional selectivity at G-protein coupled receptors: advancing cannabinoid receptors as drug targets. Biochem. Pharmacol.; Elsevier March 15, pp. 1–11 (2017). https://doi.org/10.1016/j.bcp.2016.11.014
12. Pertwee, R.G.: Endocannabinoids and their pharmacological actions. In: Endocannabinoids; Springer, Cham, pp. 1–37 (2015). https://doi.org/10.1007/978-3-319-20825-1_1
13. McCorvy, J.D., Roth, B.L.: Structure and function of serotonin G protein-coupled receptors. Pharmacol. Ther. **150**, 129–142 (2015). https://doi.org/10.1016/j.pharmthera.2015.01.009
14. Cawston, E.E., Connor, M., Di Marzo, V., Silvestri, R., Glass, M.: Distinct temporal fingerprint for cyclic adenosine monophosphate (CAMP) signaling of indole-2-carboxamides as allosteric modulators of the cannabinoid receptors. J. Med. Chem. **58**(15), 5979–5988 (2015). https://doi.org/10.1021/acs.jmedchem.5b00579
15. Hu, S.S.J., Mackie, K.: Distribution of the endocannabinoid system in the central nervous system. In: Endocannabinoids; Springer, Cham, pp. 59–93 (2015). https://doi.org/10.1007/978-3-319-20825-1_3
16. Maccarrone, M., Bab, I., Bíró, T., Cabral, G.A., Dey, S.K., Di Marzo, V., Konje, J.C., Kunos, G., Mechoulam, R., Pacher, P., et al.: Endocannabinoid signaling at the periphery: 50 years after THC. Trends Pharmacol. Sci. **36**(5), 277–296 (2015). https://doi.org/10.1016/j.tips.2015.02.008
17. Grotenhermen, F.: Clinical pharmacokinetics of cannabinoids. J. Cannabis Ther. **3**(1), 3–51 (2003). https://doi.org/10.1300/J175v03n01_02
18. Angeli, I., Casati, S., Ravelli, A., Minoli, M., Orioli, M.: A novel single-step GC–MS/MS method for cannabinoids and 11-OH-THC metabolite analysis in hair. J. Pharm. Biomed. Anal. **155**, 1–6 (2018). https://doi.org/10.1016/j.jpba.2018.03.031
19. Matsunaga, T., Iwawaki, Y., Watanabe, K., Yamamoto, I., Kageyama, T., Yoshimura, H.: Metabolism of Δ9-tetrahydrocannabinol by cytochrome P450 isozymes purified from hepatic microsomes of monkeys. Life Sci. **56**(23–24), 2089–2095 (1995). https://doi.org/10.1016/0024-3205(95)00193-A
20. Kamali, F.: Introduction to drug metabolism (Third Edition). B. J. Clin. Pharmacol. *56*(3), 345–345 (2003). https://doi.org/10.1046/j.1365-2125.2003.01855.x
21. Elmes, M.W., Kaczocha, M., Berger, W.T., Leung, K.N., Ralph, B.P., Wang, L., Sweeney, J.M., Miyauchi, J.T., Tsirka, S.E., Ojima, I., et al.: Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). J. Biol. Chem. **290**(14), 8711–8721 (2015). https://doi.org/10.1074/jbc.M114.618447
22. Meyer, A.H., Dybala-Defratyka, A., Alaimo, P.J., Geronimo, I., Sanchez, A.D., Cramer, C.J., Elsner, M.: Cytochrome P450-catalyzed dealkylation of atrazine by Rhodococcus sp. strain NI86/21 involves hydrogen atom transfer rather than single electron transfer. Dalton Trans. *43*(32), 12175–12186 (2014). https://doi.org/10.1039/c4dt00891j
23. Coon, M.J.: Enzyme ingenuity in biological oxidations: a trail leading to cytochrome P450. J. Biol. Chem. **277**(32), 28351–28363 (2002). https://doi.org/10.1074/jbc.r200015200
24. Burstein, S.H.: The cannabinoid acids: nonpsychoactive derivatives with therapeutic potential. Pharmacol. Ther. *82*(1), 87–96 (1999). https://doi.org/10.1016/S0163-7258(98)00069-2
25. Akhtar, M.T., Shaari, K., Verpoorte, R.: Biotransformation of tetrahydrocannabinol. Phytochem. Rev. **15**(5), 921–934 (2016). https://doi.org/10.1007/s11101-015-9438-9
26. Sharma, P., Murthy, P., Bharath, M.M.S.: Chemistry, metabolism, and toxicology of cannabis: clinical implications. Iran. J. Psychiatr. **7**(4), 149–156 (2012)
27. Nichols, D.E.: Dark classics in chemical neuroscience: lysergic acid diethylamide (LSD). ACS Chem. Neurosci. **9**(10), 2331–2343 (2018). https://doi.org/10.1021/acschemneuro.8b00043
28. Gicquel, T., Lepage, S., Morel, I. Histoire Du LSD. De l'ergot de Seigle à l'utilisation Thérapeutique. La Presse Médicale *44*(7–8), 832–836 (2015). https://doi.org/10.1016/j.lpm.2015.04.033
29. Liester, M.B.: A review of lysergic acid diethylamide (LSD) in the treatment of addictions: historical perspectives and future prospects. Curr. Drug Abuse Rev. **7**(3), 146–156 (2014). https://doi.org/10.2174/1874473708666150107120522

30. Wang, R.Z., Vashistha, V., Kaur, S., Houchens, N.W.: Serotonin syndrome: preventing, recognizing, and treating it. Clevel. Clin. J. Med. **83**(11), 810–817 (2016). https://doi.org/10.3949/ccjm.83a.15129
31. Werneke, U., Jamshidi, F., Taylor, D.M., Ott, M.: Conundrums in neurology: diagnosing serotonin syndrome - a meta-analysis of cases. BMC Neurol. **16**(1), 97 (2016). https://doi.org/10.1186/s12883-016-0616-1
32. López-Giménez, J.F., González-Maeso, J. Hallucinogens and serotonin 5-HT2Areceptor-mediated signaling pathways. In: Current Topics in Behavioral Neurosciences, vol. 36, pp. 45–73. Springer, Berlin, Heidelberg (2018). https://doi.org/10.1007/7854_2017_478
33. Halberstadt, A.L. Hallucinogenic drugs: a new study answers old questions about LSD. Curr. Biol. Cell Press February 20, R156–R158 (2017). https://doi.org/10.1016/j.cub.2016.12.058
34. De Gregorio, D., Posa, L., Ochoa-Sanchez, R., McLaughlin, R., Maione, S., Comai, S., Gobbi, G.: The hallucinogen d-lysergic diethylamide (LSD) decreases dopamine firing activity through 5-HT1A, D2 and TAAR1 receptors. Pharmacol. Res. **113**, 81–91 (2016). https://doi.org/10.1016/j.phrs.2016.08.022
35. De Gregorio, D., Comai, S., Posa, L., Gobbi, G.: D-lysergic acid diethylamide (LSD) as a model of psychosis: mechanism of action and pharmacology. Int. J. Mol. Sci. Multidisciplinary Digital Publishing Institute November 23, 2016, (1953). https://doi.org/10.3390/ijms17111953
36. Buchborn, T., Grecksch, G., Dieterich, D.C., Höllt, V.: Tolerance to lysergic acid diethylamide: overview, correlates, and clinical implications. In: Neuropathology of Drug Addictions and Substance Misuse, vol. 2, pp. 846–858. Academic Press (2016). https://doi.org/10.1016/B978-0-12-800212-4.00079-0
37. Coleman, R.G., Carchia, M., Sterling, T., Irwin, J.J., Shoichet, B.K.: Ligand pose and orientational sampling in molecular docking. PLoS ONE **8**(10), e75992 (2013). https://doi.org/10.1371/journal.pone.0075992
38. Nichols, D.E. Chemistry and structure–activity relationships of psychedelics. In: Current Topics in Behavioral Neurosciences, vol. 36, pp. 1–43. Springer, Berlin, Heidelberg (2018). https://doi.org/10.1007/7854_2017_475
39. Wacker, D., Wang, S., McCorvy, J.D., Betz, R.M., Venkatakrishnan, A.J., Levit, A., Lansu, K., Schools, Z.L., Che, T., Nichols, D.E., et al.: Crystal structure of an LSD-bound human serotonin receptor. Cell **168**(3), 377-389.e12 (2017). https://doi.org/10.1016/j.cell.2016.12.033
40. Klette, K.L., Anderson, C.J., Poch, G.K., Nimrod, A.C., ElSohly, M.A.: Metabolism of lysergic acid diethylamide (LSD) to 2-oxo-3-hydroxy LSD (O-H-LSD) in human liver microsomes and cryopreserved human hepatocytes. J. Anal. Toxicol. **24**(7), 550–556 (2000). https://doi.org/10.1093/jat/24.7.550
41. Gomes, M.M., Dörr, F.A., Catalani, L.H., Campa, A.: Oxidation of lysergic acid diethylamide (LSD) by peroxidases: a new metabolic pathway. Forensic Toxicol. **30**(2), 87–97 (2012). https://doi.org/10.1007/s11419-011-0131-4
42. Gomes, M.M., Dörr, F.A., Catalani, L.H., Campa, A.: Oxidation of lysergic acid diethylamide (LSD) by peroxidases: a new metabolic pathway. Forensic Toxicol. **30**(2), 87–97 (2012). https://doi.org/10.1007/s11419-011-0131-4
43. Strang, J., Babor, T., Caulkins, J., Fischer, B., Foxcroft, D., Humphreys, K.: Drug policy and the public good: evidence for effective interventions. Lancet **379**(9810), 71–83 (2012). https://doi.org/10.1016/S0140-6736(11)61674-7
44. Connors, N.J., Hoffman, R.S.: Amphetamines and derivatives. In: Critical Care Toxicology, pp. 1–26. Springer International Publishing, Cham (2016). https://doi.org/10.1007/978-3-319-20790-2_4-1
45. Sitte, H.H., Freissmuth, M.: Amphetamines, new psychoactive drugs and the monoamine transporter cycle. In: Trends in Pharmacological Sciences, pp. 41–50. Elsevier Current Trends January 1, 2015 (2015). https://doi.org/10.1016/j.tips.2014.11.006
46. Aoun, E.G., Christopher, P.P., Ingraham, J.W.: Emerging drugs of abuse: clinical and legal considerations. Rhode Island Med. J. (2013) *97*(6), 41–45 (2014)

47. Geisner, I.M., Huh, D., Cronce, J.M., Lostutter, T.W., Kilmer, J., Larimer, M.E.: Exploring the relationship between stimulant use and gambling in college students. J. Gambl. Stud. **32**(3), 1001–1016 (2016). https://doi.org/10.1007/s10899-015-9586-2
48. Wille, S.M.R., Richeval, C., Nachon-Phanithavong, M., Gaulier, J.M., Di Fazio, V., Humbert, L., Samyn, N., Allorge, D.: Prevalence of new psychoactive substances and prescription drugs in the belgian driving under the influence of drugs population. Drug Test. Anal. (2017). https://doi.org/10.1002/dta.2232
49. Leslie, E.M., Smirnov, A., Cherney, A., Wells, H., Legosz, M., Kemp, R., Najman, J.M.: Simultaneous use of alcohol with methamphetamine but not ecstasy linked with aggression among young adult stimulant users. Addict. Behav. **70**, 27–34 (2017). https://doi.org/10.1016/j.addbeh.2017.01.036
50. Karinen, R., Høiseth, G.: A literature review of blood concentrations of new psychoactive substances classified as phenethylamines, aminoindanes, arylalkylamines, arylcyclohexylamines, and indolalkylamines. Forensic Sci. Int. **276**, 120–125 (2017). https://doi.org/10.1016/j.forsciint.2017.02.024
51. Taylor, M.F., Marquis, R., Coall, D., Wilkinson, C.: Substance misuse-related parental child maltreatment: intergenerational implications for grandparents, parents, and grandchildren relationships. J. Drug Issues **47**(2), 241–260 (2017). https://doi.org/10.1177/0022042616683670
52. Pei, Y., Asif-Malik, A., Canales, J.J.: Trace amines and the trace amine-associated receptor 1: pharmacology, neurochemistry, and clinical implications. Front. Neurosci.; Frontiers April 5, 2016 148 (2016). https://doi.org/10.3389/fnins.2016.00148
53. Spencer, R.C., Devilbiss, D.M., Berridge, C.W. The cognition-enhancing effects of psychostimulants involve direct action in the prefrontal cortex. Biol. Psychiatry. Elsevier June 1, 2015, 940–950 (2015). https://doi.org/10.1016/j.biopsych.2014.09.013
54. Cameron, K.N., Solis, E., Ruchala, I., De Felice, L.J., Eltit, J.M.: Amphetamine activates calcium channels through dopamine transporter-mediated depolarization. Cell Calcium **58**(5), 457–466 (2015). https://doi.org/10.1016/j.ceca.2015.06.013
55. Sulzer, D., Maidment, N.T., Rayport, S.: Amphetamine and other weak bases act to promote reverse transport of dopamine in ventral midbrain neurons. J. Neurochem. 527–535 (1993). https://doi.org/10.1111/j.1471-4159.1993.tb03181.x
56. Haile, C.N., Kosten, T.R., Kosten, T.A.: Pharmacogenetic treatments for drug addiction: cocaine, amphetamine and methamphetamine. Am. J. Drug Alcohol Abuse **35**(3), 161–177 (2009). https://doi.org/10.1080/00952990902825447
57. Wang, K.H., Penmatsa, A., Gouaux, E.: Neurotransmitter and psychostimulant recognition by the dopamine transporter. Nature **521**(7552), 322–327 (2015). https://doi.org/10.1038/nature14431
58. Welter-Luedeke, J., Maurer, H.H.: New psychoactive substances: chemistry, pharmacology, metabolism, and detectability of amphetamine derivatives with modified ring systems. Ther. Drug Monit. **38**(1), 4–11 (2015). https://doi.org/10.1097/FTD.0000000000000240
59. Feio-Azevedo, R., Costa, V.M., Ferreira, L.P., Branco, P.S., Pereira, F.C., de Lourdes Bastos, M., Carvalho, F., Capela, J.P.: Amphetamine and its metabolite 4-hydroxyamphetamine neurotoxicity in differentiated SH-SY5Y neurons. Toxicol. Lett. *229*(229), S241 (2014). https://doi.org/10.1016/j.toxlet.2014.06.805
60. Badenhorst, C.P.S., van der Sluis, R., Erasmus, E., van Dijk, A.A.: Glycine conjugation: importance in metabolism, the role of glycine N-acyltransferase, and factors that influence interindividual variation. Expert Opin. Drug Metab. Toxicol. **9**(9), 1139–1153 (2013). https://doi.org/10.1517/17425255.2013.796929
61. Kaufman, S., Friedman, S.: Dopamine-β-hydroxylase. Pharmacol. Rev. *17*(2) (1965)
62. Casale, J.F., Mallette, J.R., Jones, L.M.: Chemosystematic identification of fifteen new cocaine-bearing erythroxylum cultigens grown in colombia for illicit cocaine production. Forensic Sci. Int. **237**, 30–39 (2014). https://doi.org/10.1016/j.forsciint.2014.01.012
63. Oliveira, L.F.M.: A Cocaína e Sua Adulteração. Revista Intertox de Toxicologia, Risco Ambiental e Sociedade **6**(1), 15–28 (2013)

64. Stankowski, R.V., Kloner, R.A., Rezkalla, S.H.: Cardiovascular consequences of cocaine use. Trends Cardiovasc. Med.; Elsevier August 1, 2015; 517–526 (2015). https://doi.org/10.1016/j.tcm.2014.12.013
65. Koob, G.F., Volkow, N.D.: Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry; Elsevier August 1, 2016; 760–773 (2016). https://doi.org/10.1016/S2215-0366(16)00104-8
66. Simmler, L.D., Anacker, A.M.J., Levin, M.H., Vaswani, N.M., Gresch, P.J., Nackenoff, A.G., Anastasio, N.C., Stutz, S.J., Cunningham, K.A., Wang, J., et al.: Blockade of the 5-HT transporter contributes to the behavioural, neuronal and molecular effects of cocaine. Br. J. Pharmacol. **174**(16), 2716–2738 (2017). https://doi.org/10.1111/bph.13899
67. Lizasoain, I., Moro, M.A., Lorenzo, P.: Cocaína: aspectos Farmacológicos. Adicciones 57–64 (2002). https://doi.org/10.20882/adicciones.513
68. Alves, B.E.P.; Carneiro, E.D.O.: Drogas psicoestimulantes: uma abordagem toxicológica sobre Cocaína e metanfetamina; Goiás (2013)
69. Hansen, S.B., Taylor, P.: Galanthamine and non-competitive inhibitor binding to ACh-binding protein: evidence for a binding site on non-α-subunit interfaces of heteromeric neuronal nicotinic receptors. J. Mol. Biol. **369**(4), 895–901 (2007). https://doi.org/10.1016/j.jmb.2007.03.067
70. Gambelunghe, C., Rossi, R., Aroni, K., Gili, A., Bacci, M., Pascali, V., Fucci, N.: Norcocaine and cocaethylene distribution patterns in hair samples from light, moderate, and heavy cocaine users. Drug Test. Anal. **9**(2), 161–167 (2017). https://doi.org/10.1002/dta.1903
71. Ladona, M.G., Gonzalez, M.L., Rane, A., Peter, R.M., de la Torre, R.: Cocaine metabolism in human fetal and adult liver microsomes is related to cytochrome P450 3A expression. Life Sci. **68**(4), 431–443 (2000)
72. de Oliveira Silveira, G., Belitsky, Í.T., Loddi, S., Rodrigues de Oliveira, C.D., Zucoloto, A.D., Fruchtengarten, L.V.G., Yonamine, M.: Development of a method for the determination of cocaine, cocaethylene and norcocaine in human breast milk using liquid phase microextraction and gas chromatography-mass spectrometry. Forensic Sci. Int. *265*, 22–28 (2016). https://doi.org/10.1016/j.forsciint.2016.01.007
73. Ekim, Y.: Butyrylcholinesterase : Structure and Physiological Importance. Turk. J. Biochem. **28**(August), 54–61 (2003)
74. Zhan, C.G., Gao, D.: Catalytic mechanism and energy barriers for butyrylcholinesterase-catalyzed hydrolysis of cocaine. Biophys. J. **89**(6), 3863–3872 (2005). https://doi.org/10.1529/biophysj.105.070276
75. Carvalho, V.M., Da Matta Chasin, A.A., De Carvalho, D.G.: A study on the stability of anhydroecgonine methyl ester (crack biomarker), benzoylecgonine, and cocaine in human urine. Revista de Psiquiatria Clinica **35**(1), 17–20 (2008). https://doi.org/10.1590/S0101-60832008000700005
76. World Health Organization: Global status report on road safety 2015 (2015)
77. World Health Organization: The ICD-10 classification of mental and behavioural disorders. The ICD-10 classification of mental and behavioural disorders 86–95 (1992)
78. Koob, G.F., Volkow, N.D.: Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry; Elsevier August 1, 2016; 760–773 (2016). https://doi.org/10.1016/S2215-0366(16)00104-8
79. Volkow, N.D., Morales, M.: The brain on drugs: from reward to addiction. Cell 712–725 (2015). https://doi.org/10.1016/j.cell.2015.07.046
80. Miller, J.D., Wilcox, R.E.: Mechanisms of stimulant drug dependence. J. Addict. Prev. *5*(1), 1–6 (2017). https://doi.org/10.13188/2330-2178.1000038
81. Raman, V., Lata, H., Chandra, S., Khan, I.A., ElSohly, M.A.: Morpho-anatomy of marijuana (Cannabis Sativa L.). In: Cannabis sativa L. - Botany and Biotechnology, pp. 123–136. Springer International Publishing, Cham (2017). https://doi.org/10.1007/978-3-319-54564-6_5
82. Schoeler, T., Bhattacharyya, S.: The effect of cannabis use on memory function: an update. Subst. Abuse Rehabil. **4**(January), 11–27 (2013). https://doi.org/10.2147/SAR.S25869

83. Gaoni, Y., Mechoulam, R.: Isolation, structure, and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. **86**, 1646–1647 (1964). https://doi.org/10.1021/ja01062a046
84. Howlett, A.C., Breivogel, C.S., Childers, S.R., Deadwyler, S.A., Hampson, R.E., Porrino, L.J.: Cannabinoid physiology and pharmacology: 30 years of progress. Neuropharmacology **47**, 345–358 (2004). https://doi.org/10.1016/j.neuropharm.2004.07.030
85. Hebert-Chatelain, E., Reguero, L., Puente, N., Lutz, B., Chaouloff, F., Rossignol, R., Piazza, P.-V., Benard, G., Grandes, P., Marsicano, G.: Cannabinoid control of brain bioenergetics: exploring the subcellular localization of the CB1 receptor. Mol. Metab. **3**(4), 495–504 (2014). https://doi.org/10.1016/j.molmet.2014.03.007
86. Zou, S., Kumar, U.: Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int. J. Mol. Sci.; Multidisciplinary Digital Publishing Institute March 13, 2018; 833 (2018). https://doi.org/10.3390/ijms19030833
87. Onaivi, E.S., Ishiguro, H., Gong, J.-P., Patel, S., Perchuk, A., Meozzi, P.A., Myers, L., Mora, Z., Tagliaferro, P., Gardner, E., et al.: Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. Ann. N. Y. Acad. Sci. **1074**(1), 514–536 (2006). https://doi.org/10.1196/annals.1369.052
88. El Khoury, M.-A., Gorgievski, V., Moutsimilli, L., Giros, B., Tzavara, E.T.: Interactions between the cannabinoid and dopaminergic systems: evidence from animal studies. Prog. Neuropsychopharmacol. Biol. Psychiatry **38**(1), 36–50 (2012). https://doi.org/10.1016/j.pnpbp.2011.12.005
89. Demuth, D.G., Molleman, A.: Cannabinoid signalling. Life Sci. **78**(6), 549–563 (2006). https://doi.org/10.1016/j.lfs.2005.05.055
90. Marusich, J.A., Craft, R.M., Lefever, T.W., Wiley, J.L.: The impact of gonadal hormones on cannabinoid dependence. Exp. Clin. Psychopharmacol. **23**(4), 206–216 (2015). https://doi.org/10.1037/pha0000027
91. Tashkin, D.P.: Effects of marijuana smoking on the lung. Ann. Am. Thorac. Soc. **10**(3), 239–247 (2013). https://doi.org/10.1513/AnnalsATS.201212-127FR
92. Appendino, G., Minassi, A., Taglialatela-Scafati, O.: Recreational drug discovery: natural products as lead structures for the synthesis of smart drugs. Nat. Prod. Rep. **31**(7), 880 (2014). https://doi.org/10.1039/c4np00010b
93. de Bartolomeis, A., Buonaguro, E.F., Iasevoli, F.: Serotonin-glutamate and serotonin-dopamine reciprocal interactions as putative molecular targets for novel antipsychotic treatments: from receptor heterodimers to postsynaptic scaffolding and effector proteins. Psychopharmacology **225**(1), 1–19 (2013). https://doi.org/10.1007/s00213-012-2921-8
94. Fiorella, D., Helsley, S., Lorrain, D.S., Rabin, R.A., Winter, J.C.: The role of the 5-HT2A and 5-HT2C receptors in the stimulus effects of hallucinogenic drugs III: the mechanistic basis for supersensitivity to the LSD stimulus following serotonin depletion. Psychopharmacology **121**(3), 364–372 (1995). https://doi.org/10.1007/BF02246076
95. Dolder, P.C., Schmid, Y., Haschke, M., Rentsch, K.M., Liechti, M.E.: Pharmacokinetics and concentration-effect relationship of oral LSD in humans. Int. J. Neuropsychopharmacol. *19*(1), pyv072 (2016). https://doi.org/10.1093/ijnp/pyv072
96. Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S.D., Murphy, K., Laufs, H., Leech, R., McGonigle, J., Crossley, N., et al.: Increased global functional connectivity correlates with LSD-induced ego dissolution. Curr. Biol. **26**(8), 1043–1050 (2016). https://doi.org/10.1016/j.cub.2016.02.010
97. Carhart-Harris, R.L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E.E., Nest, T., Orban, C., et al.: Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc. Natl. Acad. Sci. U.S.A. **113**(17), 4853–4858 (2016). https://doi.org/10.1073/pnas.1518377113
98. Atasoy, S., Roseman, L., Kaelen, M., Kringelbach, M.L., Deco, G., Carhart-Harris, R.L.: Connectome-harmonic decomposition of human brain activity reveals dynamical repertoire re-organization under LSD. Sci. Rep. *7*(1) (2017). https://doi.org/10.1038/s41598-017-17546-0

99. Wang, K.H., Penmatsa, A., Gouaux, E.: Neurotransmitter and psychostimulant recognition by the dopamine transporter. Nature **521**(7552), 322–327 (2015). https://doi.org/10.1038/nature14431
100. Milnes, A., Wilson, S.: Local anesthetics. In: Oral Sedation for Dental Procedures in Children, pp. 57–63. Springer, Berlin, Heidelberg (2015). https://doi.org/10.1007/978-3-662-46626-1_5
101. De Felice, L.J.: Monoamine transporters as ionotropic receptors. Trends Neurosci. **40**(4), 195–196 (2017). https://doi.org/10.1016/j.tins.2017.02.003
102. Rubinos, C., Ruland, S.: Neurologic complications in the intensive care unit. Curr. Neurol. Neurosci. Rep. (2016). https://doi.org/10.1007/s11910-016-0651-8
103. Ikemoto, S., Yang, C., Tan, A.: Basal ganglia circuit loops, dopamine and motivation: a review and enquiry. Behav. Brain Res.; September 1, 2015 17–31. https://doi.org/10.1016/j.bbr.2015.04.018
104. Xu, H., Das, S., Sturgill, M., Hodgkinson, C., Yuan, Q., Goldman, D., Grasing, K.: Extracellular dopamine, acetylcholine, and activation of dopamine D1 and D2 receptors after selective breeding for cocaine self-administration in rats. Psychopharmacology 1–13 (2017). https://doi.org/10.1007/s00213-017-4640-7
105. Willuhn, I., Burgeno, L.M., Groblewski, P.A., Phillips, P.E.M.: Excessive cocaine use results from decreased phasic dopamine signaling in the striatum. Nat. Publ. Group **17**(5), 704–709 (2014). https://doi.org/10.1038/nn.3694
106. Everitt, B.J.: Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories - indications for novel treatments of addiction. Eur. J. Neurosci. **40**(1), 2163–2182 (2014). https://doi.org/10.1111/ejn.12644
107. Howell, L.L., Cunningham, K.A.: Serotonin 5-HT2 receptor interactions with dopamine function: implications for therapeutics in cocaine use disorder. Pharmacol. Rev. **67**(1), 176–197 (2015). https://doi.org/10.1124/pr.114.009514
108. Sulzer, D.: How addictive drugs disrupt presynaptic dopamine neurotransmission. Neuron **69**(4), 628–649 (2011). https://doi.org/10.1016/j.neuron.2011.02.010
109. Sulzer, D., Sonders, M.S., Poulsen, N.W., Galli, A.: Mechanisms of neurotransmitter release by amphetamines: a review. Prog. Neurobiol. **75**(6), 406–433 (2005). https://doi.org/10.1016/j.pneurobio.2005.04.003
110. Bunzow, J.R., Sonders, M.S., Arttamangkul, S., Harrison, L.M., Zhang, G.E., Quigley, D.I., Darland, T., Suchland, K.L., Pasumamula, S., Kennedy, J.L., Olson, S.B., et al.: Amphetamine, 3,4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. Mol. Pharmacol. *60*(6), 1181–1188 (2001). https://doi.org/10.1124/mol.60.6.1181
111. Feldman Barrett, L., Russel, J.A.: The Psychological Construction of Emotion (2014)
112. Vaughan, R.A., Foster, J.D.: Mechanisms of dopamine transporter regulation in normal and disease states. Trends in Pharmacological Sciences, pp. 489–496 (2013). https://doi.org/10.1016/j.tips.2013.07.005
113. Martinez, D., Slifstein, M., Broft, A., Mawlawi, O., Hwang, D.-R., Huang, Y., Cooper, T., Kegeles, L., Zarahn, E., Abi-Dargham, A., et al.: Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. J. Cereb. Blood Flow Metab. *23*(3), 285–300 (2003). https://doi.org/10.1097/01.WCB.0000048520.34839.1A
114. Chu, S.C., Chen, P.N., Hsieh, Y.S., Yu, C.H., Lin, M.H., Lin, Y.H., Kuo, D.Y.: Involvement of hypothalamic PI3K-STAT3 signalling in regulating appetite suppression mediated by amphetamine. Br. J. Pharmacol. **171**(13), 3223–3233 (2014). https://doi.org/10.1111/bph.12667
115. Weafer, J., Gorka, S.M., Hedeker, D., Dzemidzic, M., Kareken, D.A., Phan, K.L., de Wit, H.: Associations between behavioral and neural correlates of inhibitory control and amphetamine reward sensitivity. Neuropsychopharmacology **42**(9), 1905–1913 (2017). https://doi.org/10.1038/npp.2017.61

116. Asaad, G., Brunner: Mazel clinical psychiatry, co. Hallutinations in clinical psychiatry: a guide for mental health professionals; Taylor and Francis (1990)
117. Stuckelman, Z.D., Mulqueen, J.M., Ferracioli-Oda, E., Cohen, S.C., Coughlin, C.G., Leckman, J.F., Bloch, M.H.: Risk of irritability with psychostimulant treatment in children With ADHD. J. Clin. Psychiatry **78**(06), e648–e655 (2017). https://doi.org/10.4088/JCP.15r10601
118. Rasmussen, N.: Amphetamine-type stimulants: the early history of their medical and non-medical uses. Int. Rev. Neurobiol. **120**, 9–25 (2015). https://doi.org/10.1016/bs.irn.2015.02.001
119. Richards, J.R., Albertson, T.E., Derlet, R.W., Lange, R.A., Olson, K.R., Horowitz, B.Z.: Treatment of toxicity from amphetamines, related derivatives, and analogues: a systematic clinical review. Drug Alcohol Depend. 1–13 (2015). https://doi.org/10.1016/j.drugalcdep.2015.01.040
120. Pozzi, M., Roccatagliata, D., Sterzi, R.: Drug abuse and intracranial hemorrhage. In: Neurological Sciences, vol. 29, pp 269–270. Springer, Milan (2008). https://doi.org/10.1007/s10072-008-0960-z
121. Loewenhardt, B., Bernhard, M., Pierskalla, A., Neumann-Haefelin, T., Hofmann, E.: Neurointerventional treatment of amphetamine-induced acute occlusion of the middle cerebral artery by intracranial balloon angioplasty. Clin. Neuroradiol. **23**(2), 137–143 (2013). https://doi.org/10.1007/s00062-011-0122-1
122. Parrott, A.C.: Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. In: Psychopharmacology, pp. 234–241. Springer (2004). https://doi.org/10.1007/s00213-003-1712-7
123. Parrott, A.C.: Human psychobiology of MDMA or "Ecstasy": an overview of 25 years of empirical research. In: Human Psychopharmacology, vol. 28, pp. 289–307. Wiley-Blackwell (2013). https://doi.org/10.1002/hup.2318
124. Degenhardt, L., Bruno, R., Topp, L.: Is ecstasy a drug of dependence? Drug Alcohol Depend. 1–10 (2010). https://doi.org/10.1016/j.drugalcdep.2009.09.009
125. Parrott, A.C.: Chronic tolerance to recreational MDMA (3,4-Methylenedioxymethamphetamine) or ecstasy. J. Psychopharmacol. (Oxford, England) **2005**(19), 71–83 (1994). https://doi.org/10.1177/0269881105048900
126. McKetin, R., Copeland, J., Norberg, M.M., Bruno, R., Hides, L., Khawar, L.: The effect of the ecstasy 'Come-down' on the diagnosis of ecstasy dependence. Drug Alcohol Depend. **139**, 26–32 (2014). https://doi.org/10.1016/j.drugalcdep.2014.02.697
127. Nirenberg, M.J.: Dopamine agonist withdrawal syndrome: implications for patient care. Drugs Aging **30**(8), 587–592 (2013). https://doi.org/10.1007/s40266-013-0090-z
128. Almeida, T., Monteiro, L.: Executive functions and decision making regarding drug addicts in abstinence. Acta Neuropsychol. **12**(4), 387–400 (2014). https://doi.org/10.5604/17307503.1132137
129. Kubo, C., Kuboki, T. (Eds.): Psychosomatic medicine (2006)
130. Day, A.M., Metrik, J., Spillane, N.S., Kahler, C.W.: Working memory and impulsivity predict marijuana-related problems among frequent users. Drug Alcohol Depend. **131**(1–3), 171–174 (2013). https://doi.org/10.1016/j.drugalcdep.2012.12.016
131. Pan, J.F., Mann, R., Brands, B., Stoduto, G., Wickens, C., Burston, J., Huestis, M.A., Le Foll, B.: Preliminary report on the residual effects of cannabis on young drivers' performance of driving-related skills. Drug Alcohol Depend. **156**, e170–e171 (2015). https://doi.org/10.1016/j.drugalcdep.2015.07.463
132. Broyd, S.J., Van Hell, H.H., Beale, C., Yücel, M., Solowij, N.: Acute and chronic effects of cannabinoids on human cognition - a systematic review. Biol. Psychiatry 557–567. https://doi.org/10.1016/j.biopsych.2015.12.002
133. Nielsen, S.M., Toftdahl, N.G., Nordentoft, M., Hjorth?j, C.: Association between alcohol, cannabis, and other illicit substance abuse and risk of developing schizophrenia: a nationwide population based register study. Psychol. Med. *47*(09), 1668–1677 (2017). https://doi.org/10.1017/S0033291717000162

134. Danielsson, A.-K., Lundin, A., Agardh, E., Allebeck, P., Forsell, Y.: Cannabis use, depression and anxiety: A 3-year prospective population-based study. J. Affect. Disord. **193**, 103–108 (2016). https://doi.org/10.1016/j.jad.2015.12.045
135. D'Souza, D.C.: Cannabinoids and psychosis. In: International Review of Neurobiology, pp. 289–326. Bentham Science Publishers. https://doi.org/10.1016/S0074-7742(06)78010-2
136. Hall, W., Lynskey, M.: Long-term marijuana use and cognitive impairment in middle age. JAMA Intern. Med. **6**(3), 2–3 (2016). https://doi.org/10.1001/jamainternmed.2015.7850
137. Gates, P., Jaffe, A., Copeland, J.: Cannabis smoking and respiratory health: consideration of the literature. Respirology 655–662 (2014). https://doi.org/10.1111/resp.12298
138. Joshi, M., Joshi, A., Bartter, T.: Marijuana and lung diseases. Curr. Opin. Pulm. Med. **20**(2), 173–179 (2014). https://doi.org/10.1097/MCP.0000000000000026
139. Gundersen, T.D., Jørgensen, N., Andersson, A.-M., Bang, A.K., Nordkap, L., Skakkebæk, N.E., Priskorn, L., Juul, A., Jensen, T.K.: Association between use of marijuana and male reproductive hormones and semen quality: a study among 1,215 healthy young men. Am. J. Epidemiol. **182**(6), 473–481 (2015). https://doi.org/10.1093/aje/kwv135
140. Wolff, V., Armspach, J.-P., Beaujeux, R., Manisor, M., Rouyer, O., Lauer, V., Meyer, N., Marescaux, C., Geny, B.: High frequency of intracranial arterial stenosis and cannabis use in ischaemic stroke in the young. Cerebrovascular diseases (Basel, Switzerland) **37**(6), 438–443 (2014). https://doi.org/10.1159/000363618
141. Volkow, N.D., Baler, R.D., Compton, W.M., Weiss, S.R.B.: Adverse health effects of marijuana use. N. Engl. J. Med. **370**(23), 2219–2227 (2014). https://doi.org/10.1056/NEJMra1402309
142. Verdejo-Garcia, A.: Social cognition in cocaine addiction. Proc. Natl. Acad. Sci. U.S.A. **111**(7), 2406–2407 (2014). https://doi.org/10.1073/pnas.1324287111
143. Potvin, S., Stavro, K., Rizkallah, É., Pelletier, J.: Cocaine and cognition. J. Addict. Med. **8**(5), 368–376 (2014). https://doi.org/10.1097/ADM.0000000000000066
144. Chen, W., Liu, P., Volkow, N.D., Pan, Y., Du, C.: Cocaine attenuates blood flow but not neuronal responses to stimulation while preserving neurovascular coupling for resting brain activity. Mol. Psychiatry **21**(October), 1–9 (2015). https://doi.org/10.1038/mp.2015.185
145. Bachi, K., Mani, V., Jeyachandran, D., Fayad, Z.A., Goldstein, R.Z., Alia-Klein, N.: Vascular disease in cocaine addiction. Atherosclerosis 154–162 (2017). https://doi.org/10.1016/j.atherosclerosis.2017.03.019
146. Rasimas, J.J., Sinclair, C.M.: Assessment and management of toxidromes in the critical care unit. Crit. Care Clin. **33**(3), 521–541 (2017). https://doi.org/10.1016/j.ccc.2017.03.002
147. Plush, T., Shakespeare, W., Jacobs, D., Ladi, L., Sethi, S., Gasperino, J.: Cocaine-induced agitated delirium: a case report and review. J. Intensive Care Med. **30**(1), 49–57 (2015). https://doi.org/10.1177/0885066613507420
148. Greydanus, D.E., Reed, W.J., Hawver, E.K.: Public health aspects of substance use and abuse in adolescence. Int. Public Health J. **8**(4), 455–484 (2016)
149. Schmeichel, B.E., Berridge, C.W.: Amphetamine acts within the lateral hypothalamic area to elicit affectively neutral arousal and reinstate drug-seeking. Int. J. Neuropsychopharmacol./Off. Sci. J. Coll. Int. Neuropsychopharmacol. (CINP) **17**(1), 63–75 (2014). https://doi.org/10.1017/S1461145713000734
150. Dolder, P.C., Schmid, Y., Steuer, A.E., Kraemer, T., Rentsch, K.M., Hammann, F., Liechti, M.E.: Pharmacokinetics and pharmacodynamics of lysergic acid diethylamide in healthy subjects. Clinical Pharmacokinetics, pp. 1–12. Springer International Publishing February (2017). https://doi.org/10.1007/s40262-017-0513-9
151. Degenhardt, L., Hall, W.: Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet **379**(9810), 55–70 (2012). https://doi.org/10.1016/S0140-6736(11)61138-0
152. Vahabzadeh, M., Ghassemi Toussi, A.: Misdiagnosed pruritus; formication due to chronic amphetamine abuse. Asia Pac. J. Med. Toxicol. *5*(1), 32–34 (2016). https://doi.org/10.22038/APJMT.2016.6884

153. Radfar, S., Rawson, R.: Current research on methamphetamine: epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. Addict. Health. **6**(3–4), 146–154 (2014)
154. Li, H., Scholl, J.L., Tu, W., Hassell, J.E., Watt, M.J., Forster, G.L., Renner, K.J.: Serotonergic responses to stress are enhanced in the central amygdala and inhibited in the ventral hippocampus during amphetamine withdrawal. Eur. J. Neurosci. **40**(11), 3684–3692 (2014). https://doi.org/10.1111/ejn.12735
155. London, E.D., Kohno, M., Morales, A.M., Ballard, M.E.: Chronic methamphetamine abuse and corticostriatal deficits revealed by neuroimaging. Brain Res. **1628**, 174–185 (2015). https://doi.org/10.1016/j.brainres.2014.10.044
156. Thanos, P.K., Kim, R., Delis, F., Rocco, M.J., Cho, J., Volkow, N.D.: Effects of chronic methamphetamine on psychomotor and cognitive functions and dopamine signaling in the brain. Behav. Brain Res. **320**, 282–290 (2017). https://doi.org/10.1016/j.bbr.2016.12.010
157. McKetin, R., Lubman, D.I., Baker, A.L., Dawe, S., Ali, R.L.: Dose-related psychotic symptoms in chronic methamphetamine users: evidence from a prospective longitudinal study. JAMA Psychiat. **70**(3), 1–6 (2013). https://doi.org/10.1001/jamapsychiatry.2013.283
158. Glasner-Edwards, S., Mooney, L.J.: Methamphetamine psychosis: epidemiology and management. CNS Drugs **28**(12), 1115–1126 (2014). https://doi.org/10.1007/s40263-014-0209-8
159. Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., et al.: Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. Lancet **382**(9904), 1575–1586 (2013). https://doi.org/10.1016/S0140-6736(13)61611-6
160. Bagheri, M., Mokri, A., Khosravi, A., Kabir, K.: Effect of abstinence on depression, anxiety, and quality of life in chronic methamphetamine users in a therapeutic community. Int. J. High Risk Behav. Addict. **4**(3), 1–5 (2015). https://doi.org/10.5812/ijhrba.23903
161. Wang, G., Shi, J., Chen, N., Xu, L., Li, J., Li, P., Sun, Y., Lu, L.: Effects of length of abstinence on decision-making and craving in methamphetamine abusers. PLoS ONE **8**(7), e68791 (2013). https://doi.org/10.1371/journal.pone.0068791
162. Baldacchino, A., Arvapalli, V., Oshun, A., Tolomeo, S.: Substance-induced mental disorders. In: Textbook of Addiction Treatment: International Perspectives, pp. 1925–1936. Springer Milan, Milano (2015). https://doi.org/10.1007/978-88-470-5322-9_88
163. Lev-Ran, S., Feingold, D., Frenkel, A., Lerner, A.G.: Clinical characteristics of individuals with schizophrenia and hallucinogen persisting perception disorder: a preliminary investigation. J. Dual Diagn. **10**(2), 79–83 (2014). https://doi.org/10.1080/15504263.2014.906155
164. Schmid, Y., Enzler, F., Gasser, P., Grouzmann, E., Preller, K.H., Vollenweider, F.X., Brenneisen, R., Müller, F., Borgwardt, S., Liechti, M.E.: Acute effects of lysergic acid diethylamide in healthy subjects. Biol. Psychiat. **78**(8), 544–553 (2015). https://doi.org/10.1016/j.biopsych.2014.11.015
165. Liechti, M.E., Dolder, P.C., Schmid, Y.: Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology **234**(9–10), 1499–1510 (2017). https://doi.org/10.1007/s00213-016-4453-0
166. Grof, S.: Realms of the Human Unconscious: Observations from Lsd Research. Souvenir Press (1996)
167. Passie, T., Halpern, J.H., Stichtenoth, D.O., Emrich, H.M., Hintzen, A.: The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci. Ther. **14**(4), 295–314 (2008). https://doi.org/10.1111/j.1755-5949.2008.00059.x
168. Jones, C.M., Mack, K.A., Paulozzi, L.J., Hsu, J.R., Paulozzi, L., Jones, C., Mack, K., Rudd, R., Jones, C., Mack, K., et al.: Pharmaceutical overdose deaths, United States, 2010. JAMA **309**(7), 657 (2013). https://doi.org/10.1001/jama.2013.272
169. Bjelić, D.I.: Freud's cocaine dreams and memories. In: Intoxication, Modernity, and Colonialism, pp. 141–187. Palgrave Macmillan US, New York (2016). https://doi.org/10.1057/978-1-137-58856-2_5

170. Bramness, J.G.: Prescription drug abuse: risks and prevention. In: Textbook of Addiction Treatment: International Perspectives, pp. 637–661. Springer Milan, Milano (2015). https://doi.org/10.1007/978-88-470-5322-9_29
171. Bjelić, D.I.: Freud's "Cocaine Episode" on Benjamin's Hashish. In: Intoxication, Modernity, and Colonialism, pp. 63–90. Palgrave Macmillan US, New York (2016). https://doi.org/10.1057/978-1-137-58856-2_3
172. Alves, C.J., Magalhães, A., Melo, P., de Sousa, L., Tavares, M.A., Monteiro, P.R.R., Summavielle, T.: Long-term effects of chronic cocaine exposure throughout adolescence on anxiety and stress responsivity in a Wistar rat model. Neuroscience **277**, 343–355 (2014). https://doi.org/10.1016/j.neuroscience.2014.07.008
173. Richards, J.R., Garber, D., Laurin, E.G., Albertson, T.E., Derlet, R.W., Amsterdam, E.A., Olson, K.R., Ramoska, E.A., Lange, R.A.: Treatment of cocaine cardiovascular toxicity: a systematic review. Clinical toxicology (Philadelphia, Pa.) *54*(5), 345–364 (2016). https://doi.org/10.3109/15563650.2016.1142090
174. Stephens, D.N., King, S.L., Lambert, J.J., Belelli, D., Duka, T.: GABAA receptor subtype involvement in addictive behaviour. In: Genes, Brain and Behavior, pp. 149–184. Blackwell Publishing Ltd. (2017). https://doi.org/10.1111/gbb.12321
175. Kishi, T., Matsuda, Y., Iwata, N., Correll, C.U.: Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized placebo-controlled trials. J. Clin. Psychiatry **74**(12), e1169–e1180 (2013). https://doi.org/10.4088/JCP.13r08525
176. Muzyk, A.J., Leung, J.G., Nelson, S., Embury, E.R., Jones, S.R.: The role of diazepam loading for the treatment of alcohol withdrawal syndrome in hospitalized patients. Am. J. Addict. **22**(2), 113–118 (2013). https://doi.org/10.1111/j.1521-0391.2013.00307.x
177. Carroll, K.M., Nich, C., Petry, N.M., Eagan, D.A., Shi, J.M., Ball, S.A.: A randomized factorial trial of disulfiram and contingency management to enhance cognitive behavioral therapy for cocaine dependence. Drug Alcohol Depend. **160**, 135–142 (2016). https://doi.org/10.1016/j.drugalcdep.2015.12.036
178. Haney, M., Rubin, E., Foltin, R.: Modafinil reduces smoked cocaine self-administration in humans: effects vary as a function of cocaine "priming" and cocaine cost. Neuropsychopharmacology. S257 (2015). https://doi.org/10.1016/j.drugalcdep.2016.08.232
179. Kosten, T.R., Wu, G., Huang, W., Harding, M.J., Hamon, S.C., Lappalainen, J., Nielsen, D.A.: Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β-hydroxylase. Biol. Psychiat. **73**(3), 219–224 (2013). https://doi.org/10.1016/j.biopsych.2012.07.011
180. Miller, P.M.: Elsevier Science, Interventions for Addiction (2013)
181. Gaval-Cruz, M., Liles, L.C., Iuvone, P.M., Weinshenker, D.: Chronic inhibition of dopamine β-hydroxylase facilitates behavioral responses to cocaine in mice. PLoS ONE **7**(11), e50583 (2012). https://doi.org/10.1371/journal.pone.0050583
182. De La Garza, R., Bubar, M.J., Carbone, C.L., Moeller, F.G., Newton, T.F., Anastasio, N.C., Harper, T.A., Ware, D.L., Fuller, M.A., Holstein, G.J., et al.: Evaluation of the dopamine β-hydroxylase inhibitor nepicastat in participants who meet criteria for cocaine use disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry **59**, 40–48 (2015). https://doi.org/10.1016/j.pnpbp.2015.01.009
183. Ellefsen, K.N., Concheiro, M., Pirard, S., Gorelick, D.A., Huestis, M.A.: Pharmacodynamic effects and relationships to plasma and oral fluid pharmacokinetics after intravenous cocaine administration. Drug Alcohol Depend. **163**, 116–125 (2016). https://doi.org/10.1016/j.drugalcdep.2016.04.004
184. Ballon, J.S., Feifel, D.: A systematic review of modafinil: potential clinical uses and mechanisms of action. J. Clin. Psychiatry **67**(4), 554–566 (2006). https://doi.org/10.4088/JCP.v67n0406
185. Ryan, J., Sharts-Hopko, N.: The experiences of medical marijuana patients. J. Neurosci. Nurs. **49**(3), 185–190 (2017). https://doi.org/10.1097/JNN.0000000000000283
186. Salhab, A.: Embattled cannabis: pharmacological, medical, recreational, and adverse effects aspects. J. Subst. Use **22**(2), 236–239 (2017). https://doi.org/10.3109/14659891.2016.1149237

187. Panlilio, L.V., Justinova, Z., Trigo, J.M., Le Foll, B.: Screening medications for the treatment of cannabis use disorder. Int. Rev. Neurobiol. **126**, 87–120 (2016). https://doi.org/10.1016/bs.irn.2016.02.005
188. Mason, B.L., Mustafa, A., Filbey, F., Brown, E.S., Mason, B.L.: Novel pharmacotherapeutic interventions for cannabis use disorder. Curr. Addict. Rep. **3**(2), 214–220 (2016). https://doi.org/10.1007/s40429-016-0094-y
189. Levin, F.R., Mariani, J.J., Pavlicova, M., Brooks, D., Glass, A., Mahony, A., Nunes, E.V., Bisaga, A., Dakwar, E., Carpenter, K.M., et al.: Dronabinol and lofexidine for cannabis use disorder: a randomized, double-blind placebo-controlled trial. Drug Alcohol Depend. **159**, 53–60 (2016). https://doi.org/10.1016/j.drugalcdep.2015.11.025
190. Onakpoya, I.J., Heneghan, C.J., Aronson, J.K.: Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. BMC Med. **14**(1), 191 (2016). https://doi.org/10.1186/s12916-016-0735-y
191. Allsop, D.J., Copeland, J., Lintzeris, N., Dunlop, A.J., Montebello, M., Sadler, C., Rivas, G.R., Holland, R.M., Muhleisen, P., Norberg, M.M., et al.: Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA Psychiat. **71**(3), 281–291 (2014). https://doi.org/10.1001/jamapsychiatry.2013.3947
192. Gowda, C.R., Lundt, L.P.: Mechanism of action of narcolepsy medications. CNS spectrums **19**(1), 25–27, 34 (2014). https://doi.org/10.1017/S1092852914000583
193. Punja, S., Shamseer, L., Hartling, L., Urichuk, L., Vandermeer, B., Nikles, J., Vohra, S.: Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. In: Cochrane Database of Systematic Reviews. Wiley, Chichester, UK (2016). https://doi.org/10.1002/14651858.CD009996.pub2
194. Bray, G.A.: Medical treatment of obesity: the past, the present and the future. Best Pract. Res. Clin. Gastroenterol. **28**(4), 665–684 (2014). https://doi.org/10.1016/j.bpg.2014.07.015
195. Steinkellner, T., Montgomery, T.R., Hofmaier, T., Kudlacek, O., Yang, J.-W., Rickhag, M., Jung, G., Lubec, G., Gether, U., Freissmuth, M., et al.: Amphetamine action at the cocaine- and antidepressant- sensitive serotonin transporter is modulated by alphaCaMKII. J. Neurosci. 11762 (2015). https://doi.org/10.1523/JNEUROSCI.4034-14.2015
196. Ling, W., Mooney, L., Haglund, M.: Effects and manifestations of methamphetamine use. Curr. Psychiatry **13**(9) (2014)
197. Diaper, A.M., Law, F.D., Melichar, J.K.: Pharmacological strategies for detoxification. Br. J. Clin. Pharmacol. **77**(2), 302–314 (2014). https://doi.org/10.1111/bcp.12245
198. Geyer, M.A., Richards, W.A., McCann, U., Jesse, R., McKay, C.R., Halberstadt, A.L., Greer, G.R.: Lysergic acid diethylamide and psilocybin revisited. Biol. Psychiat. **78**(8), 516–518 (2015). https://doi.org/10.1016/j.biopsych.2015.08.003
199. Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., Brenneisen, R.: Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J. Nerv. Ment. Dis. **202**(7), 513–520 (2014). https://doi.org/10.1097/NMD.0000000000000113
200. Kometer, M., Vollenweider, F.X.: Serotonergic hallucinogen-induced visual perceptual alterations. Curr. Top. Behav. Neurosci. 1–26 (2016). https://doi.org/10.1007/7854_2016_461
201. Chaudhry, S.K., Broderick, L., Penzner, J.B., Avery, J.: Benzodiazepine maintenance treatment in schizophrenia. The primary care companion for CNS disorders **17**(6) (2015). https://doi.org/10.4088/PCC.15l01818
202. Galinato, M.H., Lockner, J.W., Fannon-Pavlich, M.J., Sobieraj, J.C., Staples, M.C., Somkuwar, S.S., Ghofranian, A., Chaing, S., Navarro, A.I., Joea, A., et al.: A synthetic small-molecule isoxazole-9 protects against methamphetamine relapse. Mol. Psychiatry (2017). https://doi.org/10.1038/mp.2017.46