# Drug Abuse: Addiction and Recovery

**Chapter 1**

# Neurobiology of addiction

***Omar Walid Muquebil Ali Al Shaban Rodriguez[1*]; Maria Aida Fernandez Menendez[2]***

*[1]CSM Luarca, Asturias, Spain*

*[2]Monash University, Australia*

***Correspondence to: Omar Walid Muquebil Ali Al Shaban Rodriguez,*** *Psychiatrist, CSM Luarca, Asturias, Spain*

*Email: muquebilrodriguez@gmail.com*

## 1. Introduction

Drug addiction can be considered a chronic brain disease that affects neurotransmission between circuits of neurons that control behaviour, emotion and cognition; which is characterised by an excessive engagement in drug use, unsuccessful attempts in controlling drug intake, an increase in anxiety and emotional pain, and inaccurate beliefs about drug use [1].

The neurobiological basis of drug addiction is supported by recent advances in neuroimaging procedures, such as Functional magnetic resonance imaging (fMRI), and new findings on the neurobiology of addiction, that have made possible to gather important information around the neurological processes underlying the disruptions in emotional regulation and decision making presented in people with drug addiction [2].

These findings confirm that various neurotransmitters systems: dopaminergic, glutamatergic, GABAergic and acetylcholinergic pathways, are significantly involved in addiction, with dopamine playing a key role because it mediates reward perception and reward motivated behaviour [3]. Once a drug is consumed, the level of these neurotransmitters will vary dramatically at a synapse level, and persistent changes could occur in certain neural circuits that might outlast the presence of the drug in the brain. If exposure to the drugs becomes repetitive some brain areas might depart from its normal functioning to be able to continue functioning [4].

Moreover, it is important to consider the role of memory and learning, this is to say the

environmental associations, in drug addiction. Experiences change the brain through neural plasticity, which are changes that occur at the synapse, such as long-term potentiation (the strengthening of synaptic transmission that results in an enhanced firing of neurons after repeated stimulation). Neural substrates of these learning associations are widely distributed across cortical and subcortical brain structures [4-7]. This neural substrate "learns" that the drug produces a rewarding effect through conditioning, the repeated association of the drug rewarding effect with a specific stimulus, which can be the substance itself or other signals that foresee substance availability, for example certain places or people. Those signals (conditioned stimuli) can, by themselves, trigger dopamine release at the synapses of the limbic system and lead to substance craving, seeking and use [6-8].

Furthermore, individual differences need to be considered when investigating the neurobiology of drug addiction. Some individuals might be more susceptible to develop drug addiction than others, for example, adolescents and young adults whose brain is in a critical phase of development. For example, the prefrontal and other cortical networks that are critical for judgment, inhibition and self-regulation do not fully mature until people reach 21 to 25 years, and this could make them prone to act impulsively and ignore the negative consequences of initiating in drug use. The adolescent brain might also be more sensitive to drugs effects [9-11]. In addition, those suffering from personality and psychiatric disorders are at greater risk of drug abuse [12-14].

## 2. Neurotransmitters involved in drug addiction

Neurotransmitters are endogenous neurochemicals that facilitate the communication between neurons. The initial mechanism of addictive drugs in the brain is produced by the drug mimicking and blocking certain neurotransmitters which triggers a neural dysregulation. Some of the main neurotransmitters that are involved in the addictive process will be next discussed [15-17].

### 2.1. Dopamine

Dopamine (DA) is a neurotransmitter primarily synthesized in neurons on the ventral tegmental area (VTA) and substantia nigra, both located in the midbrain. Dopamine is the molecule most commonly implicated in the mechanisms of drug addiction related to psychostimulant reward and neuroadaptation. Administering any psychoactive drug is associated with an increased intrasynaptic levels of DA in the nucleus accumbens (NAc), which is consider a critical site of DA reward. Dopamine signals the incentive salience of events, drives motivated behaviour, and facilitates memory consolidation from salient events [18-19].

Five DA receptors have been identified and they can be classified in two groups: receptos D1, D2 and D3 are involved in motivation and reward while receptors D4 and D5 are

primarily associated with behavioural inhibition. For instance, an impairment of D4 or D5 function in the prefrontal cortex (PFC) can result in loss of capacity to inhibit behaviour which will give rise to an increased vulnerability to self-administer drugs [19-21].

### 2.2. Serotonin

Serotonin (5-HT) is a neurotransmitter that does not participate directly in motivation or reward but exerts its effects by influencing the DA system. For instance, dopaminergic neurons from the VTA that receive 5-HT increased their firing rate so it can be argued that an increased sensitivity to 5-HT stimulation could be a vulnerability factor for addiction [22].

The 5-HT receptors that have been most often associated with addictive disorders are 5-HT1A, 5-HT1B, 5-HT2A. The most significant component of the serotonergic system that influences motivation-reward is the 5-HT1B receptor which can be located on the axon terminals of many types of neurons. For example, γ-aminobutyric acid (GABA) neurons axon terminals that project from the NAc shell to the VTA contain 5-HT1B receptors that, when stimulated, inhibit GABA release. Since GABA that is released in the VTA inhibits local dopaminergic neurons, inhibition of GABA release disinhibits the mesolimbic dopaminergic neurons and thus potentiates the rewarding effects drugs. Therefore, an activation of 5-HT1B receptors will indirectly increase DA release in the VTA and therefore potentiate the drug effect.

Consequently, a person's vulnerability to develop a drug addiction disoredr can be influenced by an upregulation of 5-HT1B receptors on the axon terminals of GABAergic neurons in the NAc [23-24].

### 2.3. ɣ-aminobutyric acid

ɣ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. Three classes of GABA receptors have been identified: GABAA, GABAB, and GABAC. GABAA and DA interact together in the reward system: dopaminergic neurons in the VTA projecting on the NAc are under inhibitory control mediated by GABAA receptors located in the VTA, when these GABAA receptors are inhibited through GABAA antagonist, this produces an increase of DA released, as a result of the DA not being inhibited by the action of GABAA [25].

Additionally, GABAB receptors have a role in drug-related behavioural reinforcement, which consists on the strengthening of a behaviour by the event that follows that behaviour. GABAB receptors of VTA is closely connected with the mesolimbic dopaminergic reward pathway during rewarding processes. GABAB agonists that target inhibitory GABAB receptors of VTA dopaminergic neurons, seem to attenuate the reinforcing effects of drugs through modulation of DA transmission from the VTA to the NAc [26-28].

To summarise, GABA receptors modulate a variety drug-related reward and reinforcement behaviours, through presynaptic and postsynaptic action. Abnormal functioning of GABA neurons could disinhibit the DA neurons, which will enable them to be more active when stimulated, and thus intensify the reinforcing effects of drugs and increase the likelihood developing drug addiction. Moreover, alterations of GABA receptors might have left an individual susceptible to chronic stress and this could make the individual more prone to use drugs to relieve mental pain, which will be negative reinforced when consuming drugs and therefore more susceptible to develop drug addiction. Consequently, it can be speculated that that a deficiency or hyposensitivity of GABA receptors in the VTA could contribute to an addictive process [29-31].

### 2.4. Norepinephrine

Norepinephrine (NE) is an abundant neurotransmitter in the brain implicated in affective disorders and neuronal excitability. The NE system consists of two principal ascending projections: the dorsal noradrenergic bundle (DNB) which originates in the locus coeruleus and the ventral noradrenergic bundle (VNB) which originates in the medulla and some nuclei of the pons [32].

The NE system also regulates the mesencephalic dopaminergic system indirectly, via the PFC. When NE release is blocked, DA release is similarly attenuated. If the NE blockage is chronic, the DA system gradually compensates by increasing the density of postsynaptic DA receptors. This process will result in hypersensitivity to drugs that increases intrasynaptic DA levels [33-34].

The addictive process could be potentiated by blockade, hyposensitivity and chronic malfunction of NE transporters. Moreover, the crucial factor in a potential relationship between the NE system and addiction seems to be an increased level of extracellular NE and its effects on the DA system. Finally, stress is the most frequent correlate of increased levels of extracellular NE and it seems critical in the stress-induced reinstatement of drug-seeking and drug-abuse [35].

### 2.5. Endogenous opioids

Endogenous opioid peptides, such as endorphins, play a role in drug reward, positive reinforcement and in the development of drug addiction. Drugs of abuse stimulate opioid receptors in NAc and the release of endogenous opioids which produces the rewarding drug effect. Opioid receptor hypersensitivity produced by low baseline levels of endogenous opioid peptides would constitute a vulnerability factor to addictive engagement in any behaviour that results in the stimulation of opioid receptors, including taking drugs of abuse [36].

## 2.6. Endocannabinoids and cannabinoid receptors

The endocannabinoid (eCB) system consists of cannabinoid receptors, endogenous ligands and proteins in charge of their synthesis and degradation. Currently, there are 2 known cannabinoid receptors subtypes, termed CB1 and CB2. The CB1 receptors are the most abundant G-protein-coupled receptor in the CNS and are also found in peripheral tissues while CB2 receptors have been recently found in brainstem, cortex and cerebellum neurons [37-38].

Cannabinoid receptors are abundant in the brain reward circuitry, they have a modulatory role on the reward circuitry and participate in the addictive properties induced by different drugs of abuse. The dopaminergic neurons of the mesocorticolimbic pathway are controlled by excitatory and inhibitory inputs that are modulated by CB1 cannabinoid receptors. Additionally, the presence of CB1 receptors in other structures related to motivation and reward, such as the basolateral amygdala and the hippocampus, also contributes to this function of the endocannabinoid system. [39-41].

Endocannabinoids can be released following NAc depolarization and from dopaminergic neurons in the VTA, and they modulate glutamatergic and GABAergic afferents by acting as retrograde messengers on CB1 receptors [40,41].

Furthermore, eCB contribute to synaptic plasticity in the mesolimbic system, which contributes to the learning processes related to addictive behaviours [42]. Additionally, one of the main function of the eCB system seems to be regulation or containment of chronic stress. Disturbance of the eCB system could increase the level of chronic stress, which in turn may increase the chances of developing drug addiction [43].

To summarise, the eCB system participates in the addictive process of drugs of abuse by three complementary mechanisms: Firstly, the system is directly involved in the primary rewarding effects of drug of abuse by acting on common cellular mechanisms and by allowing the effects of these drugs on mesolimbic transmission. Secondly, the endocannabinoid system is involved in motivational drug-seeking by a dopamine-independent mechanism, in some drugs of abuse, such as psychostimulants and opioids. Lastly, eCB is implicated in relapse to drug-seeking behaviour participating in the motivational effects of drug-related environmental stimuli and drug re-exposure [44].

## 2.7. Glutamate

Glutamate is the main excitatory neurotransmitter, mediating around 70% of synaptic transmission within the CNS. Glutamate can bind to three different receptors the N-methyl-D-aspartate (NMDA) receptor, the a- amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, and the kainic acid (KA) receptor [45].

Glutamate transmission appears to be a principal contributor of enduring neuroplasticity in the brain and the development of drug addiction. During the past decade many examples of evidencing of the involvement of glutamate transmission in the development of behavioural sensitization to repeated drug administration, such cocaine and opioids, have been found [46-47].

Glutamate transmission in the ventral tegmental area has been shown to regulate dopamine-dependent alterations [48] and interaction between noradrenergic and glutamatergic systems may modulate the firing pattern of DA neurons, which in turn may underlie the reinforcing value of drugs and the establishment of addictive behaviour [49].

Drug induced changes in PFC glutamatergic synapses in the NAc have the potential of promoting compulsive drug seeking in addicts by reducing the value of natural rewards and effective regulation, weakening cognitive control and enhancing glutamatergic drive in response to drug associated stimuli [50]. In other words, the diminished ability of drug addicts to control their drug seeking arises from a loss of glutamate homeostasis, which in turn impairs pre- frontal regulation of striatal circuitry [49].

### 2.8. Glucocorticoids and cortisol.

Cortisol is type of glucocorticoid hormone that is released in periods of psychological stress. Glucocorticoid receptors (GRs) are in the hippocampus, the limbic system, and the PFC and they function as a major component of endocrine influence, specifically the stress response, in the brain. The GRs are thought to be implicated in both short and long-term adaptations in response to stressors and may be critical to the understanding of drug addiction. [50-52].

During chronic stress, repeated increase in glucocorticoid hormone secretion or increased GRs sensitivity would sensitize the mesolimbic DA system. This sensitized state, which can persist after the end of the stress, would render the subject more responsive to drugs of abuse and consequently more vulnerable to the development of addiction [43,53].

## 3. Addiction cycle phases

To facilitate understanding of the neurobiological processes behind drug addiction, three recurring phases that affect motivation, behaviour and cognition could be differentiated [2,54,55].

### 3.1. First phase: binge and intoxication

The first stage occurs when an individual who potentially can developed a drug addiction, consume drugs for the first time. Just after a drug is consumed, an increase of dopamine

release in the reward regions of the brain occur. Then, as drug intake experiences recur, drug related rewarding experiences start becoming associated to environmental stimuli that precede those experiences, at neuronal level. In other words, environmental stimuli become conditioned or "cued" with drug use and the only presentation of the "cued" environmental stimuli might elicit DA release, because DA would start firing in anticipatory response to the "cued" stimuli that predict reward delivery. This process can result in experiencing craving for the drug and lead to heavy drug use. The basal ganglia, NAc, dorsal striatum, globus pallidus and thalamus are key elements of this stage [2,54].

### 3.2. Second phase: withdrawal and negative affect

When an individual develops drug addiction, the reward system in the brain becomes desensitized to stimulation by drugs and other rewards. This is to say; drug intake will trigger a much smaller increase in DA in the presence of drug addiction that in its absence. Consequently, those suffering from drug addiction do not experience euphoria to the same degree when using the drug that when they started trying the drug. Unfortunately, these neural changes become fixed and cannot be immediately reversed by drug detoxification. Also, some neuroadaptation, triggered by neurotransmitters implicated in stress response that responded to the excessive utilization of the brain reward system, will happen in the extended amygdala and the individual reactivity to stress and negative affect will increase. These neuronal changes will cause a highly dysphoric stage that will intensify when the activity in dopamine neurons decrease and the drug effect weaken. The drug will then be taken for relieving dysphoria rather than for its pleasurable effects. Repeated drug intake will extend the dysphoria during withdrawal, thus producing a vicious cycle. The extended amygdala is highly implicated in this stage. [2,54,55].

### 3.3. Third phase: preoccupation and anticipation

The changes in the reward and emotional circuits previously described go together with changes in the prefrontal cortical regions, which are involved in executive function: decision-making, inhibitory control and self-regulation. The down-regulation of dopamine also occurs in the prefrontal brain regions impairing self-regulation, decision-making and salience attribution. Neuroplastic changes in glutamatergic signalling also disrupt prefrontal regions. Impaired dopamine and glutamate signalling in the prefrontal regions weakens the ability to resist strong urges or to follow through on decisions to stop taking the drug. It also develops compulsive behaviour and the associated inability to voluntarily reduce drug- taking behaviour, despite the potentially catastrophic consequences. The frontal cortex and allocortex, including prefrontal cortex, orbitofrontal cortex, hippocampus and insula are key elements of the last stage in the addiction cycle [2,54,55].

## 4. Neural pathways and structures involved in addiction

Drugs are chemical substances that modify how neural pathways and neurotransmission work, changing behaviour, emotion and cognition. Occasional drug intake causes temporary changes that revert to normal when the pharmacological effect of the substance finishes. However, long-term abuse can produce permanent changes on brain functioning due to the modification of neural pathways. These permanent changes could leave the individual with a higher tendency to fall back into a drug abuse routine [1,2,4].

Natural reinforces, such as water and food, activate the brain´s reward pathway which involves several parts of the brain: VTA, NAc, and PFC. Drugs make use of the same physiological mechanism that natural reinforces and the more intense the reinforcing effects of a drug, the more persistent will be the memories associated with the drug and more powerful the desire or need to experience its effects again. Addictive drugs are different from natural rewards (e.g. food, water, sex) in that dopamine cells will not stop firing after repeated consumption of the former, the drive to consume is not satiated because they continue increasing dopamine levels, which explains the likelihood of compulsive behaviours from using drugs and not as likely when using natural rewards. This desire or need is known as craving: an affective state in which the drug is strongly desired. Brain circuits responsible of learning and memory play a major role in the addiction development [94].

### 4.1. The effect of drugs on the reward pathway in the brain

The mesolimbic dopaminergic pathway is the reward pathway in the brain. It transmits dopamine from the VTA to the NAc both being central components of the circuitry underlying reward and memory of reward. The mesolimbic pathway is connected with other neurotransmission systems: endogenous opioid, serotonergic and GABAergic system and glutamatergic system among others [56].

Dopaminergic neurons, which cell bodies are in the VTA, project their axons to various cortical and limbic sites and, when activated, produce a rewarding effect. Commonly natural reinforcers, such as food, water or sexual behaviour, activate the mesolimbic dopaminergic pathway, because those behaviours have a major significance in ensuring survival and the rewarding pathway plays a key role in motivating learning of appetitive and consummatory behaviours. Addictive drugs also activate the reward pathway in the brain. The rewarding effect of drugs have one common neurobiological basis: the effect of dopamine release in the NAc [57].

There is a difference on the effect that natural reinforces and the effect that drugs exert on the reward pathway. Activation of DA from natural reinforcers quickly develops habituation: a decrease in the response to a stimulus that occurs after repeated presentations of the same stimulus. However, when it comes to drugs, sensitization of the dopaminergic system can develop, this is to say, an increased response to the drug effect. Therefore, differently from

natural reinforcers, drugs can produce a rewarding effect that generate an increased desire of drug-taking or increased incentive value after drug first intake [58].

Different types of drugs activate or inhibit particular receptors throughout the reward pathway: alcohol is classified as a depressant and is both a GABA-A agonist and glutamate antagonist that slows down central nervous system (CNS) activity and at high doses it also increases dopamine release; nicotine, the major psychoactive component of tobacco, is a brain stimulant that activates dopaminergic neurons both in the VTA and in the NAc; morphine and heroin are opioids that indirectly activates dopaminergic system, acting on GABAergic, opioid receptors and can also directly act over the NAc; cocaine blocks the reuptake of dopamine, noradrenaline and serotonin and therefore increasing its levels at the synapse; and amphetamines increase dopamine, norepinephrine and serotonin release at the synapse [59].

Together with the mesolimbic dopaminergic system, the extended amygdala plays a decisive role regulating the reinforcing actions of drugs. It is comprised for the shell of the NAc, the centromedialamydgala, the bed nucleus of the stria terminalis and the substantia innominatasublenticular region. These structures share morphological and immunohistochemical characteristics and they all received afferent connections from the hippocampus, basolateral amygdala, mesencephalon and lateral hypothalamus; and send efferent projections towards the ventral globus pallidus, ventral tegmental area, brain stem and lateral hypothalamus [60].

The extended amygdala system might regulate both the drug rewarding effects and the neural changes occurred by its chronic use. These positive rewarding effects produced by all major drugs of abuse occur simultaneously to the release of dopamine in the medial NAc and a GABAergic and opioid activation in the centromedial amygdala [61].

## 5. Theories of drug addiction for a neurobiological perspective

Early investigations focused on the negative reinforcement effect of drugs to explain drug addiction. According to the negative reinforcement view of addiction, drug use occurs because the state they alleviate, not because the state they produce. Unpleasant withdrawal symptoms might be eased by the drug. Furthermore, drugs could be used to mitigate negative inner states that occur in life, for instance, anxiety, insomnia, fear, shame, excessive worry, depression etc. Subjects who experience those psychiatric symptoms could use drugs to “self-medicate”, alleviating pre-existing unpleasant emotions or pain, although those symptoms seem to reappear, even stronger, once the effect of the drug has passed [62].

However, the negative reinforcement view had some shortcomings: first, both people and animals would self-administer drugs in the absence of withdrawal symptoms; second, some drugs produce withdrawal symptoms but do not produce addiction, for example some tricyclic antidepressants; third, some reports show that even if withdrawal is relieved, addic-

tion persist; and forth, relapse usually occurs long after withdrawal symptoms have receded [63].

In the 1960s, positive reinforcement began to gain prominence to explain drug addiction after some laboratory studies with animals showed that subjects could increase and maintain drug use in the absence of withdrawal symptoms. Drugs were thought to be addictive because they produced hedonic (subjective pleasurable) effects, such as euphoria. However further studies showed that liking the pleasurable effects of drugs was not an inevitable outcome of becoming addicted to the drug, with many subject taking drugs because its pleasurable effects and not becoming addicted as a result [64].

In the 90s Robison and Berrigde proposed the incentive sensitization theory where they addressed craving, its persistence after extended periods of abstinence and if drug craving was caused by the subjective pleasurable effects of drug. The incentive value refers to the anticipated pleasure associated with taking the drug, drug craving (drug "wanting"), whereas hedonic value is the amount of subjective pleasure that a subject experience when taking the drug (drug "liking"). Repeated exposure to addictive drugs, in individuals susceptible to addiction, might increase drug "wanting", even when drug "liking" was diminished. This theory suggests that when a drug is initially consumed, its incentive value and pleasurable effects are closely related, but once tolerance develops the pleasurable effects decrease whereas the positive incentive value increases. Addictive drugs can change critical neural systems that are naturally involved in reward and incentive motivation. Drug addiction would develop from a sensitization of the mesolimbic dopamine system and NAc related circuitry, which attributes incentive salience to drugs and drug associated cues. Incentive salience, the dominance for the cues that guide and motivate drug-seeking, would be partly responsible for drug craving, drug-seeking and drug-taking [63].

Some years later, Koob & Le Moal proposed in 2001, a neurobiological model of addiction associated with dysregulation reward and allostasis, which refers to the regulatory process of attaining stability or homeostasis, through behavioural or physiological changes. They hypothesize that progression from initial drug-taking to drug addiction results from and alloastic decrease in the brain reward pathway function. When a regulatory system chronically deviates from its normal operating level it reaches a new equilibrium, an allostatic state that when repeated over time can result in allostatic overload, leading to a pathological operating level. Two types of biological mechanisms are thought to be responsible of allostasis in drug addiction: a within-system neuroadaptation and a between-system neuroadaptation [55,64].

Within-system neuroadaptation are neural changes that occur in the brain reward system responsible for the negative motivational effects of drug withdrawal. Acute withdrawal after repeated administration leads to a dopamine and opioid peptide neurotransmission decrease

in the mesolimbic system; also, GABA and glutamate decreases in the amygdala and NAc Chronic substance abuse leads to a decrease in reward neurotransmission that can be seen with neuroimaging ashypoactivity in the orbitofrontal-infralimbic cortex system [66-68].

The between-system neuroadaptation is a neurochemical system that is involved in stress modulation which attempts to restore normal functioning while overcoming the perturbing presence of the drug. The hypothalamic-pituitary-adrenal (HTA) axis and brain stress system become dysregulated by chronic drug abuse. During acute withdrawal, neuroadaptations occur and the following systems become overactivated: the corticopin-releasing factor system (CRF), the dynorphin-κ opioid system, the norepinephrine brain stress system and the neuropeptide Y brain anti-stress system. The activation of brain stress system partly accounts for the negative motivational states common of acute withdrawal, such as chronic irritability and dysphoria [55].

To summarize: The reward system activation decreases (motivational circuits of the ventral striatum-extended amygdala) whereas the activation of the antireward system increases (CRF, norepinephrine and dynorphin activation increases). These alterations in both systems reflect the neurobiological adaptations behind compulsive drug-taking and drug-seeking [55, 64].

Currently, it is believed that four elements are implicated in the transition to addiction: increased incentive salience, decreased reward, increased stress and a decreased executive function [54].

## 6. Dual pathology

### 6.1. Neurotransmission systems in dual pathology

Psychiatric disorders, particularly schizophrenia, bipolar disorder, depression, and attention-deficit–hyperactivity disorder (ADHD), and certain personality traits, such as risk-taking or novelty-seeking traits are major conditioning factors in drug abuse and addiction. Research in dual pathology has identified the following neurotransmission systems that appear to be implicated in dual pathology: dopaminergic, GABAergic and glutamatergic, endogenous opioid, endogenous cannabinoid, nicotinic-cholinergic system and stress related systems [70].

#### 6.1.1. Endogenous opioid system

Differences among individuals in opioid neurotransmission are thought to explain why some individuals are prone to develop alcohol addiction [72,73] and this system is also involved in the pathophysiology of other psychiatric disorders such as borderline personality disorder (BPD) patients who have different concentrations of opioid receptors which explain some of the clinical characteristics of BDP sufferers who tend to abuse substances that target

opioid receptors such as alcohol and opiates [74,75].

### 6.1.2. Endogenous cannabinoid system

In some psychiatric patients, the dysregulation in the endocannabinoid system, for example an increase density of CB1 receptor binding, may contribute to development of depression or schizophrenia and may also facilitate altered behavioural responses to drug exposure such as increased drug craving and relapse, heightened stress sensitivity and persistent anxiety [76].

The dopaminergic and endocannabinoid system interact in complex ways. Agents that interact with the cannabinoid receptor system, such as the no psychoactive cannabidiol, might be beneficial in the treatment of psychosis and may help some individuals with schizophrenia to normalize frontal lobe function [77-79].

### 6.1.3. Nicotinic-cholinergic system

Some psychiatric disorders, included depression, schizophrenia, and schizotypal personality disorders, have a reduced expression of nicotinic receptors. Nicotine therapy administration appears to reduce the frequency of anger, aggression and agitation in both smokers and non-smokers with high trait hostility. Additionally, in preclinical studies, nicotine seems to reduce depressive symptoms in depressed individuals [80, 81].

Nicotine is frequently abused in patients suffering schizophrenia. Acetylcholine receptors interacts with glutamate receptors and they can be found in the hippocampus. Nicotinic receptors are present in important areas in the dopaminergic system, such as VTA and NAc and through them nicotine exerts it rewarding effects. Hence, the cholinergic system by its interactions with the glutamatergic and dopaminergic system, should be considered to explain the frequent nicotine abuse in schizophrenia [82].

Epidemiological research suggests that nicotine smokers that have a history or depression have more difficulties when attempting to quit smoking, because depressive symptoms tend to reappear. It has also been described that smoking is associated with a greater risk of suffering depression. This data might suggest that smoking, by itself, could trigger depressive symptoms. If this were the case, nicotine could be used as medication to treat some pre-existing depressive symptoms in some patients, while in others negative reinforcement would be responsible of the addiction because if nicotine was not present, depressive symptoms might reappear [83,84].

### 6.1.4. Glutamatergic system

Concurrent depressive symptoms have been associated with decreased glutamate trans-

mission. Therefore, medications targeting glutamatergic transmission have been evaluated in addiction disorders, and in other psychiatric disorders, such as depression or schizophrenia [85]. A deficient function of NMDA glutamate receptors could participate in the comorbidity among drug abuse and schizophrenia, because them both are independently and significantly affected by this deficiency [86].

Clinical studies consistently demonstrate that a single administration of a glutamatergic NMDA receptor antagonist, produces fast-acting antidepressant responses in patients suffering from major depressive disorder [87].

### 6.1.5. Dopaminergic system

Schizophrenia is a psychiatric disorder strongly related with the abnormal functioning of the DA system. As already mentioned drugs of abuse increase DA in the dopaminergic brain pathways (mesolimbic pathway, which connect the VTA to the NAc, and mesocortical pathways, which connects the VTA to the PFC), this is related to schizophrenia in that positive symptoms of schizophrenia are thought to result from an excess of dopaminergic neurotransmission in mesolimbic regions, whereas negative symptoms are believed to result from lower dopaminergic transmission in the mesocortical pathway [88].

Moreover, the pathophysiology of ADHD has been linked to DA dysfunction at brain regions comprising the cingulo-frontal-parietal cognitive/attention network, and this dysfunction is thought to underpin the vulnerability to develop a drug addiction among individuals with ADHD [89].

### 6.1.6. Neurobiological stress system

Stress is strongly related to glucocorticoids release which impacts glutamate transmission, and on the pathophysiology of stress-related neuropsychiatric disorders mechanism involved in some cases of dual pathology. Also, the study of the interaction between the stress and endogenous opioid system has shown that stress predisposes to opioid and other drug abuse. Stress is a risk factor in the vulnerability to the initiation and maintenance of drug abuse and relapse in subjects with a history of drug abuse and corticotropin-releasing factor (CRF) is a neurotransmitter involved in the stress response that plays an important role in addiction. The diathesis-stress model suggest that stress can be an environmental factor, that acting over previous diathesis could favour the onset of another psychiatric disorder. In this regard, we could consider psychosocial stress as a factor that by itself could lead a person to adopt non-adaptive strategies and start using drugs to avoid the symptoms produced by stress [90,91].

Moreover, habitual drug use could produce alterations in the CRF system and over time the reactivity to stress seem to be stronger, which could lead into a compulsive pattern of drug-

taking and drug-seeking, and in some people, that are genetically vulnerable, to the development of a mental disorder [92].

### 6.2. Future directions in dual pathology: genome-wide association studies

Genome-Wide Association Studies (GWAS), an examination of genetic variants in some individuals in search for associations between variants and specific traits is undertaken by international collaboration between psychiatrist and investigators and it is formed to conduct meta-analysis of common DNA sequences that influence an individual's genetic susceptibility to ADHD, autism, bipolar disorder, major depressive disorder, and schizophrenia, therefore GWAS may provide a further insight into the relevance of dual pathology by clarifying the neurobiological basis of psychiatric comorbidity, that is of dual pathology [93].

In summary, it is known that the rewarding brain system, mainly those neurons that belong to the mesolimbic dopaminergic system and certain neurotransmitters are partly responsible both for addictive behaviours symptoms and for some psychiatric disorders, especially schizophrenia and depression. It is also known that stress can have an impact on those neurological systems, being an environmental factor that can trigger imbalances that could result in comorbidity. The development of GWAS makes possible the creation of more accurate experimental designs which will help in attaining greater knowledge and understanding of the biological and psychosocial factors that underlie dual diagnosis [69,70,93].

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