AN EBOOK ON

DRUG ABUSE ADDICTION AND RECOVERY

Drug Abuse: Addiction and Recovery

Chapter 1

Neurobiology of addiction

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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

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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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Drug Abuse: Addiction and Recovery

Chapter 2

Licit Drug Withdrawal: Symptoms and Treatments

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Abstract

Abstinence is the deprivation of previously abused substances that lead to addiction. The long-term and excessive use of a drug causes different biochemical and neurophysiological changes. After addiction is established, deprivation causes withdrawal, whose symptoms, duration and degree vary among substances. Common symptoms include anxiety, depression, tremors, impaired thinking, and changes in autonomic nervous system functioning (tachycardia, sweating, vomiting). The most widely used licit drugs of abuse are alcohol and nicotine, and although both are considered psychoactive substances, abstinence from each differs in both neurophysiological and behavioral terms. When substance use is deemed abusive and intervention is necessary, treatment includes medical care and medication to decrease symptoms, avoid complications, and prevent patient craving. A number of prescription drugs are available for the treatment of addiction and withdrawal from alcohol and nicotine. Although treatment for more severe cases may help significantly, most individuals abandon treatment and relapse. Thus, new approaches and experimental tests have been developed in order to expand knowledge about the systemic effects of abusive drugs and alternatives to rehabilitation treatments. In this respect, this chapter intends to review the state of the art in the study of addiction and abstinence from alcohol and nicotine, and propose alternatives for addiction and abstinence treatment.

1. Introduction

Throughout human history, mankind has used drugs for pleasure or healing purposes [1]. Many of these drugs are potentially addictive, characterized by the continuous use of a substance despite its harmful consequences [2]. Drug addiction is considered a worldwide epidemic related to genetic, physiological and environmental factors that lead to health and socioeconomic problems [3]. In the United States, it is estimated that around 21.5 million adults suffer from substance abuse disorder, alcohol being the main addictive substance consumed [4].

Once addiction is established, substance withdrawal can be an arduous and painful challenge. Heavy and long-term drug consumption causes persistent changes in the neural circuitry and behavior [5]. After a period of drug discontinuation, the nervous system has to readjust to the absence of the substance, giving rise to a set of different symptoms, characterizing the withdrawal syndrome [6]. The onset of symptoms varies among drugs, generally occurring within a few hours and peaking in a few days [7,8]. It usually involves somatic, affective and cognitive manifestations [9]. Some symptoms of this syndrome are opposite to those that occur under drug action, a phenomenon known as the “opponent process” [10,11]. Withdrawal from depressants such as alcohol is accompanied by increased anxiety and agitation [5,6]; by contrast, common symptoms of withdrawal from stimulants such as nicotine are fatigue, psychomotor impairment and depressed mood [12,13].

Some addictive drugs are prohibited worldwide, while others are regulated according to the country or state. There are also substances that can be medically prescribed, such as cannabis [14]. On the other hand, oft-addictive and licit drugs such as alcohol and tobacco, which are easily acquired, are only restricted by age. Approximately 2.5 million deaths per year are attributed to alcohol, while cigarette smoking accounts for another 5.4 million deaths (WHO, 2010; 2011). The consumption of these drugs and the associated problems vary widely and remain significant in most countries. Alcohol and nicotine together are a causal factor and/or component cause in several diseases, greater than HIV and tuberculosis combined (WHO 2010; 2011).

Nicotine is a brain stimulant and the major psychoactive component of tobacco. The consumption of this substance produces positive reinforcement, and users report increased energy, attention and relaxation when using nicotine under stress [15]. However, regular use of tobacco can cause cancer, respiratory diseases, neurodegenerative diseases and death [16-18]. According to the World Health Organization (WHO 2015), tobacco has caused 100 million deaths in the last century. Nicotine consumption can start early in life: reports show that the first experience with cigarettes occurs around the age of 13-14 years [1] and is correlated with late consumption of other drugs such as cocaine and marijuana [19]. Adolescents are substitut-

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ing common cigarettes with flavored cigars [20]; electronic cigarettes are also very common and claim to be healthier, despite the fact that they contain the addictive substance [19]. In the Diagnostic and Statistical Manual of Mental Disorder (DMS-5), quitting or reducing cigarette consumption leads to tobacco withdrawal syndrome, which is characterized by increased anxiety, difficulty concentrating, depressed mood, increased appetite, insomnia, irritability, and restlessness.

Alcohol depresses the central nervous system, initially producing an anxiolytic effect [21,22]. Repeated consumption leads to tolerance and higher amounts of alcohol are necessary to achieve the same effects [23,24]. This substance is associated with a number of diseases, including alcohol dependence, cirrhosis, cancer and fetal alcohol syndrome, in addition to an increased risk of infectious diseases, car accidents and violent behavior. It is estimated that 5.9% of deaths worldwide occur due to alcohol consumption (WHO 2014). When a person becomes an alcoholic, symptoms of alcohol withdrawal syndrome appear after just a few hours of deprivation. The syndrome is characterized by autonomic hyperactivity, tremors, anxiety and restlessness. In more severe cases it can be accompanied by seizures, hallucinations and delirium, the last emerging after 3 days of withdrawal and lasting for 48 to 72 hours [25].

Despite substance abuse and addiction's being a serious health problem, withdrawal symptoms hinder drug cessation, increasing the chance of relapse. Although with different degrees of severity, the licit drugs discussed here have the potential to cause intoxication, chronic health problems and death. In this respect, effective treatments are essential. However, treatments could also be a challenge, since they require not only medical/pharmacological intervention, but an integrative approach that relieves craving and withdrawal symptoms, thereby changing an individual's perspective on life and the future. As such, understanding the mechanisms underlying addiction and withdrawal may be key to developing targeted interventions that will overcome the obstacles in current treatments and avoid relapse [26].

2. Neurochemistry Bases

Different addictive drugs act on different neurotransmitter systems in the brain, but all stimulate the dopaminergic system, increasing dopamine levels [27,28]. This neurotransmitter plays an important role in reward processing and reinforcing behavior. The addictive drugs increase up to 10 times the levels of dopamine in the brain and change the normal dopamine secretion leading to the need for more dopamine that only the drug can cause. In mammals, areas of the brain such as the ventral tegmental area (VTA), the nucleus accumbens (NAc), prefrontal cortex (PFC), the amygdala and the hippocampus seem to be related to addictive behavior [29]. Thus, the long-lasting behavioral consequences of the drugs are related to persistent changes in the brain, which only disappear long after the drug removal [30,31]. After neuroadaptation has been established, drug cessation may trigger a negative state (somatic and

affective) that contributes to drug dependence through negative reinforcement [32]. All the oft-addictive drugs function in this manner, including the most available and licit ones: alcohol and nicotine.

2.1. Alcohol

Alcohol or ethanol is a central nervous system depressant that acts through different mechanisms. For instance, alcohol mainly affects the transmission and function of the glutamatergic and GABAergic systems, as well as the adenosinergic and cholinergic systems [33]. It exerts a biphasic effect on brain activity, characterized by initial short-term stimulation, followed by depression in brain activity [34]. The acute alcohol effect is mediated by agonistic and antagonistic action on gamma-aminobutyric acid type-A (GABAA) and N-methyl-D-aspartate (NMDA) receptors, respectively [35,36]. However, prolonged alcohol consumption causes overstimulation of GABAA receptors, which culminates in its down-regulation, while on the other hand, NMDA receptors are up-regulated in order to maintain glutamate response [37]. Thus, the individual can develop tolerance to alcohol and higher amounts of the drug are needed to achieve the initial effects [38]. During alcohol withdrawal, absence of the drug causes hyper excitation of the nervous system, and the neuroadaptations derived from chronic intake initiate the reversal process [39,40].

Two major symptoms of alcohol withdrawal, namely seizures and delirium tremens, are consequences of substance interaction with NMDA receptors. Long term alcohol use increases the expression of NMDA receptors (NR1 and NR2B), due to the inhibitory effects of the drug on these receptors functioning. When the receptors density is increased and alcohol intake is absent, the normal glutamate secretion over stimulates the system, characterizing the hyper excitation state observed during withdrawal [41,42]. Studies have shown that NMDA plays a key role in the appearance of seizures [41,43,44]. For instance, blockade of NMDA receptors in hippocampal neurons eliminates this symptom [41]. In addition to direct NMDA activity regulation, continued alcohol exposure heightens voltage-dependent calcium channel activity [45], which may increase gene expression related to NMDA and GABA receptor synthesis [40,46]. Taken together, alterations in calcium influx caused by the effects of alcohol on voltage-dependent and ligand-dependent channels, such as NMDA, contribute to the emergence of withdrawal symptoms [46].

Activation of NMDA receptors enhances the expression of the early immediate gene c-fos, related to long-lasting central nervous system changes. Indeed, mRNA c-fos levels are high in different brain areas under alcohol abstinence [47]. Glutamatergic transmission is also exacerbated by the excitatory action of homocysteine, an amino acid whose levels increase due to alcohol intake [48]. Higher levels of homocysteine are predictive of withdrawal seizures, which might occur due to exacerbation of glutamatergic neurotransmission [48].

Seizure occurrence also seems to be modulated by GABA, since the administration of bicculline, a GABAA antagonist, reduces seizure thresholds [49]. Chronic alcohol use decreases the expression of GABAA receptors, due to the stimulatory effects of the drug on these receptors functioning that culminate in down regulation. The decreased GABAA receptor density is observed in combination with the increased expression of other subunits that are less sensitive to alcohol [50]. Thus, in the absence of the drug, the amount of GABA neurotransmitter normally secreted becomes insufficient to affect the post synaptic neurons that express decreased number of receptors. In the amygdala, a change in GABAA receptor activity is associated with anxiety [51]. In rats under alcohol abstinence, treatment with GABAA and GABAB receptor agonists attenuated anxiety, a result not observed in animals treated with glutamate receptor agonists [52].

Monoamines and catecholamines are also involved in the alcohol withdrawal syndrome. Dopamine receptor binding increases in key emotional processing regions during withdrawal [53]. Withdrawal also raises plasma adrenaline and noradrenaline levels, with the ratio of noradrenaline to adrenaline correlated with the severity of hyper excitability promoted by withdrawal [54]. In humans, plasma noradrenaline levels are higher after drug cessation, but serotonin levels decrease [55]. Evidence suggests that serotonin and noradrenaline are also related to alcohol abuse in animal models [56-58], and seem to mediate craving and relapse during withdrawal. However, this relation is not clear and further studies are needed for a thorough understanding [55].

Alcohol withdrawal syndrome is a complex disorder regulated by different neural mechanisms. Initially, after alcohol abuse for a long time, the drug cessation creates a general excitatory activity due to GABA and NMDA system neuroadaptations that lead to increased anxiety, seizures and delirium tremens. Some mechanisms remain unclear and the molecular basis of tolerance and craving is poorly understood.

2.2. Nicotine

Nicotine is a psychostimulant drug associated with cognitive improvement [59] and acts as an agonist on different subtypes of nicotinic acetylcholine receptors (nAChRs) [60]. These receptors play an important role in neuronal functions, including excitability, cognitive function and plasticity induction [61,62]. Nicotinic receptors are ligand-gated ion channels with high permeability to Ca^{2+} [62]. The subunits are classified into two families: the α-type (α2-α9) and β-type (β2, β3 and β4), but most receptors are formed by the coexpression of α and β subunits [63], one of the most common being the α4β2 receptor [64].

Nicotine is a full agonist of α4β2 and α7 nAChRs, but shows higher affinity for the former [59]. The binding of nicotine at acetylcholine receptors can also increase the release of dopamine, the neurotransmitter that exerts positive reinforcing effects and may lead to the

drug dependence [65]. The neuroadaptations resultant of long-term drug consumption and addiction are responsible for the physiological and behavioral symptoms during withdrawal.

Neuroadaptation related to long-term drug consumption and addiction is responsible for the physiological and behavioral symptoms during withdrawal. In the case of nicotine, a relevant withdrawal symptom is the decrease in cognitive performance that manifests itself for several days after cessation [66,67]. Nicotine activates nAChRs in the hippocampus, an important area for attention, learning and memory, in addition to inducing synaptic potentiation [68]. Chronic consumption leads to long-lasting changes in this region, which is affected by drug withdrawal. Studies have shown that α4β2 and α7 nAChRs can act differently in withdrawal-induced deficits. In mice, administration of the α4β2 agonist (i.e. varenicline) reduces withdrawal deficits in fear conditioning; however, the α7 agonist cannot reverse the animal's poor performance [69]. On the other hand, impaired attention due to withdrawal is related to the α7 receptor, since mice lacking this receptor show no withdrawal-induced deficits [70].

Another system involved in nicotine effects is the endocannabinoid system [71,72]. 2-arachidonoylglycerol (2-AG) is an endogenous endocannabinnoid that attenuates the somatic signs of nicotine withdrawal [73]. 2-AG concentration was shown to increase 10 minutes after withdrawal [74]. Despite the positive effect on physical withdrawal symptoms, activation of CB1 receptors by 2-AG is associated with cognitive impairment. Mice submitted to pharmacological or genetic inactivation of CB1 receptors in forebrain GABAergic neurons exhibit no memory deficits during nicotine withdrawal [74]. In addition, these authors found that nicotine withdrawal reduces the density of mushroom-type dendritic spines in the hippocampus, which was reversed in mice lacking CB1 receptors in GABAergic neurons. In the hippocampus, dendritic spines are important to the structural changes in synapses that underlie the learning and memory process [75]. Moreover, mushroom spines contain a high density of glutamate receptors [76,77].

The glutamatergic system has been related to many aspects of nicotine withdrawal. Nicotine induces glutamate release and activates presynaptic glutamate terminals, causing a stimulatory effect on dopamine transmission and activation of postsynaptic metabotropic Glu5 receptors, which are implicated in the reinforcing properties of nicotine [78,79]. With respect to withdrawal, these receptors participate in the somatic and affective manifestations of abstinence. Mice with metabotropic Glu5 receptor knockout showed attenuation of anhedonia and somatic withdrawal signs [78].

Many neurotransmission systems and mechanisms are involved in nicotine addiction and withdrawal. This substance can change the long-term structure and activity of the neural system. As such, its absence disrupts the newly acquired homeostasis related to the drug. Cognitive deficits and depressed mood due to withdrawal are the main causes of relapse. While

treatments are available, not all are efficient, and most patients relapse. In this respect, more studies are needed to fully understand the neural mechanisms of nicotine withdrawal.

3. Models in Addiction and Withdrawal Research

Understanding the neurobiology involved in drug withdrawal requires novel approaches to properly model the withdrawal syndrome. This can be achieved through new experimental paradigms, new biomarkers and alternative research models [80].

Drug withdrawal symptoms can be recognized and self-reported by those who experience them, and are expressed as changes in mood or behavior. The symptoms of nicotine withdrawal start about 30 min after the last use, and depend on how much has been used and for how long. Symptoms include cravings, tingling, sweating, nausea, headaches, insomnia, attention and learning deficits, anxiety, irritability and depression. Alcohol withdrawal symptoms start from 6 to 12 h after the last intake, and be more severe between 12 and 24h after ingestion, depending on how much was consumed and for how long. They include tremors, sweating, hypertension, tachycardia, and general delirious symptoms such as clouded consciousness, disorientation, disturbed circadian rhythms, thought processes and sensory disturbances, all of which fluctuate over time [81].

Clinical studies on abstinence in humans are usually retrospective, that is, first a volunteer exhibits withdrawal symptoms and is then investigated or the possible generating events of the process are recreated. Scientific control becomes more difficult when it involves human testimony, since it depends entirely on the veracity of the doses and percentages reported by each person. However, many of the withdrawal symptoms observed in humans are also observed in animal models, with the advantage of researchers controlling the exposure regime and amount. Thus, scientists are using animals as subjects to model the symptoms of drug withdrawal. Since withdrawal from these drugs of abuse commonly produces symptoms of anxiety, animal models of anxiety could be useful for studying drug withdrawal.

Alcohol withdrawal signs have been described in rats [82-85], mice [86-88], cats [89,90], dogs [91,92], fish [24,93] , monkeys [94] and chimpanzees [95,96]. These species and humans exhibit tremors and potentially fatal seizures during alcohol withdrawal.

In line with clinical findings, data on rodents describe anxiety-like behaviors evoked by acute withdrawal from alcohol [97] and nicotine [98]. In addition to the robust behavioral effects of a single withdrawal period, repeated administration and cessation of a drug treatment in animal models evoke strong withdrawal-like effects. For instance, increased anxiety-like behavior was reported in rodents following repeated withdrawal from alcohol [99].

Numerous studies on the effects of nicotine abstinence in animal models induce ab-

stinence using an 'extinction' procedure, in which the experimenter either stops delivering nicotine or no longer rewards animal responses with nicotine [100]. Both of these procedures exhibit problems. Most animal studies involve experimenter-administered nicotine. In many models, an experimenter-administered drug produces dramatically different neurobiological outcomes than a self-administered one [101]. Thus, cessation of an experimenter-administered vs. self-administered drug likely produces different results. Whether this is true for alcohol and nicotine deprivation has yet to be tested. However, there is a consensus that interrupting self-administered drugs appears to be more generalizable and translational than halting experimenter-administered drugs.

The withdrawal syndrome is one of the indicators of a drug-dependent state, which is often paralleled by drug tolerance, due to adaptations that take place within the body and the brain. In animal models, drug administration and drug withdrawal tests to determine the additive effect are more difficult, since there are only a few drug self-administration models. However, there are a number of behavioral tests to evaluate this condition. Two approaches for developing these models are presented here: Conditioned Place Preference (CPP) and Voluntary Intake.

The conditioned place preference is a common alternative to drug self-administration. In the CPP protocol, the motivational properties of the drug serve as conditional stimulus that is repeatedly paired with a series of environmental cues. During conditioning, these cues acquire secondary motivational properties [102-106]. The CPP protocol is useful because addiction is a psychiatric disorder that leads to compulsive drug-seeking behavior. As such, an animal that is conditioned to receiving a drug in a specific place will continue to seek it out long after the drug is removed [107]. The drug-induced conditioned place preference protocol offers a number of benefits, such as being a noninvasive (animal does not need to be handled, injected, etc.) and simple procedure that can be applied to studies investigating the addictive potential of many drugs of abuse [108-111]. In the CPP procedure, the conditioning phase does not usually last long due to the addictive power of the substances used. Thus, a single exposure may be enough to trigger compulsive drug seeking. Craving behavior, characterized by loss of control, and also referred to as compulsive drug seeking, shows high correlation with an increase in dopaminergic transmission in the mesocorticolimbic system [112]. However, even though CPP has long been used in science, the genetic and neurological bases of seeking behavior are not fully understood. It would be important to use CPP as a tool to develop pharmacological and psychological therapies for drug addiction and withdrawal treatment.

An alternative approach to study drug addiction and withdrawal is the drug self-administration protocol. This non-operant method is typically used for the oral route of administration, but is also available for inhalation or injection by the animal itself. The protocol is largely applied in rodent research, since the animals can access the drug in bottles (dissolved in liquid)

or food and ingest the desired amount. Ingesting the desired amount of the drug confers face and construct validity onto the protocol because it matches human alcohol consumption. It can be useful in the development of pharmacological interventions that prevent excessive intake or even lead to complete avoidance. Moreover, following the development of addiction/dependence and the neural and behavioral changes linked to it, researchers can address inter-subject differences and the neurobiological mechanisms underlying addiction. For instance, many strains or rodents selected for high and low alcohol preference have already been produced, allowing more detailed research on the genetic and environmental background that drives addiction [113].

4. Treatments Available

Drug addiction treatments are commonly believed to involve an individual's being arrested, locked up, forced to withdraw from drugs for several months, and then released onto the street. However, this is not always the case. Treatments for drug addiction and withdrawal symptoms can take several forms and degrees of effectiveness. Some users require a long withdrawal period, and suffer numerous relapses before being successfully treated, others withdraw quickly after stopping drug use, while some do not respond to any form of treatment.

Treatment does not require total abstinence, but can be considered successful with a reduction in drug use, even if not completely eliminated. Long-term drug use provokes changes in the brain systems (discussed above), thereby hindering abstinence, both psychologically and physiologically. Indeed, addiction is a brain-based disorder driven by biological and environmental factors. Recent research on drug use/abuse has shown that addiction has many different origins, including inherited traits (genetically and epigenetically), environmental/social pressure, personal habits and other indeterminate causes. Thus, to treat addiction one must face a myriad of causes and a lifestyle change involving both medical (pharmacological) and behavioral (psychological) treatments.

It is important to underscore that there is no single, highly effective treatment that can be universally applied. Different treatments have to be used in sequence or simultaneously to achieve success, and sometimes it takes longer to discover the best treatment approach for drug addiction. As such, many patients abandon treatment during the initial trials. It is also important to be resilient and have strong support from family and friends, so that the user who does not achieve immediate success will attempt an alternative treatment. A good treatment must contend with multiple problems, including family history, life history (anxiety, depression), and social history. Since many different elements contribute to drug use/abuse, it is difficult to remain drug-free without perceiving the whole picture. Moreover, many drug users are at a point where their lives are in shambles and simply stopping drug use may lead to an even more severe state. Thus, treatments have to include new opportunities and users often

need to rebuild personal and social skills through psychological therapy. Rehabilitation is usually prolonged and must be continued even after the individual is drug free. Therapies should be combined with medication, which helps in the physiological control of the addiction/withdrawal. Moreover, for those displaying anxiety/depression, medication and therapy to treat these specific disorders should be applied in conjunction with the drug addiction treatment.

Many treatments commence with a decrease in drug intake (not absolute withdrawal), so that detoxification can occur gradually. The brain systems can better deal with drug removal by slightly reducing the amount, so that the brain enzymes, neurotransmitters, and receptors can up regulate to function adequately without the drug. This avoids withdrawal syndrome and the most painful and difficult phases may be less arduous. However, it is not easy to determine how much to use or not use to avoid entering withdrawal while constantly reducing drug intake. As such, it is important to obtain the patient's personal and drug history in order to provide the most adequate treatment plan, which should involve behavior modification and medication to help the patient tolerate abstinence.

Behavior therapies use plans and practices to modify seeking behavior (craving), toxic behavior and drug intake. This can be done individually or in groups (for example: Alcoholics Anonymous), depending on the best plan for the patient. However, these therapies carry pros and cons. For instance, while individual therapies can meet specific needs and delve deeper into an individual's problems, group therapies may be cheaper, and more experienced members can serve as models to newcomers. Family therapy can also help if members are available to assist and support the patient.

Many types of behavior therapies are applied to treat addiction, such as cognitive behavioral therapy, which helps the intellectually-oriented patient avoid relapse [114], or contingency management, which uses reward to divert the patient from risky behavior [115]. Several others can be used, depending on the drug, level of addiction and other aspects of the patient's life. A recently proposed association between behavioral therapy and physical exercise showed a decline in seeking behavior in high school students [116]. However, further investigation is required to be used as a parallel instrument in the war against addiction.

With respect to medication, considerable research has been conducted on the mechanisms of action and benefits of the medications suggested to treat addiction. For alcohol addiction, the most common medications are naltrexone (an opiate receptor antagonist that inhibits alcohol seeking behavior; [117]) disufiram and clonidine (to induce nausea if alcohol is consumed; [118,119], ondansetron and topiramate (serotonin receptor antagonist and anticonvulsant, respectively, more recently applied with promising results; [120,121]). For nicotine addiction, gums and patches containing nicotine attempt replace the source of the drug and reduce smoking, but other drugs such as varenicline (nicotinic receptor agonist; [122]) and

bupropion (dopamine reuptake inhibitor [123]) are also used with relative success.

It is paradoxical to replace an addictive drug with medication or a different form of the same drug, as is the case of gums containing nicotine. While some argue that it does not help withdrawing from the drug, medications are part of a treatment that will help users free themselves from addiction and/or withdrawal, but additional steps are necessary to achieve complete rehabilitation. It is important to know that after prolonged drug intake and addiction, the user's brain systems are altered and the drug becomes part of its functioning. Thus, it is not easy to maintain proper brain function if the drug has been withdrawn. Slowly removing/replacing the drug may be useful in stabilizing the system while the user's behavior and physiology is being remodeled. For this reason, current knowledge recommends both behavior and medical therapies, but new research and insights are emerging and may lead to a different view of addiction treatment in the near future.

5. Alternative Treatments

Stress is a significant contributor to drug abuse and relapse [124-128]. It is known to increase drug use in general and alcohol and cigarettes in particular [129]. However, recent research suggests that mindfulness-based cognitive therapy, physical exercise and/or an alternative pharmacological intervention using ayahuasca are promising in drug addiction treatments.

Mindfulness reduces stress and has a potential impact on drug use and relapse. The technique is based on the user's awareness and acceptance of their experience and interruption of the craving/using/relapse cycle. It teaches how to process situations that may lead to relapse, inducing users to monitor their internal state, and react using mindful awareness, thereby making positive choices.

While cognitive-behavior treatment uses a reinterpretation of the situation with a more positive view and coping with stress [130,131], mindfulness treatment suggests accepting and viewing a negative situation as it is, then changing how one reacts to it [132]. Studies of meditation interventions as a treatment for alcohol users have shown positive results [133-135]. The use of mindfulness-based treatment has been garnering data that corroborate its successful effects on drug addiction [136,137], suggesting long-term benefits.

It is believed that reducing stress underlies the efficacy of mindfulness treatment in decreasing drug use and relapse over time [129]. Mindfulness treatment seems to be related to the control of stress outcomes in the amygdala and insula [129], areas also implicated in anxiety and anxiety disorders [138,139]. Neuroplasticity in these two structures was observed following mindfulness meditation (e.g., [140-144]). For instance, a decline in amygdala density is related to stress reduction [142] and mindfulness treatment decreases nicotine use [129].

Some authors have recently suggested the value of physical exercise as an alternative intervention to avoid drug relapse [145]. It is suggested that physical exercise exerts reinforcing effects, increasing some neurotransmitters levels that the addicted brain searches for, such as serotonin and dopamine. In fact, it was shown that exercise (wheel running) reduced ethanol seeking in rats [146], suggesting positive effects of voluntary physical exercising during withdrawal that may reduce relapse.

Other positive results associated with drug use are reported after ayahuasca-assisted treatment. Ayahuasca is a brew obtained by decoction of the bark and stems of *Banisteriopsis caapi* and leaves of *Psychotria viridis*, produced by indigenous groups in the Amazon for centuries [147]. The resulting brew, rich in N,N-dimethyltryptamine (DMT) and monoamine oxidase inhibitors (MAOIs), modulates the availability of monoaminergic neurotransmitters in the synaptic cleft. Ayahuasca consumption has been shown to activate brain areas related to emotions and memory [148], and users have reported improved concentration, better performance in cognitive tasks and a greater sense of meaning in their lives. As such, ayahuasca has recently gained attention as an alternative drug for treating mental disorders such as anxiety and depression, as well as drug addiction.

Ayahuasca intake is usually associated with positive lifestyle changes: people that experience the effects of ayahuasca have reported mind healing, increased self-knowledge, a sense of the meaning of life and persistent good mood states even after a single dose. Ayahuasca is often related to deep feelings and memories, and opportunities to re-evaluate negative behavior, events that lead to profound changes in an individual's life perspectives and expectations [149,150]. Thus, ayahuasca has been suggested as an alternative treatment for drug addiction due to its fast response, prolonged effect, absence of adverse effects and no addictive potential [151].

A number of studies have related ayahuasca consumption to reduced use of other abused substances [152-154]. The main action of ayahuasca in the brain occurs in the serotonergic system: DMT enhances the activation of 5-HT receptors (agonist effect), culminating in effects similar to those of serotonin itself. In regard to addiction, ayahuasca reduces dopamine levels in the mesocorticolimbic pathway through its action on 5-HT2A receptors expressed in dopaminergic neurons [155]. Participants in ayahuasca rituals significantly curb or even cease to take drugs of abuse, including cigarettes, alcohol and cocaine [153]. Studies in rodents showed that ayahuasca reverses alcohol sensitization [156], corroborating its potential to inhibit alcohol abuse.

6. Conclusion

Evidence of the aforementioned positive effects of mindfulness-based and ayahuasca treatments suggests therapeutic benefits. However, additional studies are needed to corrobo-

rate the positive effects of these two promising interventions. As stated above, alcohol and nicotine addiction are significant social and health problems. These two oft-addictive drugs are inexpensive and easily obtained, thereby increasing the likelihood of abuse. Consuming these drugs may lead to changes in the central nervous system that result in addiction, followed by withdrawal symptoms that impede drug cessation. While many treatments using alternative medication and therapies are available, relapse rates are between 40 and 60 percent. Thus, investment in new research and approaches to the addiction/withdrawal problem are needed. Recent techniques such as mindfulness, exercising and ayahuasca seem promising, but require more detailed investigation.

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Drug Abuse: Addiction and Recovery

Chapter 3

Abuse Deterrent Formulations for Reducing Misuse and Abuse of Prescription Opioids

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Abstract

Opioids abuse is an epidemic problem in the US, which can be gauged by consumption level. The US constitutes 5% of world population but consumes 75-80% of global opioids. Prescription opioid abuse has negative consequences on social and economic indicators. FDA has also taken a lead among other federal agencies in combating the prescription abuse by promoting the abuse deterrent formulations (ADFs). ADFs have properties that deter the abuse of prescription opioids. Although they are 5- to 15-times more expensive than non-ADFs brand and generic opioid products, their effectiveness in preventing abuse, death and diversion is limited as shown by the published data. This chapter reviews the steps taken at federal and state agencies, and ADFs status, and their advantage and disadvantage.

Key words: Prescription opioids; addiction; abuse; abuse deterrent formulations

1. Introduction

Pain is considered the fifth vital sign and monitored with vigilance as blood pressure, pulse, temperature and respiratory rate in a modern health-care facility [1-2]. About 100 million Americans suffer from acute and chronic pain [3] and opioids are frequently prescribed to alleviate pain. A consensus is lacking among clinicians about the utility of opioids' use in chronic pain management [4-5]. Moreover, opioids are associated with misuse, abuse, diver-

sion, withdrawal, addiction, overdose and death. Prescription of opioids has increased 4 folds from 2002 to 2010 due to healthcare professional standards (Agency for Health Care Research and Quality guidelines and hospital value-based purchasing program) combined with aggressive marketing by pharmaceutical companies [6-7]. Consequently, USA has become number one consumer of opioid drugs in the world. It constitutes only 5% of world population, but consumes 80% of global supply of opioids [8]. In 2015 alone 227 million prescriptions of opioids were written in the USA, which is enough to hand a bottle of pills to nine out of every ten adults [9]. All this led to an epidemic of opioid addiction and death associated with opioids' overdose. According to National Institute on Drug Abuse, two million Americans had a prescription opioids use disorder and 591,000 suffered from a heroin use disorder in 2015 [10]. Drug overdose is the leading cause of accidental deaths in US with 52,404 deaths alone in 2015, surpassing for the first time the number of people killed by gun homicides and car crashed combined [11-12]. Opioids are driving the epidemic of overdose deaths. In 2015 alone, prescription opioids overdose was responsible for 20,101 deaths, and 12,990 death were attributed to heroin [11]. The opioid products prescribed in US are 90% immediate release and 10% extended release/long acting (ER/LA). Most of ER/LA opioids have abuse deterrent property claims on their label [3]. Opioids linked to overdose deaths are Percocet® (oxycodone and acetaminophen), OxyContin® (oxycodone), heroin and fentanyl [12]. Prescription abuse has a tremendous impact on the US economy. The economic cost of prescription abuse is $78.5 billion on healthcare, law enforcement and lost productivity [13]. This chapter reviews multipronged approaches in addressing this very important issue. Multipronged approaches include steps taken by various governmental agencies including abuse deterrent formulations (ADFs), which deter the abuse of prescription opioids.

2. Steps taken at State and Federal Level to Combat Opioids Epidemic

States and federal agencies are aggressively fighting to eliminate the scourge of prescription opioids' misuse, abuse and diversion. Following actions are taken at states and federal levels:

2.1. Mandatory prescriber training

Prescribers play a critical role in preventing the misuse and abuse of opioids. They have a responsibility to help ensure the safe and effective use of opioid products. Prescriber's education is a very important element in the best use of opioids, including when and which patients they should prescribe. FDA requires companies marketing ER/LA opioids to provide risk evaluation and mitigation strategy (REMS) [14]. REMS is a strategy to manage known or potential risks associated with a drug product. It is required for pre- and post-approval of the ER/LA product of opioids since 2012. It includes communication tools (patient package insert and medication guide), communication plan and elements to assure safe use. In the communi-

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cation plan, a developed plan of communicating risk of opioids to key audiences is included in REMS. It includes sending information to healthcare providers, disseminating information about REMS to encourage implementation or explain certain safety protocols or disseminating information through professional societies about any serious risks of drug and protocol to assure safe use. Elements delete of assuring safe use are intended to mitigate a specific serious risk. This includes providing medication guide and training/education to prescribers. Training must be provided through accredited continuing education activities supported by independent educational grants from ER/LA opioids analgesic companies. The education/training on opioids should cover all elements of 'FDA's blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics' [15].

2.2. Prescription drug monitoring programs (PDMPs)

It is an electronic database system of controlled drugs prescribed by practitioners and dispensed by pharmacists and run by the state, common wealth or territory of the USA. It is designed to monitor information of suspected abuse or diversion that can give critical information about the patient's controlled substances prescription history. Prescriber and pharmacists can utilize this information in identifying patients at high-risk and recommend early intervention. It is highly effective program in controlling and reducing abuse and division of prescription controlled substances. Electronic data of controlled substances is submitted by pharmacies and dispensing practitioners. Data are used by states for educational efforts, research, enforcement and abuse prevention. Currently, 49 states, District of Columbia and Guam territory of USA have operational PDMPs. Various state agencies are involved in running this program. The state agencies managing the program are consumer protection, substance abuse, law enforcement, professional licensing, department of health and boards of pharmacy. Per the state law, PDMPs monitor the controlled substances as defined by the Federal and State Controlled Substances Laws. Most states PDMP collect information on federal schedules II-IV controlled substances while some states also collect information on federal schedules II-V controlled substances. Access to PDMPs database system is determined by each individual state. Most states allow access to PDMP data of the patients to practitioners and pharmacists under their care. Many states also allow access of PDMPs to other authorized groups. These may include, e.g. law enforcement for drug investigations (open investigations and sometime court orders are required), licensing and regulatory boards of investigating health care professionals who prescribe or dispense prescription controlled substances, state Medicaid programs for Medicaid members, state medical examiners or coroners for cause of death investigations and research organization that may provide de-identified data for analysis and research [16-18].

2.3. Overdose education and naloxone distribution (OEND)

The purpose of OEND programs is to reduce adverse events and risk of life-threatening

opioid overdose and deaths. The programs involve education and training of opioid overdose prevention, recognition of opioid overdose, opioid overdose rescue response, and distribution of naloxone kits. Education involves educating people at risk for overdose and bystanders on how to prevent, recognize and respond to an overdose. Training elements include how to recognize the sign of overdose, seek help, rescue breathe, use naloxone and stay with the person who is overdosing. Naloxone can be administered by the bystander who is also opioids user, a friend, family member, acquaintance or first responder such as police or firefighter. OEND programs of educating and training of bystander through community started in the 1990s and have expanded to 30 states. Many states have changed legal framework to allow wider access to naloxone. The prescriber is allowed to prescribe naloxone to the third-party family member as well as making naloxone available without a prescription in retail pharmacies. Although community based distribution of naloxone is still a common driver of naloxone distribution [19]. Naloxone is a potent opioid antagonist that antagonizes opioid effects by competing for the same opioid receptor, mu receptor. FDA has approved subcutaneous injection (Evzio®) and nasal spray (Narcan®) dosage forms of naloxone for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression [20-21]. The naloxone kits contain either intranasal or intramuscular dosage form of the drug. OEND programs have reduced opioid overdose deaths in the community that has it compared to one that does not have it. Furthermore, this is supported by number of reported studies and observational data [22-25].

2.4. Doctor shopping and pill mills

It is against the federal law for a doctor to prescribe opioids drug without a valid prescription or outside the usual use of the medicine. A doctor will be charged for drug trafficking if the prescription is deemed not valid. “Pill mill’ is a term used primarily by local and state investigators to describe a doctor, clinic or pharmacy that is prescribing or dispensing powerful narcotics inappropriately or for non-medical reasons [26]. Pill mills were most common in pain management clinic of Florida. Furthermore, abusers and drug traffickers were utilizing pain management clinic as a source of prescription controlled substances. Federal and state governments have cracked down on pill mills [27]. In doctor shopping practice, patient visits multiple physicians to get the medical opinion of continuing illness or to obtain prescription drugs illegally [28]. States law require opioid prescriber to check for doctor shopping through PDMPs database [29].

2.5. Drug courts

Drug courts are problem-solving courts that were created to address the underlying problems that result in criminal behavior. It is most effective justice intervention program in treating drug-addicts. The objective of drug courts is to reduce the crime by changing the be-

havior of abusers toward substance abuse. Thus breaking a cycle of drug addiction and crime. It reduces substance abuse, crime, restores lives, saves children, reunites families and saves money [30]. First drug court was established in Miami-Dade County, Florida in 1989 in response to growing crack (cocaine) problem in which court was tired of prosecuting the same individual for the same crime [31-32]. All 50 states of US have more than 3000 functional drug courts as of June 2015 [32]. It combines the intensive judicial supervision, mandatory drug testing, sanctions and treatment to help the drug abusers. The eligible abuser can be diverted to drug courts in various ways and at various stages in the judicial process. This program is offered to the abuser as an alternative to probation or short-term incarceration. The abuser who agrees to appear in drug court will have the possibility of getting charges dismissed or reduced sentence. There are two programs in drug courts: deferred prosecution and post-adjudication programs. In a deferred prosecution or diverting setting, the abuser is diverted to drug court prior to pleading to a charge. Abusers are not required to plead guilty and those who complete drug court programs are not prosecuted further. However, failure to complete the program results in prosecution. In post-adjudication programs of the drug courts, the abusers plead to their charges but their sentences are deferred or suspended until completion of the programs [33]. Successful completion of the program may results in waived or expungement of sentences. However, they will return to criminal court if they fail to meet drug courts requirement. Standard drug program run from six months to one year but many abusers stay longer in order to complete the entire program. The program's requirements include drug and arrest free for specified time, securing housing and/or employment. Abusers receive reward or face sanction based on the drug test, which is conducted frequently. Rewards include verbal praise, certificates or other tokens of approval or moving to next level of supervision which may include a less frequent visit to court. A sanction may include verbal admonishment, writing an essay, jail time, or kicked out from the program and facing traditional sentencing [34]. Eligibility for drug court varies according to state and local guidelines and on the type of drug court model [35-36].

2.6. Medication assisted treatment (MAT)

It involves treatment of opioids addiction with medicines along with counselling and support (behavioral therapy). Medicines developed for the treatment of opioids addiction act on the same receptors as the opioids drug namely opioids receptors. They can have properties of opioids agonists, partial agonists or antagonists. Medication available for the treatment of opioids addictions are methadone (a slow acting opioids agonist, Dolophine® or Methadose™) [37-38], buprenorphine (a partial opioid agonist, Suboxone® and Probuphine®) [39-40] and naltrexone (an opioid antagonist, Revia® (an immediate acting), Vivitrol® (extended release)) [41-42]. To increase patients' compliance, long acting formulation of buprenorphine and naltrexone is also available (Probuphine® and Vivitrol®). World Health Organization included

buprenorphine and methadone in “essential medicines” category [43]. Typical MAT treatment involves following steps: physician consultation, determining suitability of the abuser to MAT, prescribing medication and stabilization/maintenance of medication. The behavioral treatments include assessment of abuser psychosocial needs; counselling, an inclusion of family support and referrals to community services. Published reports indicated that outcomes of medical assisted therapy are better than without it. Data on MAT approach in addiction treatment has shown that it decreases opioid related overdose death, morbidity and mortality, criminal activity, infectious disease transmission and improves social functioning [44-46]. Substance Abuse and Mental Health Services Administration (SAMHSA) increases the access to MAT treatments to abuser based on published outcomes. SAMHSA issued new reporting requirement for the physicians who will be authorized to prescribe or dispense buprenorphine and buprenorphine/naloxone combination for opioid use disorder to a new limit of 275 patients. The new ruling does not apply to methadone, which is a schedule II drug. Only medication covered under this rule is in Schedule III, IV or V [46].

3. FDA Opioids Action Plan

Dr. Robert Califf, the FDA’s Deputy Commissioner for Medical Products and Tobacco, along with other FDA leaders, called for a far-reaching action plan to reassess the agency’s approach to opioid abuse epidemic on February 4, 2016. The focus of the plan is on policies aimed at reversing epidemic while at the same time providing access to medicine to the patient in need [47-48]. The FDA actions plan includes:

3.1. Expand use of advisory committee

Since 2016, FDA started convening an advisory committee of external experts before approving any New Drug Application (NDA) for an opioid that does not have abuse deterrent properties (ADPs). FDA will consider the reviews and advice from external experts with an opportunity for public input before approval of any new opioids that do not have ADPs. The agency will also consult an advisory committee for the novel issues of ADFs. Similarly, it convenes a Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labelling is approved [48].

3.2. Develop warnings and safety information for immediate release opioids labeling

In March 22, 2016, FDA announced class-wide safety labeling changes for immediate release opioid medications. FDA requires a new-boxed warning about the serious risks of misuse and abuse, which can lead to addiction, overdose and death. The new labelling requirement is similar to ER/LA opioids. This new information helps the prescriber about the risk of opioids and how to prescribe safely [48-49].

3.3. Strengthen postmarket requirements

The long-term impact of opioids product on human is substantially lacking [5,6]. FDA requires the companies to generate post-market data on the long-term effect of ER/LA opioids products. This information will help in better understanding the risks of misuse and abuse of ER/LA opioids and identify predictors of opioid addiction, among other related issues [48,50].

3.4. Update risk evaluation and mitigation strategy program

FDA requires REMS for ER/LA products under which the sponsor is required to fund continuing medical education providers to offer at low or no cost. FDA Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee recommended broadening the scope of REMS in 2016. The recommendation includes [48,51]:

- Expand the FDA Blueprint to incorporate pain management and extending training to other healthcare professionals involved in the management of patients with pain
- Expanding the REMS requirements to include the immediate-release opioid analgesic drug manufacturers
- Evaluating the best approach for implementing mandatory prescriber education on pain management

3.5. Support better treatment

FDA is reviewing the availability of naloxone to over-the-counter to make sure it is more accessible and thus broadening treatment access to opioid overdoses [48]. FDA also supports CDC (Center for Disease Control) guidelines for prescribing opioids for chronic pain management. Some of CDC recommendation includes [48,52]:

- Use opioids only when benefits are likely to outweigh risks
- Start with the lowest effective dose of immediate-release opioids
- Reassess benefits and risks when considering dose increase

3.6. Reassess the risk-benefit approval framework for opioid use

In March 2016, the FDA asked the National Academies of Sciences, Engineering, and Medicine (NASEM) to outline the state of the science regarding prescription opioids abuse and misuse [48,53-54]. NASEM issued recommendations in July 2017 and these include:

- Invest in research to better understand pain and opioid disorder
- Consider potential effects of illicit markets of policies and program for prescription opioids
- Improve reporting of data on pain and opioid disorder
- Invest in data and research to better characterize the opioid epidemic
- Improve access to drug take-back program
- Establish comprehensive pain education materials and curricula for health care providers
- Facilitate reimbursement for comprehensive pain management
- Improve the use of PDMPs data for surveillance and intervention
- Expand treatment for opioid use disorder
- Improve education and treatment of opioid use disorder for health care providers
- Remove barriers to converge of approved medications for treatment of opioid use disorder
- Leverage prescribers and pharmacists to help address opioid use disorder
- Improve access to naloxone and safe injection equipment
- Incorporate public health considerations into opioid-related regulatory decisions
- Require additional studies and collection of analysis data needed for a thorough assessment of broad public health considerations
- Ensure that public health considerations are adequately incorporated into clinical development
- Increase the transparency of regulatory decisions for opioids in light of the commitee's proposed systems approach
- Strengthen the post-approval oversight of opioids
- Conduct a full review of currently marketed/approved opioids
- Apply public health considerations to opioid scheduling decisions

3.7. Expand access to abuse deterrent formulations to discourage abuse

FDA believes that ADFs hold promise in combating abuse and misuse of prescription opioids as the technologies improve with time. US government, regulatory agencies and pharmaceutical companies are making efforts to increase the presence of ADFs in prescription opioids market [48]. Although short term and long-term impact of ADFs in reducing opioids abuse and misuse is limited [55-61].

4. Abuse Deterrent Formulations (ADFs)

FDA defines ADFs as products having ADPs. ADPs are those properties shown to meaningfully deter abuse but do not fully prevent abuse. Literature is using abuse deterrent and tamper resistant terminology interchangeably. However, FDA does not use tamper resistant terminology for abuse deterrent due to use of tamper resistant terminology for packaging requirement for certain classes of drug, devices and cosmetics [62-63]. FDA approved first ADF product with label claim in 2010. Even before the approval of first ADF label claim product, many ADF products were available without official recognition in FDA drug label. FDA approved two such ADF products (Lomotil® and Motofen®) in 1960 and 1978. Lomotil® and Motofen® contain diphenoxylate hydrochloride and difenoxin hydrochloride, respectively, as actives and both contain atropine sulfate as an aversive agent to prevent abuse. A subtherapeutic dose of atropine is added to discourage deliberate overdose of diphenoxylate hydrochloride and difenoxin hydrochloride [64-65]. In 1982, FDA approved Talwin NX® that contains naloxone hydrochloride as an opioid antagonist to prevent abuse of pentazocine hydrochloride by parenteral route [66]. These products do not contain official abuse deterrent properties or temper resistant claim on their labels. Reformulated OxyContin® was first ADF product with label claim in 2010 and it was originally approved in 1995 (first ER product of opioid) [67]. Reformulation of OxyContin® imparts crush resistant property to reduce the potential of abuse by snorting or dissolving by parenteral routes. Recent reports indicate that OxyContin® has captured 90% market value of the total ADFs market [3]. Since then FDA approved nine more ADF products with label claims. Nine ADF products are in the late-stage pipeline (stage III or FDA submission) [3]. ADF products have efficacy and safety profiles similar to non-ADF products. It means the same level of analgesic benefits and same profile of adverse events when used as prescribed [68]. ADF products may deter against chewing, intranasal and intravenous route of administration. However, swallowing multiple pills is a common form of abuse that cannot be deterred by ADFs use [69]. Abuse of ADFs pose same safety issue as the non-ADF product such as precipitated severe withdrawal symptoms, infections through needle sharing [70], thrombotic microangiopathy [71] and other risks associated with tampering of excipients present in ADFs [72].

4.1. Classification

The classification of ADFs is based on mechanism of abuse deterrence and follows as per FDA guidance documents [62-63]:

- Physical/Chemical barriers
- Agonist/antagonist combinations
- Aversion
- Delivery system
- New molecular entities and prodrugs
- Combination
- Novel approaches

The commercially available ADF products are based on either physical/chemical or antagonist-antagonist combination (**Table 1**). FDA requires four type of studies for the approval of NDA (new drug application) of ADF with label claim. These studies are as follows per guidance document [62].

- Premarket studies

  Laboratory manipulation and extraction studies (category 1)
  Pharmacokinetic studies (category 2)
  Clinical abuse potential studies (category 3)

- Postmarket studies (category 4)

Table 1: FDA approved abuse deterrent formulations

Brand name	Opioids	Year of approval	Company	Reported abuse deterrence mechanism	Nature of drug release	Abuse-deterrent route in the label	Commercially available
OxyContin®	Oxycodone	2010	Purdue Pharma LP	Physical-chemical	Extended/long-acting	Intranasal injection	Yes
Hysingla™ ER	Hydrocodone bitartrate	2014	Purdue Pharma LP	Physical-chemical	Extended/long-acting	Oral intranasal injection	Yes
MorphaBond ER™	Morphine sulfate	2015	Daiichi Sankyo Inc	Physical-chemical	Extended/long-acting	Intranasal injection	Yes
Xtampza ER	Oxycodone	2016	Collegium Pharm Inc	Physical-chemical	Extended/long-acting	Intranasal injection	Yes

Arymo™ ER	Morphine sulfate	2017	Egalet	Physical-chemical	Extended/long-acting	Injection	Yes
Vantrela™ ER	Hydrocodone bitartrate	2017	Teva Branded Pharm	Physical-chemical	Extended/long-acting	Oral, intranasal injection	Yes
RoxyBond™	Oxycodone hydrochloride	2017	Inspiron Delivery	Physical-chemical	Immediate release	Intranasal injection	Yes
Embeda®	Morphine sulfate and naltrexone hydrochloride	2014	AlPharma Pharms	Agonist-antagonist	Extended/long-acting	Oral intranasal	Yes
Targiniq™ ER	Oxycodone hydrochloride and naloxone hydrochloride	2014	Purdue Pharma LP	Agonist-antagonist	Extended/long-acting	Intranasal injection	No
Troxyca® ER	Oxycodone hydrochloride and naltrexone hydrochloride	2016	Pfizer Inc	Agonist-antagonist	Extended/long-acting	Oral intranasal	Yes

The comparator product for the approval of NDA can be ADF (if available) or non-ADF (if ADF is not available). Postmarket studies are mandatory for ADF products. However, OxyContin® was approved prior to mandatory requirement of category 4 studies. Post-market FDA approved studies of Hysingla™ ER and Embeda® are scheduled for completion in 2018 and 2019, respectively [3]. So far, no generics of ADF products is approved even though first ADF product was approved in 2010. ANDA (abbreviated new drug application) for ADF approval has to meet FDA equivalence criteria for ADPs (similar ADPs properties between reference and test products) in addition to pharmaceutical- and bio-equivalence requirements, (**Table 2**) [62-63]. Following are ADF products approved by FDA:

4.1.1. OxyContin®

It is the first ADF product with an official label claim of ADP. It is a film coated tablet formulation of oxycodone hydrochloride containing butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate and titanium oxide as inactive ingredients [73]. The manufacturing process involves tablet compression followed by heating above the melting point of the polymer. Polymer particles fuse and impart plastic like properties on cooling. This imparts tremendous mechanical strength to the tablets [68,74-75]. Reformulated OxyContin® is difficult to manipulate compared to Original OxyContin® formulation. The tablet resists crushing, breaking and dissolution using a variety of household and kitchen tools and solvents. It also forms a viscous hydrogel that resists passage through a needle. OxyContin® may reduce abuse by intranasal route as indicated in clinical studies using liking as a marker (OxyContin® label). Possibly, ADPs are imparted by heat pro-

cess and polymers such as polyethylene oxide and hypromellose which forms viscous mass when the tablet comes in contact with the aqueous environment [74-75].

Table 2: Studies requirement for NDA (new drug product) and ANDA (generics) approval of ADFs

NDA (new drug product)	
Types of studies	Description
Premarket	
Laboratory manipulation and extraction studies	To evaluate physiochemical properties, abuse deterrent properties and level of efforts required to defat ADP
Pharmacokinetic studies	Comparative pharmacokinetic studies of intact and manipulated product and comparator
Clinical abuse potential studies	Clinical studies in drug-experienced, recreational user population to assess potential of abuse
Postmarket studies	To assess reduction in abuse, misuse and related adverse clinical outcomes.
ANDA (generics)	Comparative studies to demonstrate pharmaceutical, bio and abuse deterrent properties equivalence

4.1.2. Hysingla™ ER

It is extended release tablet of hydrocodone bitartrate approved by FDA in 2014. The tablets contain the following inactive ingredients: BHT (an additive in polyethylene oxide), hydroxypropyl cellulose, macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyethylene oxide, polysorbate 80, polyvinyl alcohol, talc, titanium dioxide, and black ink. The tablet was assessed by in-vitro and clinical methods for the abuse deterrent potential [76]. In-vitro studies showed that it has physical chemical properties that resist crushing, breaking and dissolution under various conditions of testing such as solvents and manipulations tools. It also forms a viscous gel when exposed to the aqueous environment, which resists passage through the hypodermic needle. Polymers responsible for forming the viscous gel are polyethylene oxide and hydroxypropyl cellulose [74-75]. Clinical studies also indicated that the abuser has less liking and desire to take Hysingla™ ER. Thus, it has physicochemical properties that may reduce intranasal and oral abuse when chewed [76].

4.1.3. MorphaBond ER™

It is a tablet formulation of morphine sulfate and approved in 2015. It has following excipients: hypromellose, xanthan gum, microcrystalline cellulose, sodium alginate, alginic acid, mannitol, colloidal silicon dioxide, magnesium stearate, ethyl acrylate and methyl methacrylate copolymer dispersion, lactose monohydrate, polysorbate 80, titanium dioxide, polyethylene glycol, shellac in ethanol, isopropyl alcohol, iron oxide black, n-butyl alcohol, propylene glycol, and ammonium hydroxide [77]. MorphaBond ER™ is tested by in-vitro methods to assess abuse potential by various routes including oral, intranasal insufflation, injection and

smoking. It has increased resistance to cutting, crushing or breaking relative to morphine sulfate extended release control. Similar to OxyContin® and Hysingla™ ER, MorphaBond ER™ forms a viscous material that resists passage through a needle. Clinical studies data indicated that physicochemical properties of MorphaBond ER™ reduce abuse by intranasal route of abuse [77].

4.1.4. Xtampza ER

It is a capsule dosage form of oxycodone. It is based on DETERx® technology where drug base instead of salt is mixed with an inactive ingredient to form a lipophilic salt. Lipophilic salts of opioids have less potential of drug extraction compared to water soluble salts [78-79]. It contains oxycodone as myristate salt. Following excipients are present in Xtampza ER: myristic acid, yellow beeswax, carnauba wax, stearoyl polyoxyl-32 glycerides, magnesium stearate, and colloidal silicon dioxide [80]. The capsule shells contain titanium dioxide and hypromellose. *In-vitro* physical and chemical manipulation studies indicated that it is less susceptible to the effects of grinding, crushing, and extraction under various conditions of extraction. Furthermore, melted capsule content or microspheres suspended in water resisted the passage through the hypodermic needle. Similarly, pharmacokinetic and human abuse potential studies along with *in-vitro* data indicated that Xtampza is expected to reduce abuse by nasal route [80].

4.1.5. Arymo™ ER

It is ER tablet dosage of morphine sulfate. Inactive ingredients present in Arymo™ ER are polyethylene oxide 400,000, BHT, polyvinyl alcohol, polyethylene glycol 3350, talc, and titanium dioxide [81]. The Egalet Corporation used proprietary Guardian™ technology to deter the abuse of the product. Guardian™ technology utilizes the injection-molding process to produce tablets that are hard and difficult to manipulate for abuse and misuse [82-83]. Physical and manipulation methods were performed to defeat the extended-release properties of the Arymo™ ER. The product is resistant to cutting, crushing, grinding or breaking in comparison to morphine sulfate extended-release tablets using a variety of mechanical and electrical tools. The Arymo™ ER contains polyethylene oxide 400,000, which has property to form hard plastic material after heat exposure above the melting point of the polymer [74-75]. Injection molding is a heat process where formulation components are melted and poured into a die cavity where component takes the shape of dosage forms on cooling. The product also forms a gelatinous mass or viscous hydrogel, which is difficult to pass through the hypodermic needle. Oral pharmacokinetic and oral clinical abuse potential studies showed a difference in drug liking point but difference was not statistically significant [81].

4.1.6. Vantrela™ ER

It is an extended-release tablet of hydrocodone bitartrate. The tablets contain lactose monohydrate, ethyl cellulose, hypromellose, glyceryl behenate, and magnesium stearate as the excipients. Teva uses proprietary technology to make this ADF product. Teva received label claims of parenteral, oral and nasal abuse deterrence. Parenteral abuse deterrence is based on in-vitro data. In-vitro data results indicated that Vantrela™ ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains extended release property despite manipulation. Oral (oral abuse potential and oral pharmacokinetic studies) and nasal (intranasal abuse potential and nasal pharmacokinetic studies) abuse deterrence are based on in-vitro studies and clinical abuse potential data [84].

4.1.7. RoxyBond™

It is first and only immediate release ADF product of oxycodone hydrochloride approved by FDA in 2017. It uses SentryBond™ proprietary technologies of Inspiron Delivery Sciences, LLC to deter abuse of the product [85]. Alginic acid, ammonium hydroxide, colloidal silicon dioxide, dibutylsebacate, dimethylaminoethyl methacrylate copolymer, ethyl acrylate and methyl methacrylate copolymer dispersion, ethylcellulose, hypromellose, iron oxide black, isopropyl alcohol, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, n-butyl alcohol, polyethylene glycol, polysorbate 80, polyvinyl alcohol, propylene glycol, shellac in ethanol, sodium alginate, talc, titanium dioxide, and xanthan gum are present in the product as inactive ingredients. RoxyBond™ label has parenteral and nasal abuse deterrent claims. The product resists cutting, crushing, grinding or breaking when manipulated with commonly used household tools. Intact product resists drug extraction using selected household tools and commonly used laboratory solvents, including selected pre-treatment of the product. It forms a viscous material that resists passage through the needle. Thus, it is difficult to prepare an intravenous solution for injection of drug from RoxyBond™ compared to oxycodone immediate-release tablets. Clinical abuse potential studies by nasal route indicated that liking and desire to take it again scores were significantly lower than controlled immediate release formulation [86].

4.1.8. Embeda®

It is the first ADF product based on agonist-antagonist approach. It was initially approved in 2009 but received ADF label claim in October 2014. The agonist is morphine sulfate and antagonist naltrexone hydrochloride. The product is capsule dosage form containing pellets of morphine sulfate surrounding a central core of sequestered naltrexone hydrochloride in a ratio of 100:4 [68]. The extended release capsule contains following inactive ingredients: talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, sodium chloride, polyethylene glycol, hydroxypropyl cellulose, dibutylsebacate, methacrylic acid copolymer, di-

ethyl phthalate, magnesium stearate, sodium lauryl sulfate, and ascorbic acid. The excipients provide extended release of morphine sulfate but do not release naltrexone hydrochloride in patients. However, inadvertent release of naltrexone from non-tampered capsule produced adverse events. In vitro studies indicated that crushed beads resulted in the extraction of both morphine and naltrexone. Furthermore, pharmacokinetic and clinical studies showed that both drugs were rapidly absorbed from crushed pallets [87]. Thus Embeda® has properties that are expected to reduce abuse by nasal and oral route. Moreover, there are multiple recall of the product due to stability issues since its approval [68].

4.1.9. Targiniq™ ER

It is the second ADF product approved by FDA in July 2014 based on agonist-antagonist approach, however, it received ADF label claim before Embeda®. The product is temporarily discontinued for an unknown reason. It is an extended release tablet of oxycodone hydrochloride (agonist) and naloxone hydrochloride (antagonist). Inactive ingredients of Targiniq™ ER are lactose monohydrate, stearyl alcohol, ethyl cellulose, povidone, talc, magnesium stearate, polyvinyl alcohol partially hydrolyzed, titanium dioxide, and macrogol. In-vitro manipulation data indicated that Targiniq™ ER could be crushed and dissolved. However, both drugs will be released when the abuser tries to extract oxycodone from the product. Clinical abuse potential data indicated that Targiniq™ ER provides deterrence against intranasal and intravenous routes of administration [88].

4.1.10. Troxyca® ER

It is also based on agonist and antagonist approach. It is an extended release capsule dosage form of oxycodone hydrochloride (agonist) and sequestered naltrexone hydrochloride (antagonist). Talc, ammonio methacrylate copolymer, sugar spheres, ethylcellulose, hydroxypropyl cellulose, polyethylene glycol, dibutylsebacate, sodium lauryl sulfate, diethyl phthalate, magnesium stearate, methacrylic acid copolymer, and ascorbic acid are the excipients of Troxyca® ER. Manipulation of Troxyca® ER results in simultaneous release and absorption of both oxycodone and naltrexone in in-vitro release and oral pharmacokinetic studies, respectively. It has received oral and nasal abuse deterrence claims on the label based on data of oral abuse and nasal abuse clinical studies in which drug liking and take drug again scores were lower in Troxyca® ER administered patients compared to immediate release oxycodone as a controlled formulation [89].

4.2. ADF Products under FDA review

Nine ADF products are either in stage III or submitted to FDA for the review [3]. For example, KP201 IR and Remoxy ER. KP201 IR is an immediate release product of acetaminophen free hydrocodone and submitted by KemPharm Inc. It will be first IR ADF formulation

of hydrocodone. Sponsor of Remoxy ER is Pain Therapeutics [90]. Ensysce Biosciences is developing amino acid based prodrugs of hydromorphone, oxycodone, hydrocodone and morphine based on BIO-MDTM technologies [91].

Exalgo® (Mallinckrodt Pharmaceuticals), Nucynta® ER (Depomed Inc.), Opana® ER (Endo Pharmaceuticals Inc.), Oxaydo™ (Egalet Corporation), Xartemis™ XR (Mallinckrodt Pharmaceuticals) and Zohydro® ER (Pernix Therapeutics) are other FDA approved opioid products and reported to have ADPs. However, they did not receive FDA label claim for ADPs due to not meeting FDA requirements [92-93].

4.3. Effectiveness of ADFs in reducing abuse of prescription opioids

Evidence on the effectiveness of ADF products in reducing the misuse and abuse is mixed and limited. Most of the data is available for OxyContin® as other ADFs are recently approved and studies have indicated that reformulated OxyContin® has reduced the abuse from 12% to 75%. Moreover, there is a steep decrease in abuse by non-oral route compared to oral route that suggests a shift in the route of abuse. Additionally, investigators found a contemporaneous increase in the rate of other prescriptions abuse (ER oxymorphone, ER morphine and IR oxycodone) and heroin during the same period examined [55-56]. Similarly, rates of overdose and overdose death associated with OxyContin® declined by 34% to 65% after introduction of reformulated OxyContin® [57-59]. This is accompanied by either increase or stability in rates of overdose deaths attributed to other prescription or illicit opioids. It suggests that abusers have switched to other opioids products [57,60-61]. For example, data analysis by RAND Corporation and Wharton school indicated that each percentage decrease in OxyContin® after reformulation is accompanied by 3.1 death per 100,000 population [60]. Data on ADF diversion is extremely limited. Three papers published on OxyContin® diversion based on data obtained from RADARS Drug Diversion Program [3,55-56]. Drug Diversion Program publishes quarterly data on the number of new arrests, street buys and sales involving prescription products submitted by law enforcements and regulatory agencies [94]. Rates of diversion decreased to 89% in June 2015 (from 1.95 per 1,000,000 in the year prior to reformulation to 0.21 per 1,000,000 at year 5 following reformulation) following the reformulation of OxyContin® over a period of five years. Diversion of other prescription opioids also decreased during the same period but at a significantly lower rate (from 13.4 to 9.8 per 1,000,000) [55]. Interestingly, OxyContin® prescription sales also declined (40% since 2010) during the same period [95]. Nevertheless, data on reduction of abuse resulting from the use of ADF products is inadequate.

4.4. Health risk of ADFs

There are many reports of tampering of non-ADF Opana® (oxymorphone hydrochloride) [96] and ADF RoxyBond™ (oxycodone hydrochloride) [72] for intravenous route which

led to safety issues. Reformulated Opana® contains high molecular-weight grade of polyethylene oxide that shifted the route of abuse from nasal to parenteral. An outbreak of HIV and Hepatitis C in Indiana was caused by tampered Opana® product with shared needles [96]. A case of thrombotic microangiopathy was discovered in Tennessee, which is thought to be due to intravenous exposure of substance produced on tampering of polyethylene oxide barrier [97]. Other ADF products also contain either polyethylene oxide or high viscosity polymers. They pose similar health risk if abused by the parenteral route. The ADF products are formulated to be hard monolithic tablets with polymers that form gel when exposed to water (polyethylene oxide and hydroxypropyl methyl cellulose etc) [74-75]. This makes the tablet sticky when moistened and difficult to swallow. There are many reports of currently marketed ADF products that tablets are stuck in patient's throat, causing choking, gagging or regurgitation [3,79].

4.5. Federal and state policies on ADFs

CDC presented twelve recommendations for treatment of chronic pain with opioids in the "CDC Guideline for Prescribing Opioids for Chronic Pain" [52]. None of CDC recommendations mention ADFs product for treating patients with pain. Under 2015 National Drug Control Strategy, the Obama administration requested $27.6 billion for the fiscal year 2016 to reduce the use and its effects. ADF is not the part of National Drug Control Strategy [98]. At the federal level, the only place one finds mention of ADFs as a priority in combating the prescription abuse is the FDA [3,48].

State governments have also taken many steps to address the epidemic of opioids abuse e.g. executive led taskforce, physician education, legislation to establish prescription drug monitoring programs, restrict duration and/or quantity available in an opioid prescription, allocate more funding for abuse treatment options, and legislation requiring health insurances to provide coverage of ADFs. Massachusetts became the first state to pass the ADF legislation Chapter 258 in 2014 which requires ADF medications to be covered by insurance companies and limit cost-sharing requirements for patients. It also requires a pharmacist to automatically substitute ADFs for chemically equivalent non-ADF opioid prescriptions. Implementation of Massachusetts legislation order has been delayed because state officials are still establishing regulatory guidance for insurance and pharmacy. Maryland (Chapter 372) in 2015, and Florida (S.B. 422) and West Virginia (H.B. 4146) in 2016 have passed ADF legislations requiring that ADFs should be covered at parity to non-ADFs equivalent and prohibits step therapy with non-ADF opioids. Maine also passed ADF legislation in 2015 which requires health insurance companies to provide coverage for ADFs. However, in order to pass the legislation, legislators voted to override the Governor's veto. Similarly, 30 bills related to ADF were introduced in 20 states in 2016. Delaware, New Hampshire, Oklahoma and Virginia have passed the resolution to further study ADFs. There has been an increase in the number of legislations introduced

in 2016. However, the rate of adoption is fairly low due to budget concern and effectiveness in reducing the abuse [3,99]. Governors in New York and New Jersey vetoed the bill due to budget concern [3,99]. Furthermore, pharmaceutical companies and their associated advocacy groups spent $880 million between 2006 and 2015 on activities and efforts to influence federal and state opioid policies. One of their goal is to promote expensive ADF products [100].

4.6. Healthcare cost of ADFs

ADFs represent 10% of all the prescription opioids [3]. ADF products are relatively more expensive than non-ADF brands and generics. ADF products are 5- to 15-folds expensive than non-ADF products. It will dramatically increase healthcare cost. For example, VA (Veterans Affairs) spent approximately $100 million on overall opioids. It will dramatically increase the cost by 10-fold (average) if all opioids were to be replaced by ADF. The opioid pharmacy bill would be approximately $1 billion which represents 20% of VA pharmacy [3,101]. Due to the higher cost of ADFs, most of the insurance plans require prior authorization. Insurance plans may cover OxyContin®, Xtampza ER™, Hysingla™ ER and Embeda®. Newer ADF products e.g. Arymo™ ER, Vantreal™ ER, Troxyca® ER and RoxyBond™ were not covered by any plans. Insurance plans require patients to try non-DF, generic equivalents or preferred brand first [3].

5. Conclusion

Various actions have been taken at federal and state levels to combat opioids epidemic. One of the actions at the federal level is to encourage pharmaceutical companies to develop opioids product that has abuse deterrent properties. Since 2010, FDA has approved ten opioids products that have abuse deterrent properties. In coming years, more ADF products with better abuse deterrent features are expected to be reviewed by FDA. ADF products do not treat addiction rather deter the abuse to some extent. They are more expensive than brand and generics of non-ADFs. Moreover, the generic versions of ADF have not been approved yet. Limited evidence is available on their effectiveness in reducing abuse, overdose deaths and diversion of opioids. Multipronged approach is effective in preventing the abuse of opioids crisis and ADF is one of the components of that approach.

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Drug Abuse: Addiction and Recovery

Chapter 4

Khat (*Catha Edulis*) Addiction, Effects on General Body Health and Interventional Remedial Measures

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Abstract

The use of khat among communities where it is grown has been largely linked to socio-cultural norms and complicated by economic values. Day-to-day use of khat leads to a build-up of catecholamine and indolamine substances in synaptic clefts of neurons within the reward centers of the limbic system which, with chronicity of exposure, subsequently necessitate addiction. As a psychoactive substance, its metabolism in the body culminates into impairment of body functional systems including learning and cognitive function, oral health, cardiovascular and digestive complications and, most importantly, reproductive function. Most studies in these areas have delved mostly on adverse effects during use, including addiction. Further, studies have reported variously on withdrawal syndrome without giving a leaf of life on the other side of possible recovery from pathophysiology associated with addiction. In most research findings in these areas mechanisms of action of khat that lead to reported effects are always missed. It is because of this that in most countries where khat consumption is rampant, there has been failure of regulation due to lack

policy guidelines on how to curb the vice as well as rehabilitate victims to recovery. This chapter presents the basis of psychoactive drug dependence in terms of physical and genetic vulnerability, effects on cognitive function, neuroendocrine and morpho-functional effects in human and experimental animal model studies leading to addiction and impairment of functional systems of the body. Current findings on morphometrical studies on reproductive health as well as outline on current use and market control as well as treatment remedies that offer insights into policy making and public health service provision with accompanying approaches to recovery from addiction are also highlighted.

Nyongesa AW

1. Introduction

Khat (*Catha edulis* Forsk) is a psychostimulant that contains many biologically active alkaloids including cathinone, also referred to [S- (-) - α-aminopropiophenone], which is the most potent ingredient [1]. The World Health Organization Expert Committee on Drug Dependence included khat type preparations of *Catha edulis,* in the group of 'dependence-producing drugs'. Similarly, cathinone was regarded as a central nervous system stimulant about half as potent as amphetamine [2]. It was therefore felt that both compounds met the criteria for control under the Convention on Psychotropic Substances [3]. Like other drugs of abuse, its dependence-producing potential, analgesia and anorexic effects are mediated through alteration of brain neurotransmitters in the meso-striato-corticolimbic dopaminergic pathway [4]. In the past two decades, khat use has followed immigrants from traditional use regions around the Horn of Africa and Middle East to western countries. Its use has since been banned in the United States and most parts of Europe including United Kingdom, Sweden and the Netherlands among others. The ban led to growing anxiety in source countries because most of such economies have since lost on revenue collections from khat exports. This is particularly so in countries where khat use is associated with a lifestyle and its cultivation a strategy for national development such as Kenya and Ethiopia [5]. Long-term consumption of khat has been implicated in induction of psychological dependence confirmed by using a version of Severity of Dependence Scale validated for use in khat dependence studies [6]. Chronicity of exposure to khat has been associated with complications of central nervous system [7], cardiovascular [8], adrenocortical function [9], reproduction [10,11,12,13] among other effects on body functional systems.

2. Cognitive Function

Most available information in literature concerns studies of khat use on central nervous system using different animal models. For instance, a previous study involving daily administration of khat extract to CBA mice reported an impairment of learning with improvement of memory at high doses (120 mg/kg and 360 mg/kg body weight) although

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low dose (40mg/kg) had no effect on learning [14]. Other findings reported elsewhere include euphoria, excitation, anorexia, increased respiration, hyperthermia, logorrhoea, analgesia and increased sensory stimulation [15]. Khat chewers believe that they reason more clearly and are more alert, although their concentration and judgment of ideas or situations are objectively impaired [3]. The general understanding on these findings is that the effects observed following khat consumption are generally of central nervous system stimulation. In view of its potency and high lipid solubility [16], facilitating access into the central nervous system [17], it can be assumed that khat-induced psycho-stimulation is predominantly due to cathinone content of the leaves [18]. A number of studies have reported on psychiatric disorders with features of manic-like psychosis following prolonged khat use [19], schizophreniform psychosis [20], paranoid psychosis [21] and depression [3]. These adverse effects of khat are compounded by concomitant use of other substances such as tobacco [22], which has been associated with enhanced euphoria and psychostimulation [6]. Khat 'addicts' have also been shown to be sensitized to effects of other drugs [23].

Hypothalamo-hypophyseo-adrenocortical axis has been demonstrated to be susceptible to drug abuse via dopaminergic transmission [24]. High levels of glucocorticoids are reported to contribute to development, maintenance and outcome of substance abuse disorders [25]. Mello and Mendelson, [26] in their study reported similar findings where psycho-stimulants were shown to increase corticosterone levels. In other studies, suppression of glucocorticoids by adrenalectomy was reported to reduce extracellular concentrations of dopamine in nucleus accumbens in response to psycho-stimulants [27]. Together, these findings indicate a relationship between pleasurable effects of the drug (that influences neural behaviours in drug 'addicts') with activation of stress system in the body.

A. Dopaminergic System

The mesolimbic and meso-cortical dopamine (DA) systems are important in modulation of functions such as motivation, control of emotions and cognition controlled by prefrontal cortex and limbic regions [28]. The DA cells innervating nucleus accumbens are implicated in the pleasurable reward following psycho-stimulation by use of natural or drug enforcers [29]. Reports indicate that lesion to DA terminals in nucleus accumbens induces hypo-exploration, delayed motor responses, disturbances in organizing complex behaviours and inability to switch between behavioural activities [28]. This system is, therefore, deemed important for acquisition and regulation of goal-directed behaviours, established and maintained by natural or drug reinforcers [30]. Nigro-striatal DA system originating from the substantia nigra (SN) (A9 cell group) has been implicated in the pathogenesis of Parkinson's disease (PD) [31]. In mammals, the SN comprises of two distinct compartments: substantia nigra pars compacta (SNc) and substantia nigra pars reticulata (SNr). The latter represents the major source of striatal DA while SNr mainly contains g-amino-n-butyric acid (GABA) neurons constituting

one of the major efferents of the basal ganglia [31].

B. Serotonergic System

Serotonin (5-HT) is a neuromodulator whose properties are much more mysterious than those of dopamine although it is implicated in a wealth of important phenomena, ranging from analgesia [32], hallucinations [33] to a variety of mood disorders such as anxiety and depression [34]. Virtually all parts of the central nervous system receive innervation from serotonergic fibers arising from cell bodies located in two trunks of the midbrain serotonergic nuclei: the dorsal raphe nuclei (DRN) and the median raphe nuclei (MRN) [35]. Serotonin-containing bodies of the raphe nuclei project to dopaminergic cells in the VTA and SN, as well as nucleus accumbens, prefrontal cortex and striatum [36] (**Figure 1**). There are also serotonergic projections from the raphe to the peri-acqueductal gray involved in control of defensive and aversively motivational behaviours [37].

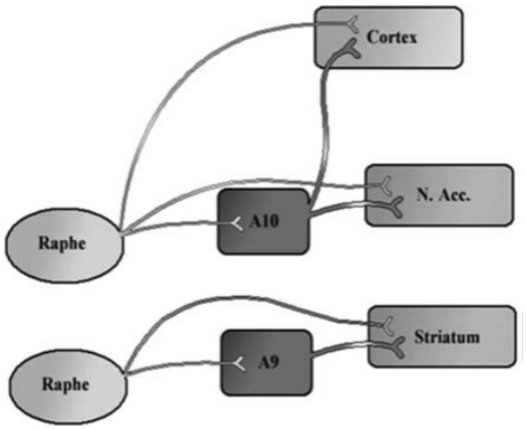

Figure 1: Schematic representation of serotonin–dopamine interaction in the meso-corticolimbic and nigrostriatal dopaminergic system. Serotonin-containing cell bodies of raphe nuclei send projections to dopaminergic cells in both the ventral tegmental area (VTA, A10) and substantia nigra (SN, A9), and to their terminal fields in the nucleus accumbens, prefrontal cortex and striatum. [Adapted from Di Giovanni et al. (38)].

At electron microscopy there is presence of synaptic contacts of 3H5-HT-labelled terminals with both dopaminergic and non-dopaminergic dendrites in all sub-nuclei of the VTA, and in the SNc and SNr [35]. There is differential distribution of 5-HT receptor subtypes within the dopaminergic systems [39] that have led to the insight of dopamine-serotonin systems interaction in the brain (**Figure 2**)

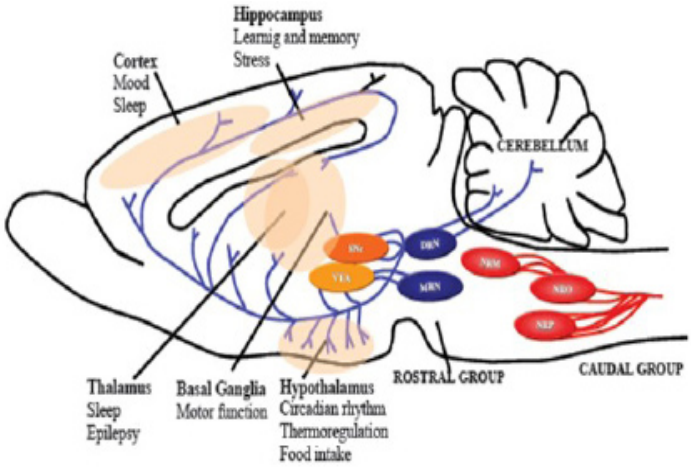

Figure 2: Mid-saggital view of the rat brain with serotonin-immuno-reactive cell bodies. The blue and red ovals comprise two major subdivisions of the brain serotonergic system. Abbreviations: DRN, dorsal raphe nucleus; MRN, medial raphe nucleus; NRM; nucleus raphe magnus; NRO, nucleus raphe obscurus; SNc, substantia nigra pars compacta; VTA, ventral tegmental area. (Adapted from Di Giovanni et al. [38]).

C. Noradrenaline

Noradrenaline, 3, 4-dihydroxyphenylethanolamine, is released from terminals of noradrenergic neurons in the brain from most postganglionic sympathetic neurons and from chromaffin cells in the adrenal medulla. The cell bodies of central noradrenergic neurons are all clustered within two bilateral groups of nuclei (A1 –A7) in the brain stem **(Figure 3)**. These comprise the locus coeruleus (LC) complex and the lateral tegmental nuclei. The activity of noradrenergic neurons within locus coeruleus is governed by GABAergic projection from nucleus prepositus hyperglossi and glutamatergic input from the nucleus paragingantocellularis [40].

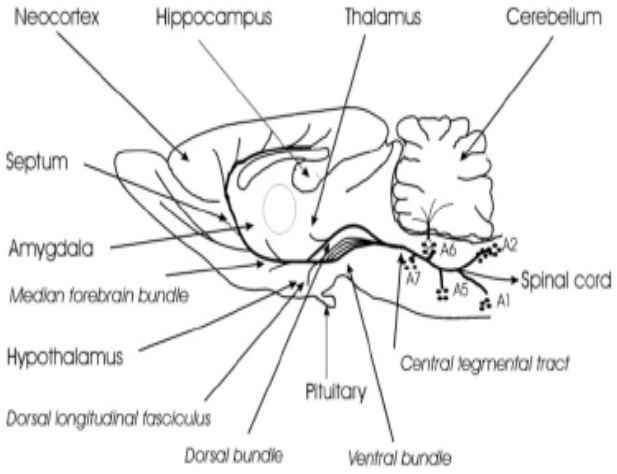

Figure 3: Figure showing distribution of noradrenergic neurons in the brain. The cell bodies are clustered in nuclei (A1 – A7) in the pons/medulla regions of the brainstem and their axons project both rostrally and caudally to most regions of the neuraxis. The major nucleus is the locus coeruleus (A6). (Adapted from Stanford, [41]).

Synthesis of dopamine, adrenaline and noradrenaline share a common pathway. The amino acid L-tyrosine is a precursor substrate that undergoes hydroxylation in the presence of tyrosine hydroxylase (TH) to form L-dihydroxyphenylalanine (L-DOPA) followed by decarboxylation by DOPA decarboxylase to form dopamine. Dopamine is transported to the

storage vesicles where dopamine β-hydroxylase converts it to noradrenaline. The process occurs in the cytoplasm of catecholamine-releasing neurons. Noradrenaline neurons influence arousal behaviours such as sleep/wakefulness, depression and anxiety [41]. The precise features of environmental stimuli that provoke increased noradrenergic transmission are unclear. Increased noradrenergic transmission in the brain mediates changes in selective attention. Another concept is that noradrenergic transmission influence emotional impact of a given stimulus. It is possible that the role and consequences of central noradrenergic transmission depends on type or severity of stimulus or individual differences in neurobiological coding behaviour.

3. Physical and Genetic Predisposition of Psychoactive Drug Dependence

Psychoactive drug dependence is a complex phenomenon characterized by interplay of several genes of an individual with respect to environmental factors associated with that individual. Individuals with genetic vulnerability to drugs of abuse experience a marked influence to drug dependence [42]. Indeed, the observed variance in behavior among substance abusers can be explained by differences in genetic make-up of the individuals. Therefore, in order to understand the genetic basis of addiction, there is need to identify genetic variation of that individual, although it only contributes partly to development of addiction.

Previous studies have reported genetic heritability of alcohol [43], opiates and cocaine [44]. The involvement of specific genes or complex of genes remains unclear. The challenge to this nature of studies is in the identification of genes that alter predisposition to drug dependence as well as in the understanding of how the function of genes interact with environmental factors influencing dependence of substance use. The difficulties in identifying genetic traits are associated with complexity of addiction as a trait. Genetic screening can help in identification of specific genes although in a general population, only probabilities rather than certainties shall be recorded. Opioid receptor genes for opioid dependence have reasonably been associated with opioid dependence [42]. In other substances of abuse, a complex of genes may be involved. For instance, alcohol heritability has been associated with genes involved in drug metabolism, alcohol receptor genes, and genes responsible for synthesis of GABA, serotonin and dopamine [45]. Heritability of alcoholism in individuals homozygous for ALDH2*2 allele encoding for less active variant of aldehyde dehydrogenase type 2 is rare [46]. Variants in different genes may contribute to addiction in different lineages thus necessitating a clear understanding of genetic and genomic variants that may possibly be implicated in development of drug addiction.

There is a direct link between an individual's genotype with predisposing/risk factors which can either be environmental (availability of drugs, poverty, social change, cultural norms, peer influence, occupation) or individual (genetic disposition, personality disorders, social deprivation, depression) that can direct a certain response to drug dependence [47]. In view of this, it is prudent to incorporate behavioral assessment when investigating genetic

vulnerability of a certain individual in the understanding of development of drug addiction. The handicap, however, is the quantification of behavioral endpoints since they are more susceptible to environmental influence thus giving variance in behavioral manifestations. But this can be fine-tuned through allowing major focus on establishment of behavioral endpoints with same degree of sophistication and inter-rator reliability as earlier reported [48]. Environmental stimuli influences brain circuitry the same way as genetic involvement hence the need to combine specific phenotypes with genetic approaches in identification of development of addiction in humans and animals. In order to understand peculiarities of addiction, it is important to analyze factors that determine its development, involve use of animal model that reflects human situation as closely as possible and identify and verify loss of control and that of reversibility in a drug addicted animal.

In behavioral profiling, studies have shown that self-administration and conditioned reinforcement paradigms give more accurate behavioral tests mapping human addiction [49] with oral self-administration being more practical [50]. Other studies that have been done involve place-avoidance assay [51] and measurement of rate and degree of tolerance with opiate dependence [52]. The stability of behavioral abnormalities that characterize addiction is a clear indicator that gene expression may be involved in drug-induced behavioral changes [53]. Most studies in humans and experimental animals [54] have approached drug addiction cases from behavioral profiling. However, it should be understood that genetic vulnerability plays a key role to development of drug addiction. Whereas the genetic variations established in animal models may be different from those of humans, their identification can shed light on mechanisms underlying addiction process. No studies have shown genetic polymorphisms associated with khat dependence in humans or even animal models hence the need for researchers to offer particular focus in this area as a way of mapping out possible treatment in khat addictive cases. It should be noted that substance abuse has contributed markedly to global burden of disease in many parts of the world including Europe, Central and East Asia, North America and most parts of Africa. For instance, individuals living with infectious conditions such as HIV/AIDS inject themselves with psychoactive substances with sole aim of suppressing their stigma. The end result is contraction of other diseases such as hepatitis B and C through use of same needles. It goes without saying that various accidents, cases of suicide, assaults and even breakage of marriages are implicated in substance use and misuse. It is, therefore, of paramount importance to understand the in-depth of involvement of psychosocial, neurobiological and genetic factors influencing development of addiction and provide these insights to relevant policy enforcing agencies and public health service providers with a sole view of minimizing or eradicating the vice. This chapter highlights various adverse effects of khat use following long-term use and subsequent addiction in some cases. Studies done in humans and experimental animals have offered subjective and objective findings. Understanding of development of the effects on drug use and misuse offer a platform on which interventional scientific research initiatives are

undertaken with sole aim of looking for remedy of the cases to recovery.

4. Effects on Body Functional Systems at Chronic Exposure

Long-term khat use has been associated with behavioural changes [55], myocardial complications [56], oral lesions [57], gastro-intestinal and cardiovascular complications [8], adrenocortical and psychological complications [58], endocrine complications [9] and sexual function [10, 11] among an array of other central nervous system complications. This chapter focuses mostly on morpho-functional and molecular dimensions on reproductive function with long-term khat use since most controversial reports center around this subject. These effects stem from hypothalamic involvement down the pituitary to testicular function. The focus of the discussion is mostly centered on the male since khat chewing is more prevalent in males [59].

I. Reproductive Endocrine Effects

Numerous findings on khat and endocrine function have been reported in experimental animal and human case studies. In a cross-sectional study on Yemeni regular khat chewers, altered adrenocortical function was reported [58] similar to findings in baboons [60] and vervet monkeys [9, 61]. The effects on hormonal profiling seem to be bi-phasic where varying khat doses influence endocrine function differently. For instance, studies in rats [11] and mice [62] showed that low dose stimulates production of testosterone while high doses cause suppression. Chronicity of khat exposure impairs steroidogenic cell function [63, 13]. These reports have further been supported by findings of Al-Habori and Al-Mamary [64] showing reduction in cholesterol following feeding rabbits with khat over 6 month period. Cholesterol is synthesized in smooth endoplasmic reticulum [65], and is a precursor molecule in steroidogenesis [66].

II. Testicular Histomorphometric Effects

Khat use has been reported to have varying effects on the reproductive function in humans and experimental animals. Numerous reports, however, show contradictory findings on male reproductive function. Some reports indicate erectile dysfunction [67] and spermatorrhoea [3] and testicular cell degeneration [68] following khat and cathinone exposure. Recently Nyongesa et al. [10] reported cytotoxic effects of khat extracts on germinal epithelium (spermatogonia and primary spermatocytes) of male rabbits at sub-chronic exposure with no observable effects on Sertoli and Leydig cells. Other reports have implicated khat with aphrodisiac properties [69], a remedy for premature ejaculation [3] and sperm power booster [70]. The mechanisms underlying pharmacological action of khat extracts on testicular function with respect to aforementioned effects remains obscure. On this strength, authors here present testicular histomorphometric findings on 12 adult male vervet monkeys treated with 0.8, 3.2 and 6.4 mg/kg body weight of khat extracts on alternate days of the week for 4 months. At the end of

treatment period, testicular tissues of one animal from each group were harvested, following anaesthesia, for histomorphometric evaluations. The morphometric evaluation employed volume densities of mitochondria, sooth endoplasmic reticulum (SER), Golgi apparatus and lipid droplets of Leydig cells that were estimated from photomicrographs of central parts of testes photographed at x 6000 magnification. Point differential counting as described by Kavoi et al. [71] was used to evaluate volume density occupied by mitochondria, lipid droplets, Golgi apparatus, SER and rough endoplasmic reticulum (RER). Briefly, a transparent test grid with a square lattice of points was overlaid with random positioning on testicular electron micrographs projected on a computer monitor. The number of points hitting the mitochondria, SER, RER, lipid droplets and Golgi apparatus and those falling on projected field of testicular interstitium were counted. Volume density of component of interest [Vv (l)] was calculated as a percentage:

$$Vv(l) = (\Sigma NPl/\Sigma NPi) \times 100,$$

Where, Vv (l) is volume density of cell component, ΣNPl is the number of test points hitting the image of the evaluated component of interest, and ΣNPi is the number of all points falling on the cell image (interstitium). By substituting in the equation above, volume densities of mitochondria, SER, RER, lipid droplets and Golgi apparatus were calculated using the following formulae, respectively:

$$Vv(m) = (\Sigma NPm/\Sigma NPi) \times 100$$

$$Vv(ser) = (\Sigma NPser/\Sigma NPi) \times 100$$

$$Vv(rer) = (\Sigma NPser/\Sigma NPi) \times 100$$

$$Vv(l) = (\Sigma NPl/\Sigma NPi) \times 100$$

$$Vv(ga) = (\Sigma NPga/\Sigma NPi) \times 100$$

Results of this study showed that high dose of khat extracts at sub-chronic exposure to vervet monkeys resulted in alteration of sub-cellular organelles in Leydig cells (Fig 4C and D) compared to low dose (**Figure 4B)** and control group (**Figure 4A**). Of particular importance were SER, mitochondrial cristae and lipid droplets implicated in steroidogenesis [72].

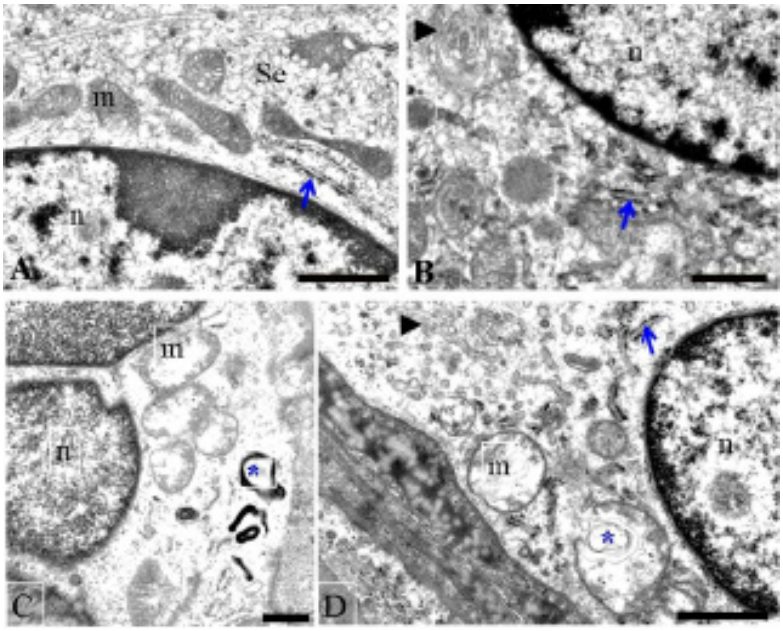

Figure 4: Vervet monkey Leydig cell ultrastructure of control (A), khat extracts-treated animals at 0.8mg/kg (B), 3.2mg/kg (C), 6.4 mg/kg (D). Note abundance of mitochondria (m), smooth endoplasmic reticulum (Se) and well-arranged rough endoplasmic reticulum (arrow) in controls. At low dose (B), rough endoplasmic reticulum were few and disorganized. Mitochondria appeared to be losing integrity of inner cristae and in some areas degenerating (star) and engulfed by other mitochondria (C and D). Rough endoplasmic reticulum were few and appeared scattered. (n = 5). Bar = 0.5 µm in A-F.

Earlier studies reported a strong correlation between testosterone secretion and volume densities of mitochondria and SER in Leydig cells of different animal species [73]. The decrease in SER in the our study may be a result of inhibition of formation of new SER membranes at high dose of khat extracts following breakdown of old ones. The decrease in the amount of SER, number of lipid droplets and mitochondria coupled with ballooning effect of mitochondria (**Figure 5**) is evidence of impaired steroidogenesis reported in humans [13], rats [11], mice [62], rabbits [63] and vervet monkeys [9].

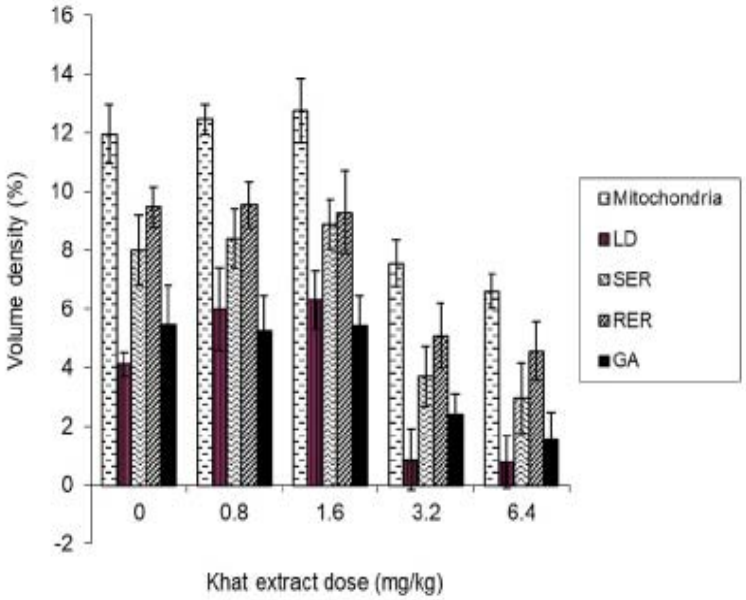

Figure 5: A graph showing mean volume densities (%) of mitochondria, lipid droplets (LD), Golgi apparatus (GA), smooth (SER) and rough endoplasmic reticulum (RER) in Leydig cell of control and khat extracts-treated vervet monkeys. Note a significant ($P<0.05$) decrease in volume densities of these organelles at dose 3.2 and 6.4 mg/kg body weight (n = 5).

The membrane-bound P_{450} cholesterol side chain cleavage enzyme (CYP11A) associated with mitochondria catalyzes conversion of cholesterol to pregnenolone through hydroxylation and cleavage of steroid substrates [74]. A large body of evidence suggests that SER, Golgi complex and lipid droplets are integral in steroidogenesis. Studies in humans showed that cytochrome P_{450} enzymes (CYP17, CYP19 and CYP21) are associated with SER [66]. Our findings on Leydig cell morphology are consistent with studies in humans [75] and birds [76] that indicated susceptibility of some sub-cellular elements to endocrine disrupters. Collectively, these findings point at adverse effects of khat extracts at high dose and long-term exposure on functions of steroidogenic organelles.

Sub-chronic exposure to high dose of khat extracts had adverse effects on developing germ cells in the seminiferous tubules, pointing towards impairment of spermatogenesis. The disorganized shape of spermatogonia as shown by cell membrane outline as well as vacuolation in spermatocytes, all point to degeneration in these cells (**Figure 6**). It is argued that immature germ cells are highly susceptible to noxious agents due to the abundance of histones in their chromatin material compared to mature forms that contain highly condensed chromatin due to argenine and cysteine-rich protamines [77].

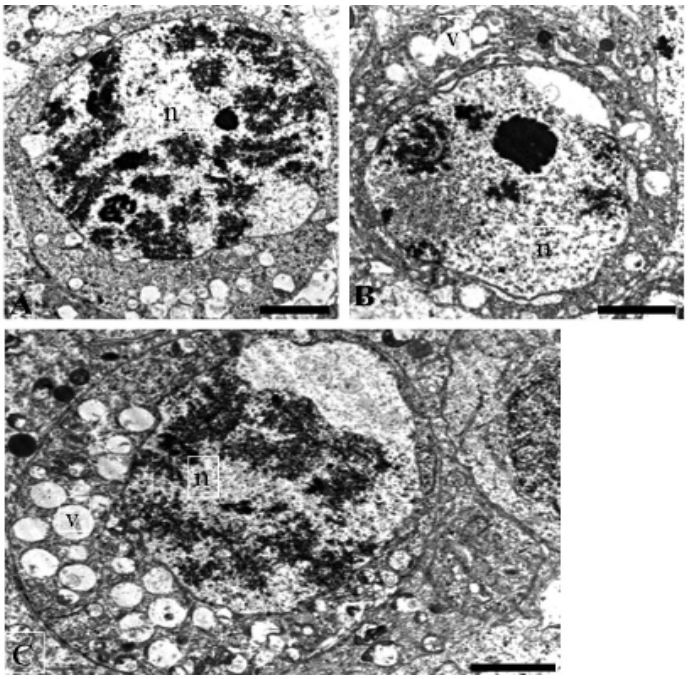

Figure 6: Spermatocytes of vervet monkeys showing controls (A) and khat extracts-treated groups (B - D). Numerous cytoplasmic vacuolations (v) accompanied by disorganization of nuclear membrane in treated groups was observed. At high dose (6.4mg/kg) (C) numerous cytoplasmic vacuolations accompanied by disruption of nuclear membrane integrity was observed. Chromatin material in the nucleus appeared more condensed indicative of degenerative changes. (n = 5). Bar = 0.5 μm in A-D.

Vacuoles in spermatogenic cells are frequently encountered following impaired spermatogenesis. For instance, rabbits treated with 40.5g/kg of khat extract [10] showed vacuolation in spermatogenic cells. There was also evidence of impairment in nuclear function in our study as shown by irregular outline of nuclear membrane in spermatocytes.

The volume of cytoplasm in these cells was generally reduced. Round spermatids also showed peripheral margination of chromatin material. Exposure to high dose of khat extracts caused a number of spermatid abnormalities such as oblong shape, missing centrioles and lacking tails. These abnormal spermatids appeared clumped together in sleeve-like pockets of Sertoli cells, possibly for subsequent phagocytosis **(Figure 7**).

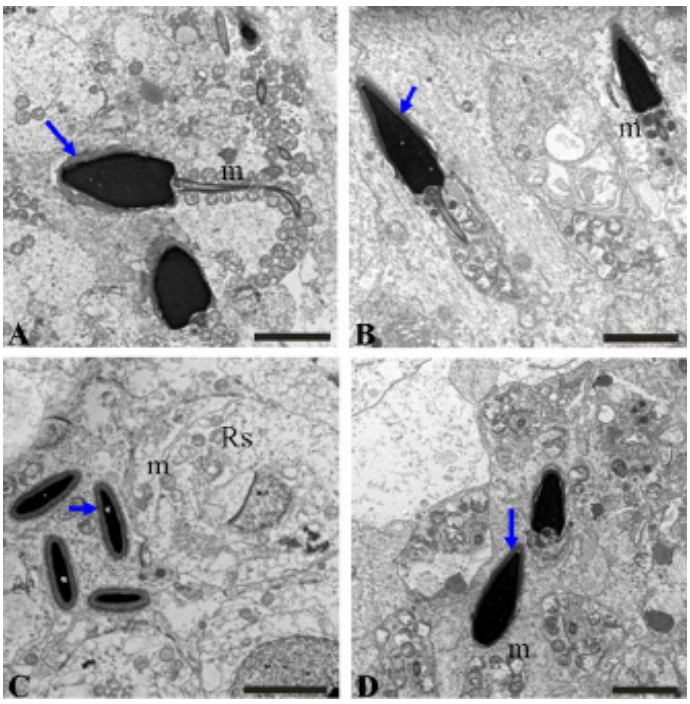

Figure 7: Elongate spermatids of vervet monkeys. Controls (A) and low dose (0.8 mg/kg) of khat extracts (B) shows spermatids with intact acrosome (arrow) and developing flagella with emerging mitochondrial sheet (m). At dose 3.2 mg/kg (C) and 6.4 mg/kg (D), normal sperm development is impaired. Note aggregation of spindle-shaped spermatids with few mitochondria next to disorganized round spermatid (Rs) in C. At medium and high doses of khat extracts spermatids appear tailless with no signs of flagella formation. (n = 5). Bar = 0.5 μm in A-D.

5. Current Status on Khat Use across Continents

Most countries of eastern Africa and Arabian Peninsula allow free possession and use of khat while in the United States, khat is classified as a Schedule IV substance and cathinone as a Schedule I drug by the Drug Enforcement Agency. The United Nations lists cathinone in the Schedule I of the UN Convention on Psychotropic Substance and cathine in Schedule IV of the Convention [78]. Khat use has since been prohibited in the United States and most parts of Europe. In the beginning of 2013, there was a ban on khat exports to Netherlands and later in 2014 in the United Kingdom. Khat use in Sweden, France, Finland, Eritrea and Jordan is also prohibited [79]. In Kenya, however, khat is planted for commercialization while locally people use it for treatment of erectile dysfunction, malaria, influenza, vomiting and headache [80]. In Ethiopia, khat export exceeds those of other commodities [81] while in Yemen khat is one of the main cash crops that contribute up to 10% of national growth development product and key source of employment its citizens [82]. In such areas, the socio-economic benefits of khat use are regarded weightier over the potential health risks. A delicate balance hangs owing to the boon and bane faces of khat in source and international export countries.

6. Treatment Remedies of Khat Addiction

Like users of other drugs of addiction such as cocaine, amphetamine and morphine, drug abstinence and subjection to rehabilitation program has been used with various degrees of success. This varies among affected individuals: those with genetically inclined traits, social/peer as well as lifestyle habits. In the Kenyan context, abstinence followed by rehabilitation seems to be the available tool of treatment of khat and other drug addiction cases. Most of individuals incriminated in this exercise are victims of con-current users of other drugs such as tobacco, marijuana and even alcohol. There are accompanying challenges to the success of this approach since the vice in the affected individuals is occasioned by various factors as mentioned above and so a combination of medical and psychological counseling appears to be most appropriate intervention. There is very scanty information on medical intervention of khat addiction cases with one study [83] which reported use of bromocriptine although it is now a banned substance. Most available literature reports from areas of endemic khat use implicate psychological counseling as the preferred tool [79].

Successful patient rehabilitation or healing relies heavily on individual case approach. It should be understood that khat, like any other addiction drug, bears withdrawal syndrome to long-term use. These withdrawal symptoms are more traumatizing to deal with compared to the real effects of khat. A proper approach therefore should consider aspects of potential genetic involvement, lifestyle habits leading to anxiety and depression, as well as environmental/peer group influence. It is also important to establish whether or not the patient concomitantly uses khat with other psychostimulants. Involvement of family members and close associates ensures collective effort in rehabilitation process that in turn minimizes cases of some patients abandoning treatment due to lack of background knowledge.

Lack of satisfactory and convincing knowledge of wholesome adverse effects of khat on human health owing to improper experimental designs, use of wrong animals in studies modeling human functional systems, lack of funding, improper simulation of real-time khat use in the human context when designing experiments, and subjectivity in reporting results owing to political and economic inclinations have contributed to a pool of findings that are primarily contradictory and therefore do not add advisory value to policy making. Government agencies in such cases are faced with challenges of enforcing laws that can best govern regularization or illegalization of khat chewing habit as well as dealing with addiction cases. In most countries where khat use is a cultural norm and considered contributor to economies of scale, such as Kenya, Yemen, Ethiopia and many countries around the horn of Africa, cases of addiction treatment are not a priority. Such perceptions have compromised any meaningful efforts from researchers who report invaluable findings that could otherwise contribute immensely to intervention measures to curb the vice.

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