Chapter

Psychopharmacological Perspectives and Diagnosis of Substance Use Disorder

Samson Duresso

Abstract

A considerable body of research has accumulated over several decades and altered the current understanding of substance use and its effects on the brain. This knowledge has improved the perception of the disease of addiction and has opened the door to new ways of thinking about diagnosis, prevention, and treatment of substance use disorders. The purpose of the current chapter is to briefly outline and summarize the major psychopharmacological framework underlying substance use disorder (SUD) and the factors that involve in the transformation of some people from recreational use or misuse of alcohol or drugs to SUD. The chapter explains the overall neurocircuitry theories of the addiction cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. It briefly discusses how psychoactive substances produce changes in brain functioning that facilitate the development of addiction and contribute to craving which eventually leads to relapse. The chapter also deals with similarities and differences among various classes of addictive substances in their effects on the brain and behavior and briefly describes the main risk factors that involve SUD. Finally, an attempt is made to briefly discuss the major DSM 5 based behavioral criteria that involve SUD, corresponding to the most abused substances worldwide.

Keywords: Addiction, Substance use, addiction cycle, substance use disorder, Neurocircuitry, Reward system, Neuroadaptation, Incentive-Sensitization, Incentive-Salience, DSM-5 criteria

1. Introduction

Addiction is the recurrent use of mood-altering substances, such as alcohol and other drugs, despite their adverse health and psychosocial consequences. The interplay among genetic, psychosocial, and environmental factors influences the development and manifestations of the disorder [1]. For some individuals, becoming physiologically dependent on a certain substance is likely to be a developmental process. Individuals may start with a positive attitude towards a substance, begin to practice using it, become regular users, progress to being heavy users and finally become dependent on it. While developing a positive attitude towards a certain substance, for instance, cigarettes and beginning to experiment with it, may be strongly related to exposures to smoking by other family members [2], becoming heavy smoker, on the other hand, is more strongly related to frequent exposures to peer smoking and being able to access cigarettes readily [3].

Addiction, which was once viewed mainly as a moral failing or character fault, is now considered as a chronic illness of the brain characterized by clinically significant impairments in health, social function, and involuntary control over drug use [4, 5]. Although the mechanisms may be different, addiction, like most physiological disorders, is chronic, subject to relapse, and influenced by genetic, developmental, psychosocial, and environmental factors. Addictive substances exert significant influences on the brain that may affect thoughts, emotions, and behaviors. Substances of abuse have powerful effects on the brain and produce euphoria (extreme pleasure) which provokes users to seek those substances repeatedly despite the risks for significant harms.

As individuals continue to misuse alcohol or other substances, neuroadaptations occur due to progressive changes in the structure and function of the brain. Neuroadaptation compromises brain function and eventually results in the transition of an individual from controlled, occasional substance use to chronic misuse, which can be difficult to control. These brain changes may persist long after an individual stops and produce a continuous or periodic craving for the substance that can lead to relapse: More than 60 percent of people treated for a certain substance use disorder experience relapse within the first year after completion of treatment [6], and some may remain at increased risk of relapse for many years.

Much of our knowledge about the effects of substance use and misuse on the brain as well as the development of addiction comes from the study of laboratory animals. Neurobiological studies in animals have examined both the immediate effects (acute impact) of addictive substance in the brain right after ingestion and the long term or chronic impact of drug use to understand, at the most basic level, the mechanisms through which substance use alters brain structure and function and facilitates the transition from occasional use to misuse, addiction, and relapse. Although the animal models do not fully reflect the human experience, animal studies help researchers investigate addiction and related behavioral changes under highly controlled conditions that may be difficult or unethical to replicate in humans [7].

To supplement the work in animals, a growing body of substance use research has been conducted with humans. The use of brain-imaging technologies, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans for studying the effects of alcohol and drugs on the human brain have significantly advanced the current knowledge of SUD by allowing researchers to see inside the living human brain. Using these technologies, researchers can investigate and characterize the biochemical, functional, and structural changes in the brain which result from addictive substances and find out how such changes may ultimately contribute to substance use, misuse, and addiction [8]. Animal and human studies are integrated and inform each other for a more complete picture of the neurobiology of addiction [9].

The structural and functional changes caused by using drugs can be long-lasting and can lead to harmful behaviors seen in individuals who continued to abuse drugs. Although the initial decision to try a drug of choice is mostly voluntary, eventually, as drug abuse takes over or an individual transforms from occasional user to heavy user, his/her ability to exert self-control may become seriously affected. Brain imaging studies conducted on drug-addicted individuals typically revealed that physical changes have been observed in the areas of the brain that are critical to judgment, decision making, learning, memory, and self-control. Scientists believe that these changes alter the way the brain works and may help explain the compulsive and destructive behaviors of addiction [10].

Susceptibility for addiction varies from individual to individual as for any other diseases. This depends on the amount and level of risk factors a person has. The

more the risk factors the greater the chance that taking drugs will lead to abuse and addiction. No single factor determines whether a person will become addicted to drugs. The overall risk for addiction is influenced by the biological makeup of the individual including sex or ethnicity, developmental stage, and the surrounding social environment such as home, school, and the neighborhood.

Individuals with mental disorders are at greater risk of drug abuse and addiction than the general population [11]. A growing body of research reveals that SUDs and many psychiatric disorders share comparable neural mechanisms. There are several clinical resemblances and symptom overlaps between SUDs and affective disorders [12]. Epidemiological studies revealed that co-occurring substance abuse and psychiatric problems are common in clinical practice. SUDs and a variety of mental illnesses have similar changes in the dopamine-mediated reward system as well as different neurotransmitter systems such as GABA, and serotonin [10]. According to recent findings from neuroimaging research, similar abnormalities in frontal-limbic brain circuitry are implicated in SUDs and depressive disorders. Individuals with SUDs have been found to have lower frontal metabolism and anterior cingulate activation [13, 14]. Depressive symptoms are typically observed after acute and chronic drug withdrawal due to anomalies in the CRF and HPA axis, as well as alterations in catecholamines, serotonin, GABA, and glutamate systems [15]. Hence, chronic stress-induced neuroadaptations in brain stress system and reward pathways may increase the susceptibility to self-administer the substances of abuse and predispose or reveal a vulnerability to psychiatric conditions, SUDs, or both [16, 17].

The influence of home and family environment is usually most important in childhood. Children who are exposed to parental substance use early in life are more likely to develop SUD in their future life through behavioral modeling [18–20]. It is more likely that parents or older brothers or sisters who abuse alcohol or drugs can increase other children's risks of developing drug problems [21]. In addition, children with poor social skills and poor academic achievement may be at more risk of developing drug problems in school [22].

The route of administration of the substance being used is also a potential factor that may influence the progress of an individual from a regular user to a heavy user or abuse. For instance, as both smoked and injected drugs enter the brain fast and produce a powerful rush of pleasure, smoking a drug or taking it through the vein increases its addictive potential. This intense high feeling of pleasure (euphoria), however, can gradually fade away and a rebound effect of agitation or low feelings may occur. Then, these feelings develop into cravings and drive individuals to recurrent drug abuse to recapture the high pleasurable state which can worsen the risk of developing addiction [23].

The age of the onset of drug use is another potential factor that increases the likelihood of drug abuse by individuals. Although starting drugs at any age can eventually lead to addiction, early substance use is a strong indicator of problems ahead related to substance abuse and addiction [24]. Research findings have shown that people who start taking drugs at an early age are more likely to be at increased risk for adult substance dependence [25]. The part of the brain, the prefrontal cortex, which is responsible for assessing situations, making sound judgment and decisions, and keeping our emotions and desires under control is still maturing during adolescence. The fact that this critical part of an adolescent's brain is still a work-in-progress puts young people at increased risk of making poor decisions regarding trying drugs for the first time and/or continuing drug abuse thereafter. Adolescents at this stage are developing judgment and decision-making skills which may limit their ability to assess risks accurately and make sound decisions about using drugs. Therefore, introducing drugs while the brain is still developing may have profound and long-lasting results concerning drug addiction. Early use of psychoactive

substances changes the structure and functions of the brain which can lead to addiction and other serious problems [26]. Thus, preventing early use of alcohol or other drugs may reduce the risk of progressing to later abuse and addiction.

Interindividual differences in addiction risk are mostly determined by genetic variation. The impact of genetic variation on total addiction risk has been estimated to be 50% in studies focusing on variability across identical and nonidentical siblings [27]. The largest study to date on 1.2 million people that looked at common genes in alcohol and nicotine use identified genes involved in dopaminergic and glutamatergic neurotransmission, transcription and translation, and brain development [28]. They also revealed that a crucial genetic component of SUDs appears to impact a vulnerability to disorders with pathological symptoms via a general-purpose underlying mechanism.

Besides these common genetic characteristics, genetic variants that are mainly unique in a particular drug have been found. The most well-known genetic variants are those that code for the alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) enzymes, which cause poor alcohol metabolism and protect against alcoholism [28]. Like other complex biobehavioral disorders, addiction is a polygenic disease involving multiple genes and genetic networks [29, 30]. Genetic research has aided our understanding of addiction-related neurobiological processes. Addiction-related gene variations can increase the risk of drug misuse and addiction by altering neurotransmitter systems, drug metabolic pathways, and brain circuitry. For example, genetic polymorphisms in the nicotinic acetylcholine receptor subunits expressed in the medial habenula are linked to development of withdrawal symptoms [31] and are at least partially accountable for the genetic predisposition or vulnerability to tobacco addiction [32, 33]. This has demonstrated that the habenula is involved not just in nicotine addiction, but also in the unpleasant emotional states associated with the long-term use of numerous drugs of abuse [29], such as alcohol [30] and opioids [34].

Epigenetic factors are a diverse set of transcriptional tuning processes that generate and sustain gene expression–mediated physiological outcomes in response to environmental inputs [13]. Plasticity is at work in the transition to compulsive drug use, changing the physiology of the brain to produce addictive states. Physiologically, the rewiring of brain reward circuitries, particularly dopamine neurons in the ventral tegmental area (VTA), is thought to cause vulnerability to relapse after periods of attempted abstinence from drugs of abuse such as cocaine use. The same enzyme that attaches serotonin to Histone 3 can also catalyze the attachment of dopamine to H3 — a process, known as dopaminylation, which may control drug-seeking behavior [35]. Cocaine-induced transcriptional plasticity in the midbrain is mediated by histone H3 glutamine 5 dopaminylation (H3Q5dop). As a result, long-term cocaine use alters neuronal circuits in the brain's reward system, necessitating a consistent intake of the drug for the circuits to function normally. To make the proteins for those changes, certain genes must be turned on and off, and this is an epigenetic mechanism activated by dopamine acting on H3, not a change in DNA sequence. Epigenetic mechanisms provide a convergent regulatory framework within which the plasticity required to produce an addicted state can emerge and then remain long after drug use has stopped [36, 37].

2. The addiction cycle

There are many theories and models of addiction. While some of the theories and models present their theoretical approaches at an individual level, some explain the addictive behavior in terms of population or group interaction and influence. It is also important to note that many theories of addiction are complex and have

evolved over time and therefore may overlap across one or more explanatory domains or perspectives.

The learning theory of addiction is relatively a broad category that emphasizes the importance of associations among cues, responses, and positive (pleasant) or negative (noxious) reinforcers. Among the specific models and theories under this category are operant learning, classical conditioning, and drug withdrawal theory [38, 39]. Moreover, the incentive sensitization theory of addiction also incorporates aspects of learning theory as it proposes that repeated exposure to drugs and drug-associated cues capitalizes on neuroplastic changes in mesocorticolimbic circuits and classical conditioning to make drugs and drug paired stimuli more motivationally salient [40, 41] .

The drive theories of addiction explain that addiction involves the development of powerful drives reinforced by homeostatic mechanisms. The drive theory is part of the disease model of addiction [42] and states that addiction is the result of pathological changes in the brain that produces overpowering urges. These changes that result in impairments may involve a structural or functional abnormality in the CNS [42]. Among the goal-focused theories of addiction are positive reward theories, acquired need theories, pre-existing need theories, and identity theories. These theories mainly explain addiction in terms of an individual's behavior that satisfies one's physiological or psychological needs, pleasure, and aspects of self-identity [43–47].

Other theories such as cognitive control theory [48], executive dysfunction theory [49–51], self-regulation theory [52], self-determination theory [53, 54], and implementation intentions theory [55, 56], describe addiction as a failure of individual's strategies, ability or skills to self-control or to counteract impulses and motives underlying the addictive behavior. The biological theories describe that addiction involves specific neural circuitry or mechanisms [57–62] and is primarily a brain disease' characterized by dysfunction of neural pathways such as those that subserve executive function. The Reflective Choice Theories focus on the individual's decisions, preferences, and actions that are made based on reasons and analysis. Therefore, according to these theories, addiction is a rational choice made by individuals in favor of the benefits of the addictive behavior over the costs. The Inhibition dysfunction theories suggest that addiction is an ongoing dysregulation of the ability to inhibit a rewarded behavior due to impairment of impulse controlling mechanisms [63]. In other words, addiction involves impairment of the inhibitory system of the brain regions related to features of response selection, inhibition, and motivation of compulsive behaviors associated with drugs. The hedonic homeostatic dysregulation theory also states that addiction is a cycle of escalating dysregulation of the brain reward systems that gradually increases and facilitates the act of compulsive drug use and a loss of control over drug-taking behavior, which are the basic concepts that underlie the addiction cycle [64].

Drug addiction is a disorder that is chronically relapsing and manifested in terms of compulsive behavior to seek and consume the drug, significant loss of ability to control and limit drug intake, and the emergence of negative and distressful emotional states such as irritability, anxiety, and dysphoria. Drug addiction is conceptualized as a three-stage cyclic disorder that consists of impulsivity and compulsivity and involves neuroplastic changes in the brain reward, stress, and executive functions [64, 65]. Impulsivity often dominates the early stages of the cycle and compulsivity dominates the terminal stages. The three stages are considered to interact with each other, become more intense, and eventually lead to the pathological state known as addiction.

Drug addiction is an excessive drug-taking behavior in which individuals compulsively seek and take drugs and lose their ability to control in limiting their drug

intake. One of the multiple motivational mechanisms that drive such behavior is the development of a negative emotional state when access to the drug is prevented or discontinued, which results in dysregulation of hedonic homeostasis [64]. At the neurobiological level, two neuroadaptive models, sensitization and counter-adaptation, have been hypothesized to contribute to the changes in motivation for drug-seeking and compulsive use (hedonic homeostatic dysregulation) and the neurobiological mechanisms, such as the mesolimbic dopamine system, opioid peptidergic systems, and brain and hormonal stress systems [64]. While sensitization has been conceptualized to be a shift in an incentive-salience state since it involves a progressive rise in the effect of a certain drug due to its frequent administration (21), counteradaptation hypotheses (20), on the contrary, were closely related to hedonic tolerance and involve the reduction of dopaminergic and serotonergic neurotransmission in the nucleus accumbens during drug withdrawal (22). Critical neurobiological sites with specific neurotransmitters and hormones have been identified that may regulate the hedonic dysregulation and provide the substrates that convey both vulnerabilities to, and protection against drug addiction. Dysregulation of key neurochemical elements in both reward and stress systems, such as decreases in dopamine and opioid peptide functions in the ventral striatum and recruitment of brain stress systems known as corticotropin-releasing factor (CRF) in the extended amygdala is hypothesized to produce the negative emotional state that initiates a condition of negative reinforcement [66]. An individual who uses a drug impulsively starts using it compulsively when a shift has occurred from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior. Impulsivity and compulsivity often coexist in the different stages of the addiction cycle. This occurrence reflects the role of dysregulated reward and stress systems in the negative emotional states associated with the withdrawal/negative affect and preoccupation/anticipation stages of the addiction cycle that drive drug-seeking behavior [67].

The addiction cycle becomes more severe and well-established as a person continues substance use and as it produces dramatic changes in the functioning of certain brain areas that reduce the person's ability to control his or her substance abuse. Three neurobiological circuits have been recognized to have empirical value for the study of the neurobiological changes associated with the development and persistence of drug addiction linked to the three-stage cycle (**Figure 1**). The key elements of the ventral tegmental area and ventral striatum are the focal points for the binge/intoxication stage and mediate the acute reinforcing effects of drugs of abuse. Acute withdrawal symptoms such as increased anxiety and dysphoria are associated with the second stage, the withdrawal/ negative affect stage, and are most likely the results of disruption in the function of the extended amygdala reward system and the recruitment of the brain stress neurocircuitry [68]. The preoccupation/ anticipation (craving) stage is a widely distributed network and involves the stress-induced processes at the central brain stress systems in the basolateral amygdala, the orbitofrontal cortex–dorsal striatum, prefrontal cortex, and the hippocampus. The prefrontal cortex is mainly responsible for executive functions like organizing thoughts and activities, prioritizing tasks, managing time, and making important decisions, including limiting substance consumption [65].

This three-stage model of addiction is largely attributed to the extensive works of George Koob [69] and his colleagues and is supported by several animal and human research findings which provide useful means to understand the aspects and symptoms of addiction and design prevention, intervention, and treatment strategies [70]. It is worth noting that the three stages of addiction being discussed do not have absolute temporal distinctions that some components of addiction such as craving, conditioned cued craving, incentive-salience related craving, craving linked to

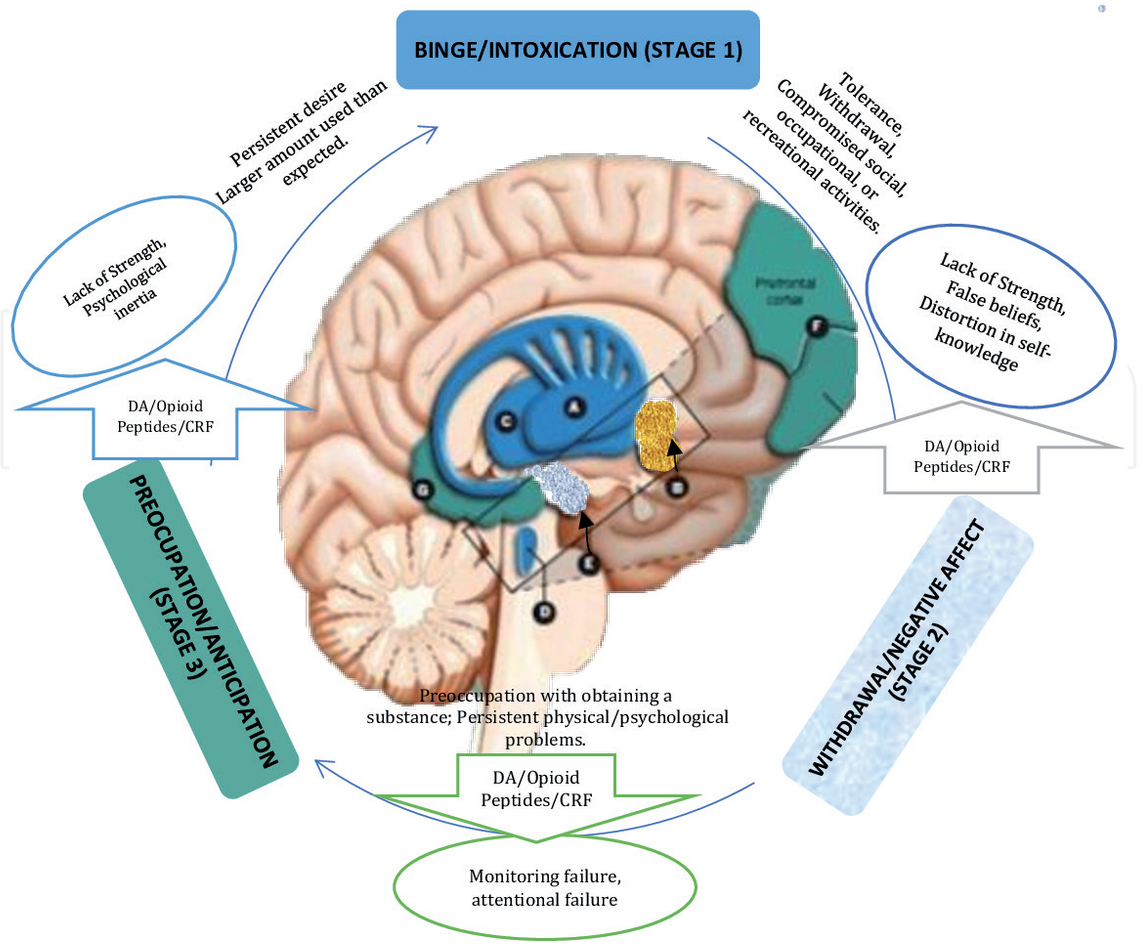

Figure 1.
A diagram depicting the spiralling distress – addiction cycle from social psychological and neurobiological viewpoints. NB. Stage 1: The reward circuit is overstimulated, resulting in a lack of control and bingeing. (A) Basal Ganglia refers to interconnected regions that are linked to learning, reward, and habit formation. (B) Nucleus accumbens (NAs) receives dopamine from Ventral Tegmental area, helps to control desire, satiation, and inhibition. (C) Thalamus is a centre that transmits sensory information and regulates arousal. (D) Ventral tegmental area: Dopamine is generated in this major structure near the top of the brain stem. Stage 2: After long-term exposure to addictive substances, the number of dopamine receptors in the nucleus accumbens decreases (B), requiring more of the addictive substance or action to feel the same. (B) The nucleus accumbens (NAs) is heavily implicated in the first and second stages of the addiction cycle. (E) The amygdala is linked to memory and emotions, particularly anxiety and dread. Stage 3: People who are addicted have a compulsive need to engage in the addictive behaviour again. The frontal cortex is thought to be affected by drug abuse. (F) The frontal cortex is in charge of ideas and actions. The orbitofrontal cortex is hypothesised to be involved in behaviour control. (G). Hippocampus: consolidated of memory. The three-stage addiction cycle incorporates some of the factors of possible self-regulation failure, such as under regulation and mis regulation, as well as the multiple DSM-5 criteria for substance dependence. The arrows depict the possible roles of several neurochemical and endocrine systems in the addiction cycle. Increased functional activity of DA, dopamine, Opioid Peptide, and CRF, corticotropin-releasing factor, is indicated by the arrows. It's worth mentioning that the addiction cycle is depicted as a circular pattern that rises in amplitude with repeated exposure, eventually leading to addiction as a pathological condition.

withdrawal, etc. appear at many places in the addictive process and that the impacts of these aspects of craving and their neural basis remain to be further elucidated.

2.1 Stage 1: binge/intoxication

In most cases, addiction is started by abusing substances that have hedonic properties. Many factors contribute to the transition from drug use to drug addiction, including availability (route of administration), genetics [71], prior drug use history, stress, and life events [72] . Initial; experimentation of drug abuse may be the result of peer pressure due to the rewarding effects of conforming to the peer

group. In some cases, the first use of a substance may be related to its therapeutic properties, such as opiate analgesics for the treatment of pain or stimulants such as amphetamine for the treatment of attention-deficit hyperactivity disorder [73].

In humans, the majority of drug users do not develop into drug abusers or drug addicts [74]. Similarly, even with intravenous drug administration in limited-access situations, stable drug intake can be observed in animals without pronounced signs of dependence. The current challenge is to discover the contribution of neurobiological factors to individual differences in drug addiction vulnerability [64]. It is broadly accepted that the key elements of the reinforcing effects of drugs of abuse involve their ability to activate large amounts of extracellular dopamine in limbic regions and the nucleus accumbens. Brain imaging studies in humans revealed that drug-induced increases in dopamine in the ventral striatum, where the nucleus accumbens is located, are significantly linked to subjective correlates of reward such as pleasure, high, and euphoria [27, 75].

The nucleus accumbens (NAs) and the dorsal striatum (DS) are the two sub-regions in the basal ganglia which are particularly important in substance use disorders. While the NAs is involved in motivation and the experience of reward the DS is responsible for forming habits and other routine behaviors [76]. The NAs is located strategically to collect important limbic information from the amygdala, frontal cortex, and hippocampus that could be transformed into motivated behavior (the acute reinforcing effects of drugs) through its connections with the extrapyramidal motor system [70]. It is the primary site mediating reward behavior and thought to directly involve in reinforcing addictive behaviors in response to drug use. It is hypothesized that the initial action of drug reward depends on dopamine release in the nucleus accumbens for cocaine, amphetamine, and nicotine; activation of the opioid peptide receptor in the VTA (dopamine activation) and nucleus accumbens (independent of dopamine activation) for opiates; and activation of the GABAA systems in the nucleus accumbens and amygdala for alcohol [70].

The dopaminergic projection from the VTA to the nucleus accumbens is known as the mesolimbic dopamine system (the mesolimbic pathway) and is strongly associated with the dependence-producing potential of addictive substances [77]. Many drugs of abuse directly or indirectly exert their powerful effects on this pathway and contribute to the development of dependence by signaling to the brain that addictive substances are especially important from a motivational perspective. The direct activation of dopamine, serotonin, opioid peptides, and GABA systems in the basal forebrain facilitates the acute reinforcing effects of drugs of abuse [74]. There are several supporting pieces of evidence for the hypothesis that addictive drugs dramatically activate the mesolimbic dopamine system and the serotonin systems, specifically, those involving 5-hydroxytryptamine-1B (5-HT1B) receptor activation in the nucleus accumbens, during limited-access self-administration [78, 79]. Several studies have shown that most addictive drugs including cocaine, amphetamine, and nicotine [79], either directly or indirectly, activate neurons that release dopamine. They produce their rewarding effects by stimulating the nucleus accumbens through the activation of the brain's dopamine and opioid signaling system. Brain imaging studies in humans who use alcohol, nicotine, and other substance have shown activation of dopamine and opioid neurotransmitters during use [80, 81]. In the same manner, the primary psychoactive component of marijuana, tetrahydrocannabinol (THC), targets the brain's endogenetic cannabinoid system and affects the reward system by influencing the function of dopamine neurons and the release of dopamine in the nucleus accumbens [30, 31].

Another key component of the binge/intoxication stage involves a second sub-region of the basal ganglia, the dorsal striatum. This part of the brain is

mainly related to habit formation [82]. With repeated drug use, the release of dopamine, glutamate (an excitatory neurotransmitter), and activation of brain opioid systems trigger changes in the dorsal striatum and strengthens substance-seeking and substance-taking habits. Studies on humans showed that the rise of DA level in the dorsal striatum was significantly correlated with the increase of craving for cocaine, [83, 84]. Likewise, pharmacological blockade of the dorsolateral striatum after forced abstinence resulted in the reduction of drug-seeking behavior in rats [85–87].

As addiction progresses compulsive drug use results and neuroadaptive changes in the structure and function of the brain occur. Neuroadaptations involve changes in the reward circuitry systems that promote compulsive drug use through sensitization and counteradaptation, by increasing a drug's positive and negative reinforcing effects, respectively [82]. Sensitization arises from repeated administration of addictive drugs and is mediated by the mesolimbic dopamine system [84]. It is an increased response to a drug effect which represents a with-in system mechanism of neuroadaptation [82]. Animal studies posit that direct injections of opiates or amphetamine into the ventral tegmental area which alter the function of the dopamine neurons ultimately produce sensitization to later injections of these drugs in the periphery [83]. However, like tolerance, sensitization may develop to a certain drug effect but not to another [82]. The second system that plays an important role in sensitization, representing a between-systems mechanism of neuroadaptation, is the CRF (corticotropin-releasing factor) mediated stress-response system [82]. The CRF is a hormone released by the hypothalamus and the amygdala in response to certain stressors. The CRF, in turn, stimulates the release of additional stress hormones into the bloodstream activating a stress response system called the hypothalamic–pituitary–adrenal (HPA) axis. Exposure to a variety of stressors implicates the CRF mediated stress-response system which promotes sensitization to the drug [82]. The role of sensitization in drug dependence is mainly linked to a motivational state described as "wanting" which progressively increases due to repeated exposure to drugs of abuse [85]. As "wanting" increases across repeated exposures to alcohol and drugs of abuse, the likelihood of relapse following periods of abstinence may increase, eventually leading to compulsive drug use [82].

Drug-associated stimuli raise dopamine levels in the dorsal striatum as addiction grows, leading to drug craving and reinforcing the habit of drug use [82]. In the new DSM-5 classification, drug craving as a motivational state for drug-seeking behavior is finally recognized as one of the main features of substance use disorders [88]. Cue reactivity and cue-elicited craving are both influenced by the process of "Positive Reinforcement," which involves learning to associate salient cues with drug-use rewards [89]. Drug craving is a complex neurocognitive emotional–motivational reaction to a variety of stimuli, ranging from internal to external settings, and from drug-related to stressful or affective experiences.

Substance craving, or "wanting" for a drug, is a common element in clinical definitions of addiction, and it appears to play a role in the maintenance of addictive behaviors [90]. According to Robinson and Berridge, sensitization processes which arise from neuroadaptations in brain reward pathways as a result of prolonged drug misuse are responsible for addicted animals' excessive "wanting" or drug-seeking behavior [91]. They propose that these neuroadaptations result in a rise in the motivational salience of drugs so that exposure to drugs and drug-associated cues causes excessive "wanting" or seeking, increasing the risk of relapse [92, 93]. Furthermore, environmental stimuli previously associated with drug use or internal cues such as stress responses, negative affect, and withdrawal-related states associated with drug abuse can function as conditioned stimuli capable of eliciting craving on their own [94, 95]. External drug-related stimuli, such as persons and places associated

with drug use, or drug paraphernalia such as needles, drug pipes, cocaine powder, or beer cans, as well as in vivo drug exposure, can increase drug craving and physiological reactivity [96].

In summary, in the nucleus accumbens of the basal ganglia, the "reward circuitry" along with dopamine and naturally occurring opioids play a vital role in the rewarding effects of alcohol and other substances. Furthermore, as the addiction progresses, stimuli or cues associated with that substance use can cause craving, substance seeking, and use. Chronic alcohol or substance use and frequent activation of the "habit circuitry" or the dorsal striatum of the basal ganglia significantly contributes to the compulsive substance seeking and taking that potentially lead to SUD. The involvement of the reward and habit neurocircuits play key roles in substance craving and compulsive substance seeking when addicted individuals are exposed to alcohol and/or other drug cues in their surroundings.

2.2 Stage 2: withdrawal/negative affect

This stage is related to a neurocircuitry pathway known as the extended amygdala and its connections including the major components of the brain stress systems associated with the negative reinforcement [84]. This pathway is composed of the central amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the NAc shell. When DA is released, it intensively activates a number of areas that belong to the lateral subdivision of the extended amygdala such as the bed nucleus of stria terminalis, BSTM, and central amygdala) [97]. The extended amygdala also integrates brain arousal–stress systems with hedonic processing systems to produce unpleasant emotional states that promote negative reinforcement mechanisms linked to the development of addiction [98]. For example, hyperactivation of amygdala has been observed in individuals with SUDs, associated with cue-induced drug craving [99].

Two primary sources of reinforcement (positive and negative reinforcement) have been implicated to play significant roles in this allostatic process. Dysregulation of specific neurochemical mechanisms in the brain reward circuits (opioid peptides, γ-aminobutyric acid, glutamate and dopamine) and recruitment of brain stress systems (CRF), which are localized in the extended amygdala, are the reinforcing factors that provide the negative motivational state in the process of addiction [16, 100]. These allostatic changes in the reward and stress systems are assumed to maintain hedonic stability and as such contribute to the vulnerability for development of dependence and relapse in addiction [101].

An important component of this stage is the within-system neuroadaptations to chronic drug exposure which is characterized by a reduction in the function of the neurotransmitter systems in the neurocircuits implicated in the acute reinforcing effects of a drug of abuse [102]. One popular theory is that dopamine systems are negatively affected during key stages of the addiction cycle, such as withdrawal, resulting in decreased motivation for non-drug-related stimuli and increased sensitivity to the abused drug [103, 104]. In animal studies, acute drug withdrawal from all major drugs of abuse results in decreased activity of the mesolimbic dopamine system and decreased serotonergic neurotransmission in the nucleus accumbens [105]. Symptoms of withdrawal may occur with all addictive substances, but with varying intensity and duration depending on both the type of substance and the frequency and severity of use. Brain imaging studies have consistently revealed a long-lasting reduction of a particular type of dopamine receptor (the D2 receptor) in substance-addicted individuals compared to their counterparts. The same dose of stimulant causes a smaller release of dopamine in addicted persons than in non-addicted persons [83]. In addition, decreases in the activity of the dopamine

system have also been observed during withdrawal from stimulants such as opioids, nicotine, and alcohol [106].

Acute withdrawal mechanisms are likely to be drug-specific and reflect changes in the biological targets of these drugs. For example, during the first few days of cocaine withdrawal, the brain becomes more sensitive to the effects of GABA-enhancing drugs, which may reflect the down regulation of this neurotransmitter in chronic cocaine users [107]. Brain imaging studies have shown decreased levels of endogenous opioids during cocaine withdrawal, which could explain the irritability, tiredness, and dysphoria experienced during the motivational phase of withdrawal [108]. Similarly, Imaging studies have documented hypofunction in dopamine pathways during protracted withdrawal, as evidenced by decreases in D2 receptor expression and decrease in dopamine release, which may contribute to the anhedonia (i.e., decreased sensitivity to rewarding stimuli) and motivation reported by drug-addicted subjects during protract withdrawal [109].

Typical neurochemical changes in these structures include not only reductions in reward system functioning, a within-system opponent processes, but also recruitment of the brain stress systems intermediated by corticotropin-releasing factor (CRF) and dynorphin- k opioid systems in the ventral striatum, extended amygdala, and frontal cortex known as a between-system opponent processes [80]. A between-system neuroadaptation is the second component of the withdrawal/negative affect stage. This process involves the activation of stress neurotransmitters such as corticotropin-releasing factor (CRF), norepinephrine, and dynorphin in the extended amygdala [85]. Regardless of the presence of the drug, the neurochemical systems involved in stress modulation may be triggered within the neurocircuitry of the brain's stress systems to overcome the persistent effects of the distressing substance and restore normal function [110]. These neurotransmitters play a role in the development of negative feelings associated with withdrawal which leads to stress-triggered substance use. Chronic khat chewers attempting to quit chewing, for example, exhibited withdrawal symptoms that followed similar overall patterns, with notable elevations after the quit day. Most of the khat users relapsed within 11 days and very few maintained abstinences [111]. Negative affects including depression, nervousness, tiredness, restlessness, poor motivation, irritability, as well as craving substantially increased and reached their peak on the first week of khat cessation and remained higher there after indicating the persistence and severity of these symptoms over time [112].

The aforementioned phenomena have been well demonstrated both in animal and human studies [113]. Administration of antagonists for neurotransmitters significantly reduced substance intake in response to withdrawal and stress. Similarly stopping the activation of stress receptors in the brain lowered alcohol consumption in both alcohol-dependent rats and humans with alcohol use disorder [86, 87]. Hence, the desire to remove the negative feelings associated with withdrawal can be a strong driving force to continuous consumption of the substance since the taking of the substance at least momentarily relieves the negative feelings caused by the withdrawal. This process is, however, a vicious cycle as taking substances to reduce withdrawal symptoms during the period of abstinence makes it even more difficult to maintain abstaining the next time a person tries to quit the drug of abuse [56].

In summary, this stage of addiction involves a reduction in the function of the brain reward systems involving dopamine receptors and the activation of brain stress hormones and neuropeptide (CRF, dynorphin, and norepinephrine) in the extended amygdala. The combination of these events significantly contributes to providing a powerful neurochemical basis that produces a negative emotional state associated with drug abstinence or withdrawal. Increases in drug desire and physiological reactivity have also been linked to negative affect, stress, or

withdrawal-related suffering [114–117]. The strong desire to relieve these adverse feelings, in turn, drives additional sources of negative reinforcement in compulsive substance taking or drug addiction.

2.3 Stage 3: preoccupation/anticipation

The preoccupation/anticipation (craving) stage mainly involves the Prefrontal Cortex, the region that controls executive functions like organizing thoughts and activities, task prioritization, time management, decision making, and regulation of one's actions, emotions, and impulses. Executive function is necessary for a person to make suitable choices about whether or not to submit to strong urges that may compel individuals to use substances, specifically, when the person encounters triggers and cues such as stimuli associated with that substance or stressful circumstances.

The preoccupation/anticipation stage, which is characterized by an increase in drug craving, is triggered by increased sensitivity to conditioned cues. An individual is driven to seek drugs of abuse again after a period of abstinence. Stress promotes relapse to drug-taking behaviors by activating brain circuits involved in reward processing as well as attentional and memory preferences for drug use cues [17, 118]. Chronic relapse is widely acknowledged as the most challenging obstacle in the fight against drug addiction. Long after encountering acute withdrawal symptoms, users are likely to return to compulsive drug use [119]. Chronic drug misuse is believed to cause a gradual restructuring of reward and memory circuits, which is thought to be critical to the mounting of these reactions. In clinical studies, both dopamine and glutamate have been identified as contributing to the neural alterations associated with conditioned responses [120].

The Incentive-Sensitization Theory of Addiction explains that drug-induced sensitization in the brain's mesocorticolimbic circuits, which assign incentive salience to reward-associated events, is the primary cause of addiction [41]. Incentive salience or "wanting," is generated by neural systems that comprise the mesolimbic dopamine. The role of this neural system is to attribute incentive salience or motivational importance to stimuli resulting their being viewed as highly salient, attractive, and "wanted" [40, 121]. Addictive drug administration, both continuous and occasional, causes incremental neuroadaptations in this neuronal system. Associative control of this sensitized neural system causes significantly increased incentive salience to be ascribed to the act of drug taking and stimuli related to drug-taking. This process is believed to occur due to hyperactivation of the dopamine system resulting in drugs and drug associated cues becoming pathologically more "wanted" by the drug user. Irrespective of other motivating variables such as the expectation of drug pleasure or the unpleasant aspects of withdrawal, sensitization of the neural system responsible for incentive salience can motivate addictive behavior such as compulsive drug seeking and drug-taking. The concomitant targeting of sensitized incentive salience to drug-related cues results in the recurrence of addictive behavior in the face of multiple barriers, including the loss of one's reputation, job, home, and family. This shows that drug addiction is motivated by a strong desire for drugs, often labeled as drug craving [122].

The Incentive-Sensitization Theory of Addiction offers a novel neuropsychological explanation for drug addiction. Due to dopamine system sensitization, drug craving is the subjective sensation that comes with the attribution of excessive amounts of incentive salience to drug-related stimuli or their mental images. This system causes pathological incentive motivation "wanting" for drugs that differ from both the unpleasant symptoms of withdrawal and drug pleasure. Although exposure to drug-related stimuli increased self-reported craving, as well as drug-opposite and drug-like effects, the cumulative effects of positive outcome

expectancies, cue-specific dysphoria, and cue-specific drug-positive reactions were able to predict 28 percent of the variance in cue-specific craving in a simple additive model [40, 123].

The changes that are taking place in the brain's reward and emotional circuits are followed by changes in the function of the cortical prefrontal cortex involved in the executive processes. Down-regulation of dopamine signals, which obscures the sensitivity of the reward circuits to pleasure, also occurs in the pre-frontal cortex and linked circuits, seriously affecting executive processes including the self-regulation, decision-making, flexibility in action selection, and initiation or assignment of salience (assignment of relativity) [124]. Neuroplastic changes in glutamatergic signals further disrupt the modulation of the reward and emotional circuits of the prefrontal regions. In people with drug addiction, the impaired signaling of dopamine and glutamate in prefrontal brain regions diminishes their ability to withstand strong urges or take strong decisions to stop taking the drug of abuse. These effects explain why people with addiction can be sincere in their desire and intention to stop using a substance while being impulsive and unable to follow through on their determination. Thus, changed signaling in prefrontal regulatory circuits, along with changes in rewards and emotional response circuits, causes an imbalance which is responsible for both progressive development of compulsive behavior in addictive diseases state and the related failure of individuals with addiction to voluntarily reduce the behavior [125].

Some scientists separate the functions of the prefrontal cortex into two opposing systems to better understand how this brain region is engaged in addiction: a "Go system" and a "Stop system" [80]. The Go system assists people in making decisions on topics that need a lot of thought and planning, as well as engaging in behaviors that are necessary for achieving life goals. When substance-seeking behavior is triggered by substance-related environmental cues (incentive salience), the Go circuits of the prefrontal cortex show significant increases in activity. As a result, the nucleus accumbens is stimulated to release glutamate, the brain's principal excitatory neurotransmitter [126]. In addition, the neurons in the Go circuits of the prefrontal cortex stimulate the habit systems of the dorsal striatum through connections that use glutamate and contribute to the impulsivity associated with substance-seeking behavior of a person [127].

Conversely, the Stop system primarily hinders the activity of the Go system [126]. The nucleus accumbens and habit responses driven by the dorsal striatum, that are areas of the basal ganglia implicated in the binge/intoxication stage of addiction, are controlled by Stop system. This system, according to researchers, helps to reduce incentive salience, or the ability of substance-related stimuli to trigger a relapse. The Stop system also plays an important role in relapse triggered by stressful life events or circumstances by exerting control on the brain's stress and emotional systems [126]. As explained above, the brain's stress and emotional systems involve the activation of stress hormones and neurotransmitters (CRF, dynorphin, and norepinephrine) in the extended amygdala caused by prolonged abstinence during the withdrawal/negative affect stage of addiction [109].

Imaging studies using laboratory animals revealed that lower activity in the Stop system of the prefrontal cortex is associated with increased activity of stress circuitry involving the extended amygdala, which increased substance-taking behavior and relapse [109]. Similar studies in humans with addiction show dysfunction of both the Go and Stop circuits [65, 109]. For example, people with alcohol, cocaine, or opioid use disorders exhibit significant deficiencies in executive functions such as impairments in the maintenance of spatial information, disruption of decision-making and behavioral inhibition. These executive function deficits are equivalent to the changes in the prefrontal cortex which suggest decreased activity in the Stop system and greater reactivity of the Go system in response to substance-related

stimuli. Moreover, research findings suggest that humans with post-traumatic stress disorder (PTSD), a syndrome that is usually accompanied by drug and alcohol use problems, have decreased prefrontal cortex control over the extended amygdala [75]. These findings add to the growing body of evidence supporting the importance of the prefrontal cortex-extended amygdala circuit in stress-induced relapse and imply that strengthening prefrontal cortex circuits may be crucial for the intervention and treatment of substance use disorders. The preoccupation/anticipation stage of the addiction cycle is characterized by a disruption of executive function caused by a compromised prefrontal cortex [128]. It is a key element of relapse in humans and the basis for defining addiction as a chronic relapsing disorder. While the over-activation of the Go system in the prefrontal cortex is related to habit-like substance seeking, the under-activation of the Stop system in the prefrontal cortex stimulates impulsive and compulsive substance seeking.

Overall, the study of neurobiological changes has identified three neurobiological circuits with heuristic value concerning the development and persistence of SUD. The three stages which involve different brain regions, neuro-circuits, and neurochemicals are interrelated to bring about specific kinds of changes in the brain. Activities in the nucleus accumbens-amygdala reward system, ventral tegmental dopamine input, and local opioid peptide and GABAergic circuits are among the acute reinforcing of drugs involved in the binge/intoxication stage addiction cycle. In contrast, acute withdrawal symptoms that are critical for addiction, such as dysphoria and heightened anxiety, are thought to be caused by reduced function of the extended amygdala reward system and activation of brain stress neurocircuitry during the withdrawal/negative affect stage [78]. The preoccupation/anticipation (or craving) stage of addiction is characterized by the considerable increase of activities in the Go systems of the prefrontal cortex as incentive salience initiates substance seeking behavior. This results in major afferent projections to the nucleus accumbens and extended amygdala, in particular, the prefrontal cortex (for drug-induced reinstatement) and basolateral amygdala (for cue-induced reinstatement). Increased activities in this circuit further boost incentive salience and produces strong desire to use the substance in the presence of drug-related stimuli. The dorsal striatum's habit-response mechanisms are also activated by the Go system, which contributes to the impulsivity associated with substance seeking [126]. It's considered that the shift from ventral striatal-ventral pallidal-thalamic-cortical loops to dorsal striatal-pallidal-thalamic-cortical loops is implicated in compulsive drug-seeking behaviour [129].

Molecular neuroadaptations start with the stage of binge/intoxication and as substance abuse progresses, transitions through the addiction cycle may bring about changes in long-term transcription which may convey a risk of relapse. A person may go through this cycle for weeks or months or progress through it several times in a day due to several factors including the type, amount, and frequency of substances used. There may also be a difference in how a person progresses through the cycle and the intensity with which he/she experiences each of the stages. In addition to this, it is to be noted that there are not absolute functional nor temporal boundaries that can be drawn between the stages in the process of addiction and therefore as the withdrawal/negative affect aspects of addiction develop those effects from stage 1 persist (though reward may be attenuated) and those in stage 3 begin to emerge. Moreover, deficits in executive function are potential risk factors for developing addiction.

3. DSM-5 substance use disorder

Drug abuse, substance-related problems, and substance use disorders (SUDs) have all been viewed in different ways throughout history and cultures. How drug

use and SUDs are conceptualized and how symptoms manifest and are interpreted are all influenced by culture. Sociocultural beliefs can influence how people approach and behave when it comes to substance use and misuse. Individuals' assumptions regarding potential drug-related problems are shaped in large part by their culture [130]. While in some cultures alcohol use was heavily controlled and was allowed only for ceremonial purposes [131], acculturation, on the other hand, has made significant contribution to accelerated abuse of alcohol and use of illegal drugs among certain groups of people [132, 133].

Although the characterization of substance problem syndromes as medical diseases or disorders has a long history, drug abuse and inebriety were historically regarded from a moralistic perspective [134]. Attempts to define and refine diagnostic criteria for SUDs began in the mid-twentieth century and are still ongoing. Research has identified some limitations in the existing diagnostic criteria for SUDs, which can help with the conception of future classification systems [135].

According to modern theories of substance dependence, chronic substance use can cause neuroadaptations in brain systems involved in reward, motivation, emotional regulation, inhibitory control, and tolerance/withdrawal, all of which can lead to compulsive drug use behavior [136]. Illicit drug usage has been documented all over the world with the highest estimates in Europe, North America, and Australasia. Regular use, "problem drug use," and drug addiction are less commonly measured, although they are critical to quantify in order to determine disease burden and risk factors for illicit drug use [137]. To better understand the harms associated with illicit drug dependency, future research should focus on collecting better estimates of mortality and morbidity.

Substance use and SUDs follow standard epidemiological age-related trends, with an onset often in late adolescence or early adulthood, showing peak prevalence in emerging adulthood, and then a decline. Although substance abuse is less common among older persons, often has a greater impact when it does occur, making it a public health concern [137]. A careful review of the population-based empirical literature reveals the importance of considering substance use in the context of development, with specific developmental aspects linked to the origin, course, and resolution of the problem.

SUDs are defined and thought of in a variety of ways. They have a lot in common with other chronic, recurrent diseases like diabetes or high blood pressure from a public health standpoint. Chronic diseases with significant behavioral health components may necessitate a lifelong commitment to manage and control. Many professionals believe that SUDs are inherently progressive. To put it another way, if these diseases are not treated, they tend to worsen over time. This chronic disease viewpoint has sparked significant controversy. For example, there is abundant evidence that many people, especially those suffering from the most severe kinds of addiction, follow a chronic, relapsing, escalating cycle. However, many people with SUDs seem to "recover" without undergoing professional therapy. This pattern, however, does not apply to everyone who has been diagnosed with a SUD. Many persons with milder, earlier-stage SUDs do not relapse and their substance-related problems do not progress [138]. Some experts, on the other hand, contend that, despite their history of chronic substance abuse, these individuals may not have been suffering from a severe SUD. Because of the great degree of individual variability in the course of addiction, it appears imprudent to employ a single treatment approach for all people diagnosed with the illness [138]. Despite age-related norms, significant individual course variability seems to be observed and contemporary statistical approaches have found numerous unique prototypic courses that appear to differ in their factors and outcomes. Research on substance use and misuse from a lifetime

perspective has significant implications for the design and implementation of successful, developmentally informed diagnosis, prevention, and intervention programs [136].

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is a classification manual for mental illnesses. It establishes a classification system for clinicians, insurance providers, researchers, and policymakers to utilize during diagnosing, researching, and treating mental illness. The 4th edition (DSM-IV) of the DSM, which had been in use for almost a decade, was replaced in 2013 by the 5th edition (DSM-5) [134, 135]. This version included organizational modifications as well as significant revisions to the diagnostic criteria for nearly every DSM-IV disorder. Some SUDs had just minor wording modifications, while others had significant criterion revisions. Some disorders have been added to and some removed from the list [136].

The transition from DSM-IV to DSM-5 has relevance in a multitude of settings, and it is essential for diagnosing and treating mental illness and SUD, as well as medical billing procedures and mental health research. Furthermore, if the modifications result in significant changes in the estimate of illness burden in the United States, they may be relevant to policymaking [136]. Every year, the National Survey on Drug Use and Health (NSDUH) gathers data on substance abuse and mental health from roughly 70,000 occupants of households and noninstitutional group quarters (e.g., shelters, rooming houses, and dormitories) as well as civilians residing on military bases. The NSDUH data give current, relevant information on the nation's substance use and mental health status to the drug use and mental health prevention, treatment, and research communities. Stakeholders and policymakers can utilize this data to learn more about the disease burden, temporal patterns, and repercussions of substance abuse and mental illness, as well as identify high-risk groups [136]. Professionals in the United States currently rely extensively on the diagnostic method outlined in the DSM-5 for diagnosing substance use disorders [136]. Many nations throughout the world use the 11th edition World Health Organization's (WHO, 2016) International Statistical Categorization of Diseases and Related Health Problems version 10, (ICD-10).

According to the DSM-5, SUDs are a type of a class of disorder (substance-related disorders) that are "associated to the use of a drug of abuse (including alcohol)". Although there are changes at various levels in the shift from DSM-IV to DSM-5 for SUDs, the core criteria stay the same [134, 135, 139]. However, there have been changes at the category/class level (see **Table 1** for the specific disorders considered within the overall group of disorders), substance level (which substances are considered "drugs of abuse"), disorder level (the template of criteria that is applied, with some deviations, across all substances), and individual criteria level (the number and types of symptoms needed to meet criteria for a disorder) [140]. Changes in relation to categorization refer to a disorder's "class," which is used in the DSM to designate groups of related disorders (e.g., personality disorders and anxiety disorders). The DSM-5 includes several revisions to the classification system, one of which is the classification of SUDs. SUDs were classified as substance-related disorders in the DSM-IV, which contained solely substance/drug-based illnesses. Gambling disorder has been added to this classification in DSM-5, and the section has been renamed Substance-Related and Addictive Disorders [136]. Changes from DSM-IV to DSM-5 in the types of substances assessed have been minor, but some reclassification has occurred. Based on empirical evidence since they have similar mechanisms of action (boosting synaptic dopamine), symptom profiles, consequences, and prognoses, cocaine (including crack) and amphetamines have been merged with other stimulants (except caffeine) into a distinct stimulant class [140].

Characteristic	DSM-IV	DSM-5
Disorder Class	Substance-related disorders, included only SUDs	Substance-related and addictive disorders now include SUDs and gambling disorders (formerly pathological gambling)
Disorder Types1	Because of the hierarchical diagnostic guidelines for abuse and dependence, people who met the criteria for dependence were never diagnosed with abuse for the same class of substance.	SUD, substance abuse, and dependence have all been replaced with one diagnosis, SUD.
Substances Assessed	11 classes of substances assessed, plus 2 additional categories	10 classes of substances assessed, plus 2 additional categories
	Alcohol	Alcohol
	Amphetamine and similar sympathomimetics	Stimulant use disorder, which includes amphetamines, cocaine, and other stimulants
	Caffeine (intoxication only)	Caffeine (intoxication and withdrawal)
	Cannabis (no withdrawal syndrome)	Cannabis (with withdrawal syndrome)
	Cocaine	Combined with other stimulants (e.g., amphetamines) under stimulant use disorder
	Hallucinogens Phencyclidine and similar arylcyclohexylamines	Separated into phencyclidine use disorder and other hallucinogen use disorder
	Inhalants (no withdrawal syndrome)	Inhalants (no withdrawal syndrome)
	Nicotine (dependence only)	Tobacco
	Opioids	Opioids
		Merged with hallucinogens
	Sedatives, hypnotics, and anxiolytics	Sedatives, hypnotics, and anxiolytics
	Other drug abuse/dependence	Any other SUD
	Polysubstance dependence	Dropped polysubstance use disorder

Table 1.
Comparison of DSM-IV and DSM-5 Substance Use Disorder Assessment.

The merging of substance abuse disorder and substance dependency disorder into a single SUD is a fundamental alteration in the criteria for substance use disorders from DSM-IV to DSM-5. DSM-5 has combined what had previously been considered as two distinct and hierarchical disorders (substance abuse and substance dependence) into a single construct, SUD, classifying it as mild, moderate, or severe, with the severity of an addiction based on how many of the established criteria are met. Diagnosis of SUD requires two out of eleven criteria to be met in a 12-month period. In addition, the DSM-5 has included a craving criterion to replace the abuse criterion associated with recurring substance-related legal difficulties (e.g., arrests for substance-related disorderly conduct). Due to low endorsement, poor fit with other items, and poor discrimination of this item (nearly everyone endorsing the legal criteria also endorsed other criteria), the

legal problems criterion was omitted (see **Table 2**) [136, 141]. The majority of cases that met DSM-IV abuse criteria will not receive a DSM-5 diagnosis since they do not meet the minimum two-criterion threshold for a mild SUD. Most DSM-IV abuse cases will now be classified as mild SUD if they also endorsed two dependence criteria, but those who endorsed multiple (i.e., two or three) abuse criteria and two to three dependence criteria will now be classified as moderate SUD [137]. DSM-IV dependence cases that met three dependence criteria and no more than two abuse criteria will be classified as moderate SUDs in DSM-5, whereas nearly all cases that met four or more dependence criteria will be classified as severe SUDs [140]. The withdrawal dependence criterion is another criterion that has undergone some changes in DSM-5. Unlike other criteria, withdrawal symptoms are unique to the substance's physiological action (see **Table 2**). Withdrawal is manifested by (1) a person experiencing the substance's characteristic withdrawal symptoms, or (2) a person taking the same or a closely comparable substance to avoid the substance's unique withdrawal symptoms in both DSM-IV and DSM-5. Except for cannabis, the DSM-IV and DSM-5 withdrawal criteria remain intact [136].

For that category of substances, the DSM-IV requires the endorsement of one or more symptoms (out of four, at any time) and no history of substance dependency (see **Table 2** for the specific criteria) [136]. In addition, in order to meet the substance dependence criteria, three or more symptoms (out of seven) have to be confirmed in 12-month period. According to DSM-IV diagnostic hierarchy standards, people who met both substance abuse and substance dependence criteria for a particular substance were labeled as having substance dependence alone. The objective of this was to highlight the severity of dependence as compared to the abuse diagnosis [136].

The separate abuse and dependence disorders have been eliminated from DSM-5 for several reasons: (1) the separation has little guidance for treatment; (2) the separation created "diagnostic orphans" (those who endorsed two dependence symptoms but no abuse symptoms and hence did not meet any diagnostic criteria); (3) the hierarchical structure did not follow the expected relationship between abuse and dependence (that abuse was largely a less severe symptom of dependence); and (4) the division caused the abuse diagnosis to suffer from substantial reliability problems [136, 140, 142, 143].

A cluster of symptoms related to cannabis withdrawal has been uncovered in research undertaken following the release of the DSM-IV, and this new information has been included in the DSM-5 [2]. The presence of three or more symptoms occurring within one week of stopping severe and persistent cannabis use is known as cannabis withdrawal syndrome. (1) irritability, anger, or depression; (2) nervousness or anxiety; (3) sleep problems (e.g., insomnia or unpleasant/vivid dreams); (4) decreased appetite or weight loss; (5) restlessness; (6) depressed mood; and (7) at least one physical symptom that causes considerable discomfort such as abdominal pain, shakiness/tremors, sweating, fever, chills, or headache, are all possible symptoms [136].

The severity Criteria were another significant change between the two versions of diagnostic criteria. The DSM-IV did not directly measure the severity of SUDs, though dependence was generally thought to be more severe than abuse, and patients who were diagnosed with dependence did not obtain an abuse diagnosis even if the criteria for abuse were met [136]. A symptom count-based severity indicator has been added to DSM-5, with two to three symptoms classified as mild, four to five symptoms categorized as moderate, and six or more symptoms categorized as severe. A study found that a simple symptom count was as successful at evaluating severity as more advanced algorithms [144], prompting the establishment of a severity index [136].

	DSM-IV	DSM-5
Disorders Assessed	**Substance abuse:**	**SUD: Two out of 11 criteria clustering in a 12-month period**
One or more symptoms	Recurrent substance-related legal problems	Dropped
	The substance is used in larger amounts or for a longer period of time than was intended (1).	Same
	There is a persistent desire or unsuccessful efforts to cut down or control substance use (2).	Same
	A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects (3)	Same
	Craving (4): no craving	Added
Three or more symptoms in the same 12-month period (or one symptom if dependence criteria have been met previously in the lifetime	**Substance dependence:**	
	Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (5)	Same
	Continued substance use despite continuous or recurring social or interpersonal issues created or aggravated by the substance's effects (6).	Same
	Important social, occupational, or recreational activities are given up or reduced because of substance use (7)	Same
	Recurrent substance use in situations where it is physically hazardous (8)	Same
	Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use (9)	Same

	DSM-IV	DSM-5
	Tolerance, as defined by either: (1) a need for markedly increased amounts of substance to achieve intoxication or desired effect or (2) a markedly diminished effect with continued use of the same amount of the substance (10)	Same
	Withdrawal, as manifested by either: (1) the characteristic withdrawal syndrome for the substance (excludes Cannabis, Hallucinogens, and Inhalants) (2) the substance (or a similar substance) is taken to relieve or avoid withdrawal symptoms (11).	Withdrawal, as manifested by either: (1) withdrawal syndrome characteristic for the substance (excludes Phencyclidine, Other Hallucinogens, and Inhalants) (2) the substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms (Except for those taking opioids, sedatives, hypnotics or anxiolytics, or stimulant medications solely under appropriate medical supervision).
Severity	No severity criteria	Severity is determined by the number of symptoms Mild: 2 to 3 symptoms. Moderate: 4 to 5 symptoms. Severe: 6 or more symptoms.
Additional Specifications	With or without physiological dependence, early full remission, early partial remission, sustained full remission, sustained partial remission, on agonist therapy, and in a controlled environment	Early or sustained remission and if the person is in a controlled environment where access to the substance is restricted

Table 2.
Comparison of DSM-IV and DSM-5 Substance Use Disorder Criteria.

3.1 Criteria for diagnosing substance use disorders

Drug addiction is a progressive and chronically relapsing disorder that develops from infrequent, limited, and regulated use of a substance to compulsive usage [145]. When people are unable to obtain the substance to which they are addicted, they suffer from unpleasant emotional states (dysphoria, anxiety, irritability, and other negative feelings) due to low level of reward, excessive stress, and compromised executive function. Eventually, the individual returns to excessive drug-seeking and excessive drug taking behavior. This, in turn, activates CRF in the medial PFC accompanied by executive function deficits that may aid the transition to compulsive like behavior [146].

The addiction process is cyclic and consists of three stages which are interconnected and can lead to a recurrent sequence of addictive behaviors characterized by increasing and persistent levels of psychological and physical problems over time [145]. Each of the components of the cycle involves a distinct psychosocial and behavioral manifestation relevant to the DSM-5 diagnostic criteria (see **Figure 1**).

The changes in various components of reward neurocircuitry may represent the different social psychological and behavioral components involved in the addiction cycle. The social-psychological components of lack of strength and self-regulation with regard to controlling substance use, for example, may reflect increased activity in the stress system and be linked to individuals' failures despite their persistent desire to limit or quit using addictive substances and using them in larger quantities than intended (refer to **Figure 1**). This process signifies the preoccupation/anticipation stage which eventually leads to a cycle of binge use and relapse [68]. In this stage, increased dopaminergic and opioidergic neurotransmission may be involved, resulting in sensitization. On the other hand, monitoring or attentional failures are linked to people's preoccupation with getting drugs, and they may reflect cognitive alterations impacted by broadly distributed brain monoamine systems. In this situation, counteradaptation is caused by compromised dopamine, serotonin, and opioidergic neurotransmission, as well as increased stress neurotransmitters, which may be responsible for the negative emotional state developed due to withdrawal. The combination of a change in the hedonic set-point caused by repeated counteradaptation and a different mechanism for sensitization would provide a powerful motivational drive for drug addiction to persist [68].

The DSM-5 states that a person must fulfill certain criteria to be diagnosed with a substance use disorder. Currently, there are 11 criteria (see **Table 2**) used to make such a diagnosis which can be divided into four categories [141].

a. **Impaired control:** Impaired control can manifest itself in a variety of ways: (1) Using a substance for longer than the intended time or in higher amounts than intended; (2) Wanting to cut down on usage yet failing to do so; (3) Excessive time spent obtaining, using, and recovering from drug use; (4) Cravings that are so strong that thinking about anything else is difficult.

b. **Social impairment** (5) Substance use negatively affects the ability to fulfill responsibilities at home, workplace, and school. People may continue to use despite recurring and worsening social problems or problems with work, school, or family/social obligations. This might include repeated work absences, poor school performance, neglect of children, or failure to meet household responsibilities. (6) Addiction may also be suggested if a person continues to use substances while having interpersonal problems due to substance use. Interpersonal problems may include arguments with family members concerning substance use, as well as the loss of vital friendships as a

result of prolonged substance use. (7) Giving up Important social, work, and recreational activities for the sake of substance use. Substance abuse may cause important and meaningful social and leisure activities to be abandoned or curtailed. A person may spend less time with his or her family or quit outdoor plays with his or her friends.

c. **Risky Use:** The central issue of this criterion is the failure to quit using the substance despite the harm it causes.

(8) Addiction may be indicated when someone takes substances in physically unsafe or dangerous conditions regularly. For instance, using alcohol or other drugs while operating machinery or driving a car. (9) Some people continue to use addictive substances even if they are aware that addictive substances are creating or exacerbating bodily and psychological problems. An individual may continue to smoke cigarettes despite having a respiratory condition such as asthma or chronic obstructive pulmonary disease (COPD), such as chronic bronchitis.

d. **Pharmacological indicators: Tolerance and Withdrawal**

This criterion describes how the body adjusts or attempts to maintain homeostatic equilibrium to the sustained and frequent usage of a substance. For most people, tolerance and withdrawal are hallmark markers of progressing addiction. (10) Tolerance develops when people require a higher dose of a substance to obtain the same effect. To put it another way, it's when someone gets less of a result with the same amount of effort. Either the desire to avoid withdrawal symptoms or to become high could be the "desired effect." Tolerance is experienced differently by different people, i.e., people's sensitivities to different drugs differ. The rate at which tolerance develops and the dose required for tolerance to develop will differ depending on the substance [88]. (11) Withdrawal is the body's reaction to abrupt discontinuation of a drug once the body has built a tolerance to it. Each drug produces a distinct set of (sometimes unpleasant and lethal) symptoms (refer to the previous section for the unique symptoms in each category of substance). Although withdrawal is painful, it usually does not necessitate medical intervention. However, withdrawing from certain drugs, on the other hand, can be so deadly that medical advice may be critical before trying to quit them after a long period of use [88].

While an individual must meet at least two of the above criteria to be diagnosed with a SUD, the severity of the addiction is decided by the number of criteria met. A mild SUD might be the diagnosis, if two or three of these symptoms are present. A moderate SUD would be a more appropriate diagnosis if a person exhibits four or five of these symptoms. Ultimately, a severe SUD occurs when a person exhibits six or more of these symptoms. Substance withdrawal, however, is a distinct diagnosis that may or may not be associated with a substance use disorder diagnosis [88].

4. Conclusion

Addiction is caused by the brain's gradual adaptation of neuronal activity to long-term drug exposure, which results in fundamental neuroplastic changes. The extended amygdala (EAc) is a network made up of the central amygdala and the stria terminalis' bed nucleus. This important location is in charge of controlling drug cravings and seeking behaviors [147]. Drug addiction signifies a three-stage intense dysregulation of motivational circuits due to a combination of excessive

incentive salience and habit formation [148], reward deficits and excessive stress, and impaired executive function [64, 80, 126].

Changes in dopamine and opioid peptides in the basal ganglia are involved in the rewarding effects of drugs of abuse, the development of incentive salience, and the development of drug-seeking habits in the binge/intoxication stage. In the withdrawal/negative affect stage, decreases in the function of the dopamine component of the reward system, as well as recruitment of brain stress neurotransmitters like corticotropin-releasing factor and dynorphin in the neurocircuitry of the extended amygdala, lead to an increase in negative emotional states and dysphoric and stress-like responses. The dysregulation of critical afferent projections from the prefrontal cortex and insula, particularly glutamate, to the basal ganglia and extended amygdala, causes craving and executive function deficiencies in the preoccupation/anticipation stage [68].

Almost all addictive substances have the common property of increasing mesolimbic dopamine function. The mesolimbic dopamine (DA) pathway by which the DA cells in the ventral tegmental area (VTA) projecting into the nucleus accumbens (NAc) seems to be crucial for drug rewards. Most psychostimulants such as cocaine [149] amphetamine [150] narcotic analgesics [151], nicotine [152], alcohol [153], and phencyclidine [150] stimulate dopamine transmission in the nucleus accumbens [151], the main area of the ventral striatum. A couple of other dopamine pathways the mesostriatal (DA cells in substantia nigra [154] projecting into dorsal striatum) and the mesocortical (DA cells in VTA projecting into frontal cortex) are recently recognized to have a contribution to drug reward and addiction. Alcohol and other substances of abuse are fundamentally rewarding in that they are consumed by humans or self-administered by laboratory animals. As a result, individuals exposed to drugs, though small in percentage, will become addicted and move from controlled drug use to compulsive and uncontrolled drug consumption despite adverse consequences.

The three stages involving the different neurochemicals and regions of the brain are integrated and feed each other producing strong drives for substance seeking. The addiction cycle tends to intensify over time and progress to greater physical and psychological harms. People with such disorders may have distorted thinking and abnormal behaviors as a result of changes in the brain's structure and functions. Brain imaging studies on people who frequently use psychoactive substances show marked changes in the areas of the brain that are linked to judgment, decision making, learning, memory, and behavioral control, which can last long after the period of intoxication.

Even though there are no specific biological markers of substance abuse disorders currently on use, there are a number of intriguing neurobiological aspects of substance abuse disorders that can help in the diagnosis of substance use, misuse, and SUD. An impaired reward system, overactive brain stress systems, and compromised orbitofrontal/prefrontal cortex function are some of the major neurobiological changes in the brain revealed in both human and animal studies which are quite relevant for the diagnosis of substance use, misuse, and SUD [155]. Although addictive substances have common properties, there are still considerable variabilities among classes of drugs in terms of primary and long-term physical and psychological effects, mechanisms of action, development of tolerance, and withdrawal. Differences in the availability, cost, legality, marketing, and cultural attitudes towards addictive substances and their use also influence which substances are used, and the development of dependence upon them. Thus, the study of substance use disorder and addiction must take these factors into account, while at the same time noting the similarities across drug classes.

Conflict of interest

The authors declare no conflict of interest.

Author details

Samson Duresso
University of Tasmania, Hobart, Australia

*Address all correspondence to: samson.duresso@utas.edu.au

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