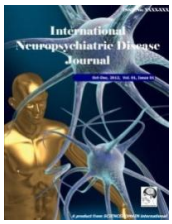

International Neuropsychiatric Disease Journal
3(4): 112-122, 2015; Article no.INDJ.2015.017
ISSN: 2321-7235

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Substance Use Disorder: Biological Mechanisms, Clinical Effects and Neuroadaptations

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/INDJ/2015/16015
Editor(s):
(1) Zhefeng Guo, Department of Neurology, University of California, Los Angeles, USA.
Reviewers:
(1) Sushil Sharma, Saint James School of Medicine, Bonaire, Dutch Caribbean, Netherlands.
(2) Peter Olutunde Onifade, Federal Neuropsychiatric Hospital, Abeokuta, Nigeria.
(3) . Luca Gallelli, Department of Health Science, University of Catanzaro, Italy.
(4) Avinash De Sousa, Lokmanya Tilak Municipal Medical College, Mumbai, India.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=840&id=29&aid=8150

Review Article

Received 31st December 2014
Accepted 5th February 2015
Published 16th February 2015

ABSTRACT

Substance use disorder is characterized by a psychological dependence on a substance or a drug that is beyond voluntary control and that can cause serious harm to the individual when used repetitively. The use of drugs, including alcohol, opiates and psychostimulants, is a wide spread behavior in human societies that pose massive public health costs. This paper aims at explaining the neurobiology of drug addiction and investigating the effects of substances such as psychostimulants, opioids, nicotine and alcohol on an individual's health. Moreover, this paper gives an overview of the neurotransmitters and brains structures that are altered following the excessive use of drugs, and illustrates some of the neurobiological changes that occur during drug addiction. At the molecular level, drug abuse induces functional and morphological changes of specific brain structures, which generally lead to adverse consequences such as drug relapse. Although previous studies have significantly improved our understanding of the neurobiological mechanisms of substance use disorder in humans, more work need to be done to identify potential therapeutic targets and develop new treatment strategies.

Keywords: Addiction; alcohol; neuroadaptation; opioid; psychostimulant.

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1. INTRODUCTION

Substance use disorder is a disease characterized by a compulsive need to use asubstance in order to function normally [1,2]. It is associated with severe problems for the individual [3], and often shows a high comorbidity with other psychiatric disorders and symptoms, such as depression, obsessive-compulsive disorder, anxiety, aggression and suicide [4,5,6]. In the previous diagnosis manual DSM-IV, substance use disorders were classified as substance abuse or substance dependence, whereas in the DSM-5, the terminology of these diagnoses is replaced by 'substance use disorder' [2]. Addictive behaviors usually begin with a period of experimentation with a particular drug or substance, which most often escalates over repeated exposures associated with the appearance of tolerance [6]. At this point, increasing amounts of the substance are needed to reach the same level of pleasure and reward produced by earlier lower quantities, and the individual is often in a negative emotional state when access to the substance is prevented [4,6]. As an individual heads towards dependence, there is an increase in the motivation to obtain and continue consuming the drug or substance. There is a growing awareness of the emotional consequences associated with drug use and a link to environments associated with accessing or taking the drug [3,6]. It is also well documented that genetic factors, along with social and psychological factors, are tightly linked to addiction. To date, 1,500 genes have been associated to an addiction phenotype in humans [7]. Epidemiological studies have shown that genetic factors account for 40–60% of the risk factors for alcoholism, as well as for other types of drug addiction [8,9].

Drugs known to cause addiction can be legal or illegal, and can also be prescribed for medical use [10]. In the United States (US), close to 3.1% (5.8 millions) of the adult population will go on to drug abuse [11]. Among US adults, 12.8% are nicotine dependent, and 51 % (120 millions) are current consumers of alcohol, with 7.7% (18 millions) meeting the criteria of substance abuse and drug dependence [12,13]. Other substances known to cause addiction include stimulants, such as cocaine, caffeine, and sedatives including barbiturates, benzodiazepines and methaqualone. Drugs of abuse also include opiate and opioid analgesics. Several medications have shown to be effective in treating opioid addiction, but there is still no maintenance medication that has been approved for the treatment of psychostimulants addiction [14].

The main priority of the current neurobiological research is to understand the pharmacological and neuroadaptive mechanisms within specific brain circuits that translate to chronic addiction [1]. Enormous progress has been made in brain imaging technology that eventually provided accurate quantitative approaches and enhanced our understanding of the role that neurology plays in psychiatric disorders [15,16]. Indeed, modern imaging techniques enable researchers to observe drug actions as they occur in the brains of addicted individuals, which can help us better understand the pathophysiology of substance and drug addiction [16]. It was shown that certain drugs could produce long-lasting changes in specific brain pathways, which significantly increase the risk of relapse. Moreover, drugs of abuse induce profound modifications in the activity of extracellular serotonin, which can also have impact on the activity of other neurotransmitters [17]. This paper first discusses the clinical effects of substances including psychostimulants, opioids, alcohol and tobacco, and finally describes the functional and structural changes that occur in the brain in addicted individuals. For this analysis, studies were identified using predefined search criteria that included the following keywords: drug abuse, addiction, alcohol, opioid and psychostimulant, in the PubMed and Medline databases. The studies discussed in this paper are primary peer-reviewed articles that were published in high-quality journals.

2. CLINICAL EFFECTS OF SUBSTANCE AND DRUG ABUSE

2.1 Effect of Psychostimulants

Psychostimulants are psychoactive drugs that can induce temporary enhancement in mental or physical functions, like alertness, wakefulness, and locomotion. Although psychostimulants are widely used as prescription medication, they are most often taken as illicit substances for recreational use. By enhancing the activity of the central and peripheral nervous systems, psychotimulants are able to produce different kinds of effects. Particularly, they are capable of improving mood and relieving anxiety, and some have proven to be efficient in the therapy of treatment-resistant depression [18]. In the 1950s, psychostimulants were replaced by the newly

developed antidepressants, and their use is now limited to the therapy of attention deficit disorder, narcolepsy, and refractory obesity [18,19]. Psychotimulants exert their effects through a variety of pharmacological mechanisms, the most prominent of which include facilitation of norepinephrine and dopamine (DA) activity [20]. The first psychostimulant was amphetamine, and it was synthesized in 1887 and has been used since the 1930s in affective disorders, obsessive-compulsive disorders, and schizophrenia [19]. Moreover, a significant release of biogenic amines is observed in patients that use amphetamine. It was also demonstrated that amphetamine reduces impulsive choice [21], and that it exerts direct agonistic effects on presynaptic receptors for serotonin, while having a mild inhibiting effect on monoamine oxidase [22]. Table 1 illustrates other psychostimulants that could beused for medical purposes, and these include caffeine, dextroamphetamine, ephedrine, lisdexamfetamine, mephedrone and methylphenidate [23,24]. Caffeine is the world's most widely used psychoactive drug and by far the most common stimulant [25]. It has been used for centuries to alleviate fatigue and enhance performance [26]. Another well-known psychostimulant is tetrahydrocannabinol, which is the main psychoactive constituent in cannabis. It has several effects on an individual, including relaxation, decreased anxiety, fatigue, and appetite stimulation [27]. Cocaine is another psychostimulant frequently used that appears capable of improving or impairing response inhibition, and is involved in the firing of midbrain dopaminergic neurons [21,28,29]. When administered intranasally, cocaine produces stimulant effects including fatigue reduction, sense of well-being, and increased confidence. The effects produced with amphetamines are very similar to those produced by cocaine, but they are much longer in duration. Other acute effects of amphetamines and cocaine include a decrease in appetite and significant weight loss [30]. Chronic use of these psychostimulants induces profound changes in the level of certain neurotransmitters in the brain, often lead to addictive behavior and comorbid medical conditions. For instance, people taking benzodiazepine, a class of psychoactive drugs, often develop depressive-like symptoms and cognitive impairments.

2.2 Opioids

An opioid is a psychoactive chemical that reduces the perception of pain by acting on the nervous system. Opioids, which are among the world's oldest known drugs [31], work by blocking the afferent and efferent pain signals of the brain, and have sedative effects that help the patient rest and sleep. These pain relievers work by binding to opioid receptors in the gastrointestinal tract and the peripheral nervous system. The term opioid refers to both opiates and synthetic substances, as well as to opioid peptides. There are several natural and synthetic opioids that are useful for the treatment of pain [32], with codeine being the most commonly used. Codein is less potent than morphine and can be effectively used for the management of chronic pain [33]. The analgesic effects of opioids are due to decreased reaction to pain as well as increased pain tolerance. At higher doses, opioids can produce local anesthesia by acting on the dorsal root entry zone in the spinal cord [34].While opioids are very effective in relieving acute pain, they are only moderately effective in treating long-term chronic pain, and their effectiveness often diminishes over time [35]. Moreover, opioids are not used as a first-line treatment for pain because they impair alertness, bring risk of dependence, and increase the risk that episodic headaches will become chronic [36,37]. Therefore, other less risky pain relievers are often used as a first-line of treatment for chronic pain, such as acetaminophen or ibuprofen [38].

There is a risk of addiction when a person consumes several opioids on a daily basis. Drug addiction is a growing problem in today’s society as these medications are being more available to the public [35]. Several studies have shown that opioids addiction can be a lifelong condition for some individuals [39,40]. In most patients, undesirable withdrawal effects take place when opioid use is abruptly discontinued. Although there are some differences between the different subtypes of opioids, they more or less produce the same side effects. The withdrawal symptoms for the majority of opiates include severe dysphoria, depressive-like symptoms, craving for another opiate dose, irritability, sweating, increased blood pressure, and vomiting [41]. Table 2 gives a list of some of most frequently used opioids with their associated class and side effects.

Table 1. A list of commonly used psychostimulants and their clinical effects

Psychostimulant	Class	Medical use and clinical effect
Amphetamine	Phenylethylamine	Used to treat depression and attention deficit hyperactivity disorder (ADHD).
Benzodiazepine	Psychoactive drugs	Used to treat seizures, anxiety, and insomnia.
Caffeine	Xanthine	Enhances mental performance and reduces fatigue.
Dextroamphetamine	Amphetamine stereoisomer	Prescribed for the treatment of ADHD as well as sleep disorders such as narcolepsy.
Ephedrine	Sympathomimetic amine	Used to enhance concentration and suppress appetite. Can also be used to treat hypotension.
Lisdexamfetamine	Phenethylamine and amphetamine	Used to treat ADHD and narcolepsy. Is also effective against depression and obesity.
Mephedrone	Amphetamine and cathinone	Causes elevated mood, decreased hostility, and improved mental function.
Methylphenidate	Phenylethylamine	Used for the treatment of ADHD and postural orthostatic tachycardia syndrome.

Table 2. Class and side effects of most commonly used opioids

Opioid	Class	Side effects
Allylprodine	Prodineanalogue	Nausea, itching, vomiting
Codeine	Natural opiate	Drowsiness, constipation, itching, nausea
Morphine	Natural opiate	Constipation, psychological dependence
Fentanyl	Semisynthetic derivative	Diarrhea, nausea, constipation, dry mouth
Oxycodone	Semisynthetic derivative	Constipation, fatigue, nausea, dizziness
Pethidine	Phenylpiperidine	Nausea, vomiting, dizziness, sedation
Volazocine	Benzomorphan	Fever, agitation, hallucinations

2.3 Alcohol and Tobacco Use

Tobacco is the most commonly used substance in the world and constitutes a worldwide health problem. Approximately 35% of adults consume tobacco, and the most majority of these users live in low or middle-income countries [42,43]. Initially used to avoid fatigue, treat abscesses, heal wounds and relieve thirst [44], tobacco can have devastating effects in terms of cost to the society, such as human death and medical expenses. For instance, in the US, tobacco alone is responsible for the death of roughly 440 000 individuals annually [45]. Although tobacco contains several hundreds of chemicals that could potentially contribute to its addictive effect, it's mainly the psychopharmacological action of nicotine that plays a major role in addiction [46]. Nicotine, a potent parasympathomimetic alkaloid and a stimulant drug present in a variety of edible plants [47], has been found to improve impulsive action in healthy individuals [48]. Nicotine also produces positive reinforcing effects such as mild euphoria, increased energy, as well as reduced stress, anxiety and appetite [49]. Moreover, nicotine enhances attention and cognition [50,51], and is responsible of regulating sensations of pleasure and euphoria [52]. Side effects of nicotine withdrawal include a down regulation of dopamine production and other stimulatory neurotransmitters, which results in a decreased mood and loss of pleasure [53].

Alcoholism has very similar effects to the use of nicotine in terms of the harm generated to the society and the individual. The development of alcoholism is mainly due to environmental factors such as stress, genetics, and the direct reinforcing effects of alcohol [54,55]. Alcohol is widely used in our society in forms of alcoholic beverages for beneficial effects. It is estimated that approximately 90% of the adult population have used alcohol at least once in their lifetime. Only a small minority of patients receives medication for their alcoholism, and there remains an urgent need for the development of new medications to treat such condition [56,57]. Alcohol abuse can lead to a variety of medical problems and cause serious damage in terms of costs to the society. A study has shown that alcohol abuse accounts for more than $180 billion in costs per year in the United States, which include health care expenditures, negative impacts on productivity, as well as increased in crime and vehicle crashes [58]. The principal

psychoactive constituent in alcoholic beverages is ethanol, which affects several systems in the brain, especially the activity gamma-aminobutyric acid (GABA) receptors [59]. Other psychoactives such as benzodiazepines, exert the same effect by binding to the same receptor complex, and have also been shown to impair response inhibition [60]. Among alcohol dependent individuals, more than 80% excessively consume tobacco [61,62,63]. It's also estimated that smokers have a significantly increased risk for developing alcohol related disorders [13,43]. Table 3, illustrates the link that exists between tobacco and alcohol consumption, as well as the percentage of addictive patients affected by one or several psychiatric disorders [64,65].

3. SUBSTANCE AND DRUG-INDUCED MODIFICATIONS

3.1 Functional and Morphological Changes in the Brain

Recent advances in brain imaging technology render it possible to obtain detailed images of brain structures and to correlate them to mental disorders, such as addiction [66]. The brain imaging techniques most commonly employed are the following: structural magnetic resonance imaging (MRI), functional MRI, magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission computed tomography (SPECT). Not only do they provide an accurate image of the brain, but they also enable the observation of drug actions and consequences as they take place and persist in the brains of addicted individuals [66]. Table 4 depicts the main clinical applications of neuroimaging techniques employed in individuals with substance use disorder.

The frontal cortex is a region of the brain implicated in planning, goal setting, and moderating social behavior [70]. It is well documented that substance abuse and decision-making problems are associated with volume and tissue composition changes in this region. A reduction in gray matter density in the prefrontal cortex was observed in persons addicted to psychostimulants such as methamphetamine [71]. Moreover, people with cocaine and alcohol use disorders often exhibit reduced gray matter density in regions of the frontal cortex, without any differences with respect to white matter density [72,73]. Another region involved in addiction is the nucleus accumbens, which is located in the basal forebrain. The nucleus accumbens plays a primordial role in reward, learning, aggression and impulsivity [74,75]. Studies using experimental animals have shown that the level of dopamine in the extracellular fluid of the nucleus accumbens is significantly increased when rats are injected with psychostimulants such as cocaine [76,77]. These results indicate that the alteration of DA at the level of the nucleus accumbens is responsible for the reinforcing effects that generate substance dependency. In humans, brain-imaging studies have also shown that environmental cues associated with drugs of abuse release DA in the nucleus accumbens.

Table 3. A comparison between tobacco and alcohol users, and the percentage (%) of psychiatric patients among tobacco and nicotine dependent individuals [64,65]

Comsumption level		Tobaco Use	Alcohol Use
Light	Male	8%	33%
	Female	8%	41%
Moderate	Male	12%	24%
	Female	13%	18%
Heavy	Male	12%	8%
	Female	11%	3%
Psychiatric Disorder			
Schizophrenia		33%	23%
Bipolar disorder		46%	29%
Depression		29%	17%
Others		28%	18%

Table 4. Imaging techniques employed in individuals with substance use disorder

Neuroimaging Technology	Application and Use
PET	Used to quantify processes such as glucose metabolism, drug distribution and pharmacokinetics [67]
MRI	Used to map tissue morphology and anatomical composition, and differentiate between white and grey matter [67]
SPECT	Can be used to visualize changes in oxygenation and blood flow associated with brain activities [68]
MRS	A powerful method used for drug analysis in the brain of individuals with substance use disorder [69]

The amygdala, another structure of the limbic system, performs a primary role in the processing of memory, decision-making, and emotional reactions [78]. Several brain stress systems and neurotransmitters, localized near the circuitry of the central nucleus of the amygdala, produce the negative emotional state that becomes the powerful motivation for substance and drug seeking behavior [79,80]. An example of such neurotransmitter is the corticotropin-releasing factor (CRF), which is involved in mediating the increased self-administration associated with substance use disorder. Several studies have demonstrated that after chronic administration of drugs of abuse, there is an increase in the extracellular level of CRF from the amygdala, suggesting that this structure is involved in the development of motivational effects associated with the drug-seeking behavior. The ventral tegmentum area (VTA), also involved in addiction, is a group of neurons located close to the midline on the floor of the midbrain [81]. The VTA is the origin of the dopaminergic cell bodies, and is part of the brain reward circuitry. It plays major roles in cognition and motivation, and is implicated in a variety of psychiatric disorders [82]. For instance, it has been shown that cocaine, alcohol, amphetamine and nicotine all act primarily at the level of the VTA by altering the neuromodulatory influence of dopamine neurons [83]. Moreover, chronic exposure to drugs of abuse increases the activity of the dopamine-synthesizing enzyme, as well as the level of brain-derived neurotrophic factor in VTA neurons [84].

3.2 Neuroadaptation and Synaptic Plasticity in Addiction

Most drugs of abuse cause molecular adaptations and changes in brain function that facilitate a pathological desire to seek and take drugs. Since the early 1990s, a neurobiological explanation of the addictive potentials of several drugs has been that compulsive drug use and relapse are due to specific neuroadaptations in the mesocorticolimbic dopamine system and in the glutamatergic corticolimbic circuitry, which embeds a variety of dopamine projections [85,86,87]. Functional alterations of the ventral tegmental area and adaptations in the nucleus accumbens are also very frequent in addiction [88]. The chronic consumption of some substances and drugs causes several changes in neural activity and protein expression. Some of these changes yield structural and functional modifications in the synaptic connections among neurons [87]. In this way, a sensitization takes place, which is often referred to as neural adaptations or plasticity, and is believed to explain how individuals learn and adapt in their behavior [89,90]. It is also well documented that addiction involves processes of associative learning, such as the formation and recovery of memories associated with substance and drug use [91].

Both opiates and psychostimulants induce various changes in intracellular signal transduction pathways in the mesocorticolimbic dopamine system [92]. Withdrawal from these substances is associated with short-term decreases in DA levels at the level of the nucleus accumbens. In addition, a study done on drosophila has shown that ethanol consumption leads to cognitive alcohol dependence due to various neural adaptations and changes in the brain metabolism [93]. There is also large evidence that synaptic plasticity plays a primordial role in addiction [94]. Changes in synaptic strength often result from a change in neurotransmitter release or neurotransmitter receptors. In other cases, it is due to morphological changes, such as the generation of new synaptic connections, which can occur following chronic consumption of certain substances and drugs. Although it was initially assumed that synaptic plasticity and neuroadaptation are independent of drug class,

several studies have contradicted this theory. Studies using whole-cell electrophysiology have shown that morphine and cocaine differ in their ability to induce long-term potentiation and depression at GABAergic synapses on VTA dopamine neurons [95]. Differences in synaptic plasticity between opiates and psychostimulants are also seen in the consequences of drug withdrawal on LTP in the mPFC [96]. These studies bring us to the conclusion that the development of addictive behaviors is mediated by neuroadaptation in both the VTA and the nucleus accumbens, and by an increase in the synaptic strength of the mesolimbinc dopamine system. The field would certainly benefit from more systematic examinations of the roles of synaptic-plasticity mechanisms in addiction, and of the neuroadaptations that accounts for compulsive substance use and relapse.

4. CONCLUSION AND FUTURE PERSPECTIVES

This paper highlighted the clinical effects of addictive disorders, including psychostimulants and opioids dependence, as well as alcohol and tobacco use. Not only can addictive diseases cause serious harm to the individual and generate significant public health costs, but they also produce long-lasting changes in specific brain structures, which most often increase the risk of relapse. Using examples from both human studies and animal models, scientists confirmed the existence of a complex relationship between drug-induced neuroadaptations in the brain and addictive behaviors. Indeed, there is strong evidence suggesting that drugs of abusecause synaptic plasticity and molecular changes in the circuits of the brain involved in addiction, which include a change in the activity of the amygdala, the stria terminalis and the nucleus accumbens. Moreover, chronic use of drugs can cause comorbid medical symptoms, and patients who consume several drugs simultaneously are a greater risk of developing life-threatening conditions. Because drug-drug interaction is one of the leading causes of mortality, people on several medications are always closely monitored by their physician [97].

To date, there are still many unanswered questions about the impact of drug interaction and nature of addiction, and until its mechanisms are fully understood, treatment of drug abuse will be a challenging task. Clearly more work need to be done using appropriate animal order to identify the genes and specific pathways that could act as potential therapeutic targets.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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