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Daniela Luiza Baconi

Carol Davila University of Medicine and Pharmacy, daniela_baconi@yahoo.com

Anne-Marie Ciobanu

Carol Davila University of Pharmacy and Medicine

Ana Maria Vlăsceanu

Carol Davila University of Medicine and Pharmacy

Oana Denisa Cobani

St. John Emergency Hospital

Carolina Negrei

Carol Davila University of Medicine and Pharmacy

See next page for additional authors

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Authors

Daniela Luiza Baconi, Anne-Marie Ciobanu, Ana Maria Vlăsceanu, Oana Denisa Cobani, Carolina Negrei,
and Cristian Bălălău

Current concepts on drug abuse and dependence

Daniela Luiza Baconi¹, Anne-Marie Ciobanu², Ana Maria Vlăsceanu¹, Oana Denisa Cobani³, Carolina Negrei¹, Cristian Bălălău⁴

¹ Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Department of Toxicology

² Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Medicines Control

³ St. John Emergency Hospital, Bucur Maternity, Bucharest

⁴ Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, St. Pantelimon Hospital

Corresponding author: Daniela Luiza Baconi, e-mail: daniela_baconi@yahoo.com

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Abstract

Drug addiction is a complex disease characterized by compulsive and uncontrollable desire to seek and consume the drug. In time, drug-related terminology has undergone many changes, arising from the deepening of the mechanisms of action, but also about the need for a greater precision in the definition.

Drug dependence can be assigned not only to pharmacological effects of the drugs of abuse, but also to their interaction with each particular neurological and psychological constitution. The research on the neurobiological mechanisms of addiction processes allows both a better understanding of current pharmacotherapy and the development of new treatment strategies in drug abuse and dependence. In this review we intend to present the current concepts related to drug abuse and dependence.

Introduction

In 1957, the WHO Expert Committee on Drug Dependence defined *habituation*. This term is closely related to another one as old, but widely used today: *addiction* – the behaviour distinguished primarily by a conscious, intense desire for the drug and a tendency to relapse due to persistence of attitudes clearly established in the early stages of addiction. In 1964, the WHO Expert Committee replaced the terms addiction and habituation with "*drug dependence*" which has been redefined in 1969. In this definition the compulsive use of a drug for its psychological effects is the only feature, both necessary and sufficient to define the drug dependence.

DSM-5 (Diagnostic and Statistical Manual), published by the American Psychiatric Association, combines the DSM-IV criteria for substance abuse and substance dependence into single "*substance use disorders*", specific to each substance of abuse, within a new "Addictions and related disorders" category. ICD-10 (The 10-th Revision of the International Classification of Diseases and Health Problems), is edited by WHO and defines "*dependence syndrome*". ICD 10 replaced the term "physical dependence" with "neuroadaptation". Also, the term "abuse" is considered relatively ambiguous and replaced with more specific term "hazardous use" or "harmful use". ICD 11, planned for 2017, includes "*disorders due to substance use*" under the category "Mental and behavioural disorders".

Deepening of the molecular mechanisms of drug abuse and addiction has shown that psychological and physical dependence are not the only component of long-term drug dependence; in addition to positive and negative reinforcement, conditioning is a significant component in support the drug dependence. The common feature for the addictive drugs is that they have a positive reinforcement ("reward") action associated with mesolimbic dopaminergic pathway activation.

Discussion

Drug addiction has been conceptualized as a complex and chronic relapsing mental disorders characterized by compulsive drug seeking, the lack of capacity to limit the consumption, the emergence

of a withdrawal syndrome during cessation and the use despite the awareness of the harmful consequences (1, 2).

According to American Society of Addiction Medicine (ASAM), addiction is a primary chronic disease of brain reward, motivation, memory and related circuits, characterized by inability to consistently abstain, impairment in behavioural control, craving, diminished recognition of the significant behavioural problems and in interpersonal relationships and also dysfunctions of the emotional response (3). Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can lead to disability or premature death.

Usually, addiction represents the syndrome manifested by a particular behaviour in relation to the use of a substance or a class of psychoactive substances, purchasing and consumption of which is the priority; in advanced stages, the compulsive behaviour becomes obvious. Compulsion is a behavioural disorder characterized by an irresistible effusion to perform some acts to which the subject cannot resist, without finding his inner peace. In usual terms, drugs are illegal substances or diverted from legal use; however, some specialists do not hesitate to name drugs other substances or products (e.g. alcohol, tobacco), legal and relatively well integrated social.

Psychoactive substance is defined as any substance which alters perception, behaviour, motor or cognitive functions (4). It is emphasized that the term psychoactive does not necessarily imply dependence-producing. Together with its equivalent, psychotropic drug, the term psychoactive substance is descriptive for the whole class of substances, licit and illicit, of interest to drug policy. Some authors refer to psychotropic the drugs used primarily in the treatment of mental disorders (sedatives, anxiolytics, antidepressants, neuroleptics), while others apply the term to substance with abuse susceptibility, because of the effects on disposition or consciousness (stimulants, hallucinogens, sedative-hypnotics, alcohol). In the context of international control of drugs, psychotropic substances are

those set out in the Convention on Psychotropic Substances (1971). In line with the socio-legal status of substances used, consumption of psychoactive substances can be classified into 3 categories (Figure 1).

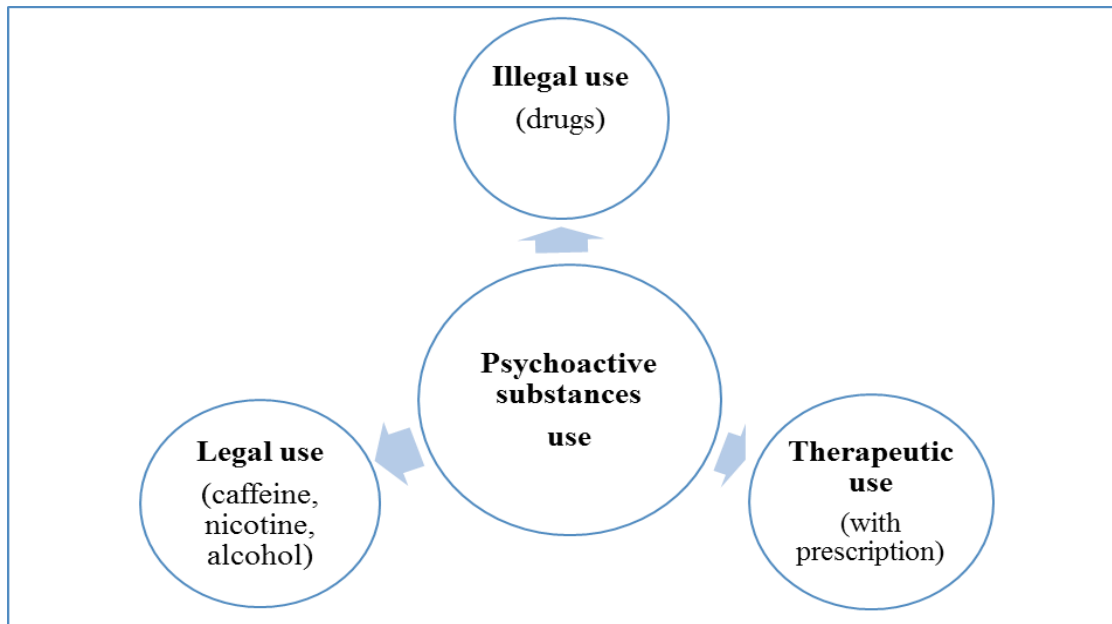


Figure 1 Classification of the psychoactive substances use

Illegal use of psychoactive substances refers to drugs themselves, while the legal consumption concerns psychoactive substances not subject to legislative control (e.g. caffeine, nicotine, alcohol). The therapeutic use refers to the administration of psychoactive substances with prescription. In this context, it is important to distinguish between tolerance and physical dependence phenomena or "rebound" effect and addiction. Tolerance and physical dependence are physiological adaptations conditions and does not imply compulsory abuse or addiction. The compulsion phenomenon, an obsessive seeking and use of the substance is usually seen in addiction behaviour (5, 6).

Classification of the psychoactive substances.

Substances of abuse are often classified by type of action on the central nervous system (CNS) and/or class to which they belong in terms of chemical structure. Louis Lewin classified the psychoactive abuse substances in five psychopharmacological groups (7, 8):

- ✓ Euphorica: euphoric and narcotic substances that induce a state of physical and mental well: opium and opium compounds (morphin); cocaine)
- ✓ Phantastica: hallucinogenic substances of vegetable origin (mescal buttons, Cannabis)
- ✓ Inebriantia: substances that produce a first excitation followed by depression (alcohol, ether, chloroform)
- ✓ Hypnotica: sleep producing substances (chloral hydrate, barbiturates)
- ✓ Excitantia: substances that cause mental stimulation; substances from plants that produce general stimulation without impairment of consciousness (caffeine, tobacco, betel etc.)

In 1967, Jean Delay has proposed the psychiatric classification criteria for the substances acting on the central nervous system (CNS). He introduced the general term psychotropic for the natural or synthetic substances that produce psychological changes or alter mental activity, regardless of the nature of the change or modification. Classification of Jean Delay refers to (9):

- ✓ Psycholeptics (mental sedative): hypnotics (chloral hydrate, barbiturates); neuroleptics (phenothiazines, reserpine, butyrophenones); tranquilizers (meprobamate)
- ✓ Psychoanaleptic (mental stimulant): vigilance stimulants (amphetamines); mood stimulants (iproniazid, imipramine); other stimulants
- ✓ Psychedelics (producing mental deviation): hallucinogens, substances that produce depersonalization effects

The initial classification of drug addiction, pharmacological based include dependence of: Alcohol, Barbiturates and other sedatives; Opiates; Cocaine; Amphetamines and other stimulants; Khat; Hallucinogens (LSD); Cannabis (marijuana); Volatile solvents (inhalants) (10). A modern classification, based on the mechanism of action distinguishes three classes of drugs (11):

- ✓ I - substances which activate the membrane receptors coupled to G-proteins (e.g. opiates, cannabinoids, LSD, mescaline etc.)
- ✓ II - substances which bind to the ionotropic receptors and ion channels (barbiturates, benzodiazepines, nicotine, phencyclidine etc.)

- ✓ III - substances which bind to the biogenic amine transporters (cocaine, amphetamine, Ecstasy)

The evolution of terminology

Since the early decades of the twentieth century, there have been attempts to define the dependence on psychoactive substances (toxicomania); these attempts have been shown a difficult process, as this ensemble of behavioural disorders involves complex biochemical, physiological and psychological mechanisms distinct from one substance to another.

An official, unitary definition for addiction has been trying to give since 1931 by the Commission on Narcotic Drugs, and later by World Health Organization (WHO), in 1957, 1964 and 1969. Etymologically, the word "toxicomania" comes from the Greek language from *toxikon* (*poison*) and *mania* (*madness*); therefore "*madness of poison*" (5, 12). First official terms assigned to the toxicomania refer to habituation and addiction (Figure 2). The term "habituation" refers to the repeated use of a drug for a psychological desire (without the signs of tolerance or abstinence). The second notion suggests a vice, a bad habit; however, etymologically, the term addiction comes from Latin: *addicere* in the Roman law used to designate the relationship between two people in a debtor-creditor relationship; *addictus* was a slave coming from a debtor.

In 1964, the WHO Expert Committee on Drug Dependence has replaced the terms habituation and addiction with "drug dependence", redefined in 1969 (13). According to WHO (1964, 1969), the drug dependence is a state psychic and sometimes also physical, resulting from the interaction between an organism and a drug, condition characterized by behavioural and other responses that always include the compulsion to take the drug in a continuously or periodically way to experience its psychic effects, and sometimes to prevent the discomfort given by its absence. Tolerance may or may not be present. In this definition, the compulsive use of a drug for its psychological effects is the only feature, both necessary and sufficient to define the drug addiction. Physical dependence and tolerance may be present, but none is either necessary or sufficient in itself to define the drug addiction. This definition makes

psychological dependence the only condition for drug dependence, cancelling the physical dependence as necessary or sufficient.

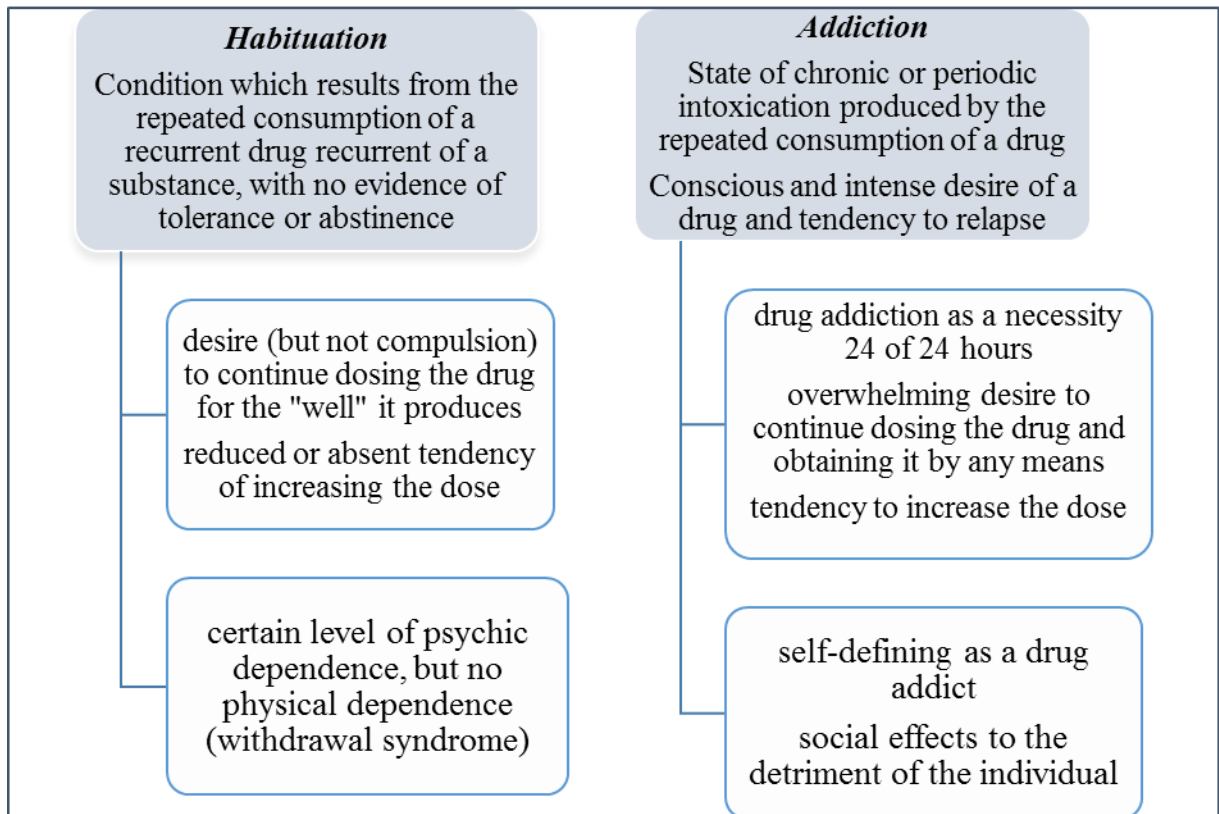
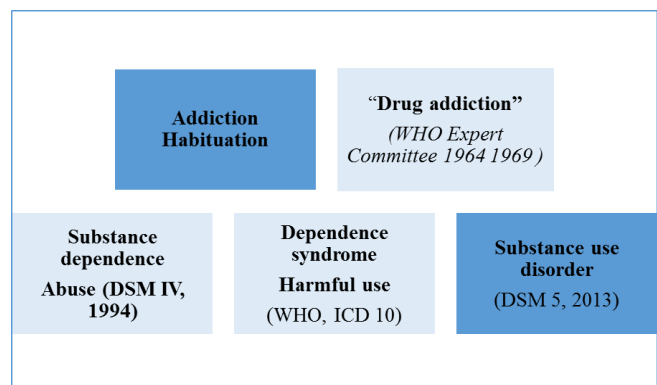


Figure 2 The characteristics of habituation and addiction

Diagnostic and Statistical Manual (DSM) and International Classification (ICD)

Two diagnostic systems are now recognized: Diagnostic and Statistical Manual (DSM 5 in force) published by the American Psychiatric Association (APA) and International Classification (ICD), published by WHO (ICD 10 in force) (14, 15). Terminology concerning the drug



consumption and the developing of addiction evolved **Figure 3** The evolution of terminology on drug dependence from the first notions that defined habituation and addiction to present concepts of "dependence syndrome" (ICD 10) or "substance use disorder" (DSM 5) (Figure 3).

The diagnostic system for mental disorders published in 1994 (DSM IV) by the American Psychiatric Association has used the term "*substance dependence*", for the general behavioural syndrome produced by repeated use of substances. Thus, DSM IV has defined and established distinct diagnostic criteria for dependence and abuse (16).

Substance dependence was defined as a set of symptoms that indicate continued use of a substance despite the major problems generated by it. Withdrawal symptoms and tolerance may be present, but not a sine qua non for the diagnosis of substance dependence. It is a way of self administration of a substance that typically causes tolerance, withdrawal and compulsive consumption behaviour. According to DSM IV, the abuse is less severe diagnostic and involves a series of adverse events caused by repeated use of a substance which does not meet the criteria for substance dependence.

DSM 5 (in force from May 2013) does not distinctly conceptualize anymore the abuse and dependence, but puts them together in what it calls "*substance use disorder*". DSM 5 combines abuse and dependence into a single disorder of graded clinical severity and requires two criteria to make a diagnosis. The DSM-IV diagnosis of substance dependence requires the presence of as few as 3 of 7 symptoms possible (17- 22). This modification has been made as there is no evidence of a distinction between abuse and dependence. Specifically, DSM 5 refers to "substance use and addictive disorders", including both "substance use disorder" and addictions that are not induced by substances (eg. gambling disorder, formerly called impulse control disorders). In DSM 5 are established diagnostic criteria for: use disorder, intoxication and withdrawal status and on various psychoactive substances (examples are shown in Table I):

Table I Diagnostic criteria for substance use addictive disorder (according to DSM 5, 2013)

Diagnostic criteria (DSM V)		
<i>Use disorder</i>	<i>Intoxication</i>	<i>Withdrawal</i>
Alcohol	Alcohol	Alcohol
Amphetamines	Amphetamines	Amphetamines

Cannabis	Cannabis	Cannabis
Cocaine	Cocaine	Cocaine
Hallucinogens	Hallucinogens	-
Inhalants	Inhalants	-
Opioids	Opioids	Opioids
Phencyclidine	Phencyclidine	-
Sedatives, hypnotics, anxiolytics	Sedatives, hypnotics, anxiolytics	Sedatives, hypnotics, anxiolytics
Tobacco	-	Tobacco
*	Caffeine	Caffeine
Others(or unknown)	Others(or unknown)	Others(or unknown)

* the disorder of the caffeine use is proposed for the section III of DSM-V, which includes the conditions that require further research.

* patients in treatment under medical supervision, with analgesics, antidepressants, anxiolytics, and beta-blockers are excluded.

Substance use disorder (DSM 5) is defined as a maladaptive pattern of the use of a substance, leading to clinically significant deficiency or distress, characterized by two (or more) of the following criteria for classification, occurring within a 12-month period (14):

- Recurrent substance use, resulting in failure to fulfil the major obligations at work, school or home
- The repeated use of the substance in situations of physical risk (driving a car, operating machinery)
- Keep consuming despite the persistence or recurrence of certain social or interpersonal problems caused or exacerbated by the effects of the substance
- Tolerance*, reflected in the need of a significantly higher dose in order to achieve the intoxication state or the desired effect or by substantially diminished effect on the continued use of the same amount
- Withdrawal*, manifested by the characteristic withdrawal syndrome or by taking the substance (or one related) to relieve or avoid withdrawal symptoms

- The substance is often taken in larger amounts or over longer periods than was intended
- Persistent desire or unsuccessful efforts to stop or control substance use
- Much of the time spent with activities for purchasing the substance, its use or for recovery from the effects produced
- Important social, professional or recreational activities are abandoned or reduced because of substance use
- The substance use is continued despite knowledge of some physical or mental problems, persistent or recurrent, caused or exacerbated by the substance used
- Craving, intense wish and or need for using a certain substance

To be specified: the severity, the presence or absence of physiological dependence, the evolution: early complete remission, early partial, fully supported, partially supported on agonist therapy in a controlled environment. In assessing the severity of substance use disorder, meeting 2-3 criteria indicates a mild disorder; fulfilment of 4-5 criteria shows a moderate disorder, and 6 or more criteria, a severe disorder. DSM 5 combines the diagnostic criteria for dependence and abuse of DSM IV, removes the criterion relating to the commission of illegal acts and introduces the criterion of "craving" ("appetite", "psychological thirst"). In DSM V is also included the criteria for the diagnostic of cannabis withdrawal.

ICD 10 (The 10th Revision of the International Classification of Diseases and Health Problems), developed by WHO defines *dependence syndrome* as a cluster of physiological, behavioural and cognitive phenomena where the use of a substance or class of substances acquires a much higher priority for an individual than other behaviours that previously had a higher value. ICD 10 does not refer to medicines or drugs, but to psychoactive substance self-administrated due to its reinforcing properties, and also to the non-therapeutic substances used.

As the term "abuse" is considered ambiguous, ICD replaced it with a more specific phrase "risky use" or "harmful use" (ICD 10) (Table II). This represents a maladaptive pattern of a psychoactive

substance use causing danger (harmful) to physical or mental health; it has usually, but not invariably adverse social consequences (15).

The criteria of ICD 10 for dependence syndrome have provoked debates regarding the compulsory of quantifiable criteria (e.g. tolerance, withdrawal) for diagnostic, because most of the criteria required involves cognitive elements less accessible to the biological measurements (ex. strong desire or compulsion), which involves insight in the consumer perception and associate the idea of craving (also with difficulties in defining).

Removing dichotomy abuse/dependence has sparked much discussion and debate in the pre-emergence phase of DSM V, because this change has considered, primarily, the lack of evidence to support an intermediate stage and a distinction between the behavioural disorders of abuse and addiction. Furthermore, the new terminology in DSM V was proposed to avoid the confusion between physical dependence or "rebound" type phenomena, possible in the context of a proper use of the prescribed drugs for various conditions (pain, anxiety, even HTA) and addiction as disorder behaviour.

Introducing the new terminology in DSM V ("substance use disorder"), included in the "addiction and related disorders" removes such controversies regarding the creation of "medical addicts" by prescribing opioids. Based on clinical data, some experts are reluctant in giving up separated categories of addiction and abuse and show that, in addition, DSM V is no longer correlated with ICD.

The ICD 11 edition prepared by the WHO is planned for 2017. In the draft of ICD 11, now under debate, disorders due to substance use are included in "07 Mental and behavioural disorders" (Table II). Disorders due to substance use are defined as mental and behavioural disorders that develop as a result of the use of predominantly psychoactive substances, including medications (23). In line with ICD 11, disorders due to substance use include:

- ✓ Substance intoxication
- ✓ Harmful use of substances
- ✓ Substance dependence

- ✓ Substance withdrawal
- ✓ Substance-induced mental disorders (specific types of mental or behavioural symptoms developing as a result of substance use).

Table II Current diagnostic criteria on drug dependence

DSM V*	<i>Substance use disorders</i>	
ICD 10*	<p><i>Dependence syndrome</i></p> <p>at least three of the following criteria occur within 12 months:</p> <ul style="list-style-type: none"> ▪ strong will or compulsion ▪ difficulty in controlling the use behaviour ▪ withdrawal at the discontinuance or reducing of consumption ▪ proofs of tolerance ▪ progressively neglect the alternative interests and concerns, increasing the time required for the purchase, consumption or recovery from the effects ▪ persistence in consumption, despite of the clear evidences of harmful consequences <p>“physically dependence” was replaced with cu “neuroadaptation”</p>	<p><i>“harmful use” (harmful use)</i></p> <p>pattern of use of a psychoactive substance, harmful to the physical or mental health</p>
ICD 11**	<i>Disorders due to substance use</i>	

* in force; ** planed for 2017

Current concepts on drug dependence

Drug dependence usually involves the following:

- ✓ *psychological dependence* – impaired psychological control over drug use; it is the result of a interaction of a set of pharmacological (potential conditioning factors), psychological (primary conditioning factors) and social (group influences or the social acceptability of the drug) factors
- ✓ *physical dependence* - embodied in withdrawal syndrome at the interruption of the chronic consumption, on long periods or at reduction of the doses
- ✓ *tolerance* - reducing sensitivity to a substance after its repeated administration; is manifested by the need to increase the dose to achieve the same effect

- ✓ *psychotoxicity* - serious behavioural change, of psychotic grade, following prolonged use of high doses (obvious to alcohol, barbiturates, cocaine, LSD, amphetamines).

As a result of the rapid development of neuroscience in the last two decades the concepts on abuse of addiction-forming substances have been revolutionized and nowadays drug abuse is a phenomenon (24). Constant efforts to deepen the mechanisms of action of various drugs have led to changes in terminology and the emergence of new concepts. In literature, the concepts of reward and positive reinforcement are often used to describe the effects of drug abuse. Thus, the term “reinforcement” refers to the strengthening of an action by increasing the probability of its occurring in response to a stimulus, in order to obtain a reward or avoid discomfort and is closely related to the concept of conditional learning. Research has concluded that drug self-administration acts as a positive reward (getting effects) and/or negative reward (to avoid withdrawal symptoms) (25). Thus, the abuse substances can be defined as reinforcers, as they increase and maintain the development of a specific behaviour. A behavioural response that increases as a "reward" after the dose is called "positive reinforcement", and the response that increases after the suppression of dose ("punishment") is called "negative reinforcement". Accordingly, the abuse substances are defined as positive reinforcers and negative reinforcers.

Research regarding the action mechanisms of drugs of abuse indicates that their reinforcing properties may be due to actions on a common neural circuit, these substances altering the normal neurochemical processes. As a result of repeated administration of drugs of abuse neuroadaptive responses occur. The tolerance develops to at least some of the effects, and a withdrawal syndrome is associated with most drugs of abuse. Certain aspects of withdrawal, such as changes in mood and motivation, induced by chronic consumption of the drug may be key factors for relapse and drug obsessive search behaviour (2, 26).

The most consistent and coherent theory of the mechanisms involved in the development of drug addiction is that substances of abuse activate the mesolimbic dopamine system, which reinforces both

pharmacological natural rewards. Thus, CNS regions which are believed to be critical in mediating the highs and reinforcing effects of the abuse substances include dopamine mesocorticolimbic system comprising the efferent neurons of the ventral tegmental area dopamine to the nucleus accumbens and the amygdala, cingulate cortex, and prefrontal cortex. The natural rewards (food, sexual attraction) stimulates the release of dopamine in the nucleus accumbens; with habituation, they no longer causes the activation of dopamine neurons, which is activated by stimuli (cues) in the environment that predict reward availability. Unlike to natural rewards, abuse substances increase dopamine in nucleus accumbens even after reinforcement is learned and thus the brain continues to perceive the drug as a new or unexpected reward. However, the chronic administration of drugs results in molecular changes in various neurotransmitter systems, that are involved in the development of dependence on a single drug (1).

The developing of drug addiction is a complex and insufficiently clarified process. Among the factors favouring the development of drug dependence, there are factors related to drug such as pharmacodynamic profile, pharmacokinetic characteristics, the amount consumed, frequency of use, route of administration). Subject relating and environmental factors (socio-cultural, community attitudes, etc.) are also implied. Over the last few decades, numerous genetic and environmental factors that contribute to the development of addiction have been identified. Genetic factors account for 30-60% of the overall risk for the development of drug addiction as it is suggested by the twin and familial studies (12).

Conclusions

Drug dependence is a complex behavioral, cognitive, and psychological phenomena. It develops under repeated administration (continuous or episodic) of a abuse substance, through the stages of experimentation; recreational or social conditioned use; abstention; habitual consumption; abuse; addiction. Drug dependence occurs in a wide range of psychoactive substances acting through different mechanisms.

Drug dependence can be assigned not only to pharmacological effects of the drugs of abuse, but also to their interaction with each particular neurological constitution. This constitution varies as a first

result of the individual's genetic inheritance, and, second, of the experiences and influences from the environment.

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