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# Drug Addictions: An Historical and Ethological Overview

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## 1. Introduction

### 1.1 Preliminary considerations: Focus on cocaine and heroin

It is well established that several psychoactive substances can lead to addiction. These include legal drugs such as alcohol and nicotine which generate the major part of the addiction-related social and economical costs to modern societies (1), and a pleiad of illegal drugs amongst which cannabis, cocaine and heroin are the most commonly used.

When one wants to consider the harmful consequences of an addictive drug, both the dependence and physical harm potencies of the drug should be considered for these two aspects contribute to the deterioration of the user's life. A recent classification of the major classes of addictive drugs reveals that heroin and cocaine are clearly the most dangerous ones since both their addictive properties and physical harm potency are high (2). Cocaine and heroin are followed by barbiturates and street methadone, but tobacco is shown to have addictive property of the same magnitude as cocaine, thereby demonstrating that the legal status of a substance is not a predictive factor of least addictive properties.

In the present chapter, we will consider exclusively cocaine and heroin addictions, not only because these two drugs are clearly the most dangerous ones, but mainly because cocaine and heroin use have been increasing among western countries populations in the last ten years. This focus is one limitation of the general conclusions that will be provided in the following chapters that will also address alcoholism and food addiction that will be joined by another addiction, namely pathological gambling, in the clinical definition of addictions in the upcoming DSM-V. Thus, addictions are increasingly recognised as abnormal persistent maladaptive behaviours driven by specific, initially reinforcing, stimuli in the environment that are not anymore restricted to psychoactive substances.

### 1.2 Drug use: A behaviour as old as humankind?

Drug use seems to have entered human customs as early as the emergence of human societies. Evidences that recreational drug use has emerged early on after human sedentarisation, perhaps with the development of religious rites, can be found for several drugs and routes of administration.

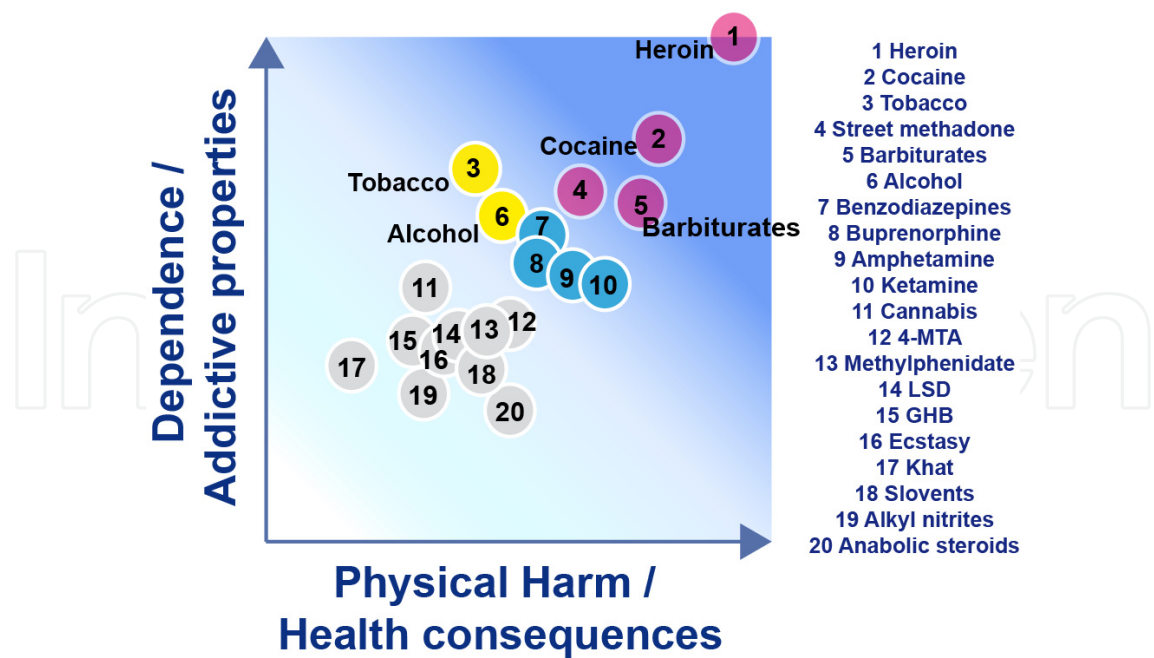


Fig. 1. Rational scale to assess the harm of drugs of potential misuse, after (2).

The addictive potential of a drug varies from substance to substance, and from individual to individual. Dose, frequency, pharmacokinetics of a particular substance, route of administration, and time are critical factors for physical harm and addictive potency. Heroin and cocaine are clearly the most dangerous ones since both their addictive properties and physical harm potency are high.

Thus, 5000 B.C. the sumerians used opium, as suggested by the fact that they had an ideogram for it which has been translated as HUL, meaning « joy » or « rejoicing » (3). A 3500 B.C. egyptian papyrus provides the earliest historical record of the production of alcohol in the description of a brewery (4).

Interestingly, 3000 B.C. is also the approximate date of the supposed origin of the use of tea in China. It is likely that coca leaf chewing began in the Andes at the same time since traces of coca have been found in mummies dating 3000 years back (5). The cocaine content of coca leaf is under 1% but after 1859, when cocaine was first isolated from coca leaf by Albert Niemann, cocaine was available legally in concentrations that were nearly 100% pure. Cocaine was first used recreationally in the 1860s, almost as soon as it was synthesised. A few years after its synthesis by Richard Willstätter in 1898 (6), cocaine appeared in cigarettes, ointments, nasal sprays, and tonics. The most popular cocaine-based product was Mariani Wine (Vin Mariani). It was a wine and cocaine mixture that was launched in 1863. Nearly all popular personalities of the day, including Queen Victoria, Thomas Edison and Pope Leon XIII endorsed it. Cocaine has also been popularised by Sigmund Freud who prescribed it for the treatment of digestive disorders, asthma, depression or opiate and alcohol dependence (7).

At the same time, more precisely in 1898, heroin (diacetylmorphine) was synthesized by Felix Hoffmann, 23 years after a first academic synthesis by Alder Wright. Akin to the launch of cocaine as a medicine, heroin was then introduced by Bayer as “safe preparation free from addiction-forming properties”.

The broad availability of the pure form of cocaine and heroin has contributed to the marked development of addiction to these substances which, in their primary forms and routes of administration, were far less addictive. This phenomenon has been suggested to stem from a discrepancy between our brain and our modern environment, i.e, Nesse and Berridge wrote in 1997: «We are vulnerable to such fitness-decreasing incentives because our brains are not designed to cope with ready access to pure drugs, video games, and snack foods. Hundreds of generations of exposure would likely shape resistance to their allure and their deleterious effects» (8). This interesting consideration suggests that drug addiction may be a matter of mismatch between Human evolution and the recent revolution of human environment, a problem to which Evolution may be the best solution.

	All illicit drugs	Cannabis	Amphetamine- type stimulants		Cocaine	All opiates	Heroin
			Amphe- tamines	Ecstasy			
Number of users (in millions)	185.0	147.4	33.4	7.0	13.4	12.9	9.20
Proportion of global population (%)	3.1	2.5	0.6	0.1	0.2	0.2	0.15
Proportion of population 15 years and above (%)	4.3	3.5	0.8	0.2	0.3	0.3	0.22

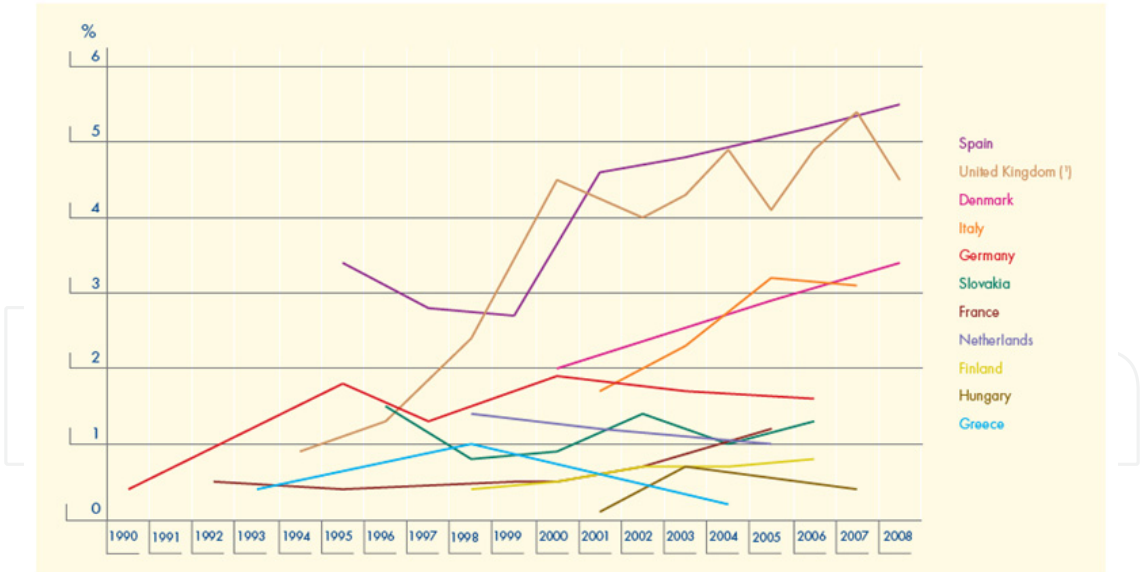


Fig. 2. Illicit drug use state at the beginning of the 21st century

Top panel: Annual prevalence of global, worldwide, illicit drug use over the period 1998-2001 (11). Bottom. A trend to increased cocaine use in European countries (10).

However, before these evolutionary, and rather fatalistic considerations, human societies have developed social and legal strategies to cope with addiction, as early as 10 years following the synthesis of heroin and cocaine. Indeed, the United States prohibited the

importation of smoking opium (9) and the manufacture of heroin in 1909 and 1924, respectively, while the Harrison Narcotics Act of 1914 prohibited the use of cocaine. Since then law enforcement has limited, but not eradicated, heroin and cocaine use, as illustrated by figure 2 (EMCDDA) (10), the bottom panel of which shows a general increase in cocaine use within European countries over the past 20 years. Such a trend may induce an increase in the prevalence of drug-related health problems, and most importantly, of drug addiction.

### 1.3 Drug use: An evolutionary feature of animal kingdom

Drug use seems inherent to animal behaviour, perhaps because of the evolutionary selection of a reward system developed to maintain species survival, bringing animals towards sources of reinforcement. Thus spontaneous drug use has been observed in several species in the wild. Elephants would intoxicate with alcohol contained in ripe fruits and baboons would readily eat over-ripe fruits from the marula tree until they cannot walk anymore. Birds also use alcohol in that song thrush, for instance, struggle to fly after eating ripe grapes.

An exhaustive list of examples of spontaneous drug use in animal kingdom is beyond the scope of this chapter, but a last example should be enough to emphasise how broad are sources of intoxication in mammals: in the south of the United States, sheep and horses eat astragalus and then show hyperactive behaviour akin to human beings.

In experimental settings, it has been demonstrated that all drugs abused by humans are reinforcing in many species including planarians (12) and flies (13, 14), and they are readily self-administered by vertebrates such as mice (15-21) or rats (22-26), dogs (27, 28) and non human primates (29, 30).

Thus not only is drug used common to several species of the animal kingdom but the demonstration that pure forms of psychoactive drugs have reinforcing properties in animals under experimental conditions suggests that drug taking is not a specific behavioural feature of human beings. Drug use in animals seems rather to be the evidence that the neurobiological substrates of primary motivational and reinforcement processes selected by evolution have been shaped early on and maintained from planarians to human beings, and that drugs hijack these systems.

However, it remains unclear the extent to which these findings help inform our understanding of drug addiction in humans since it is a brain disorder that is clearly far removed from primary reinforcement mechanisms.

## 2. Drug addiction: A human-specific disorder?

### 2.1 What is drug addiction?

Drug addiction is a complex brain disorder (31), affecting the motivational (32, 33), learning (34-37) and behavioural control systems of the brain (38-40). Several definitions of drug addiction, ranging from the psychiatric to the social view have been presented by Koob and Le Moal (1) and will not be discussed any further.

Drug addiction is defined as a chronic relapsing compulsive habit characterised by loss of control over drug intake, maintained drug use despite adverse consequences (36, 41, 42) and the development of negative psycho-affective distress when access to the drug is prevented (42, 43).



Because the aetiology and pathophysiology of drug addiction remain unknown, this prominent psychiatric disorder is best defined by the clinical features of the DSM-IV (44) (figure 3). The diagnostic of drug addiction is currently based on a categorial dichotomous approach in that the patient must present at least three out of the seven clinical criteria listed in figure 5 to be said addicted to a substance.

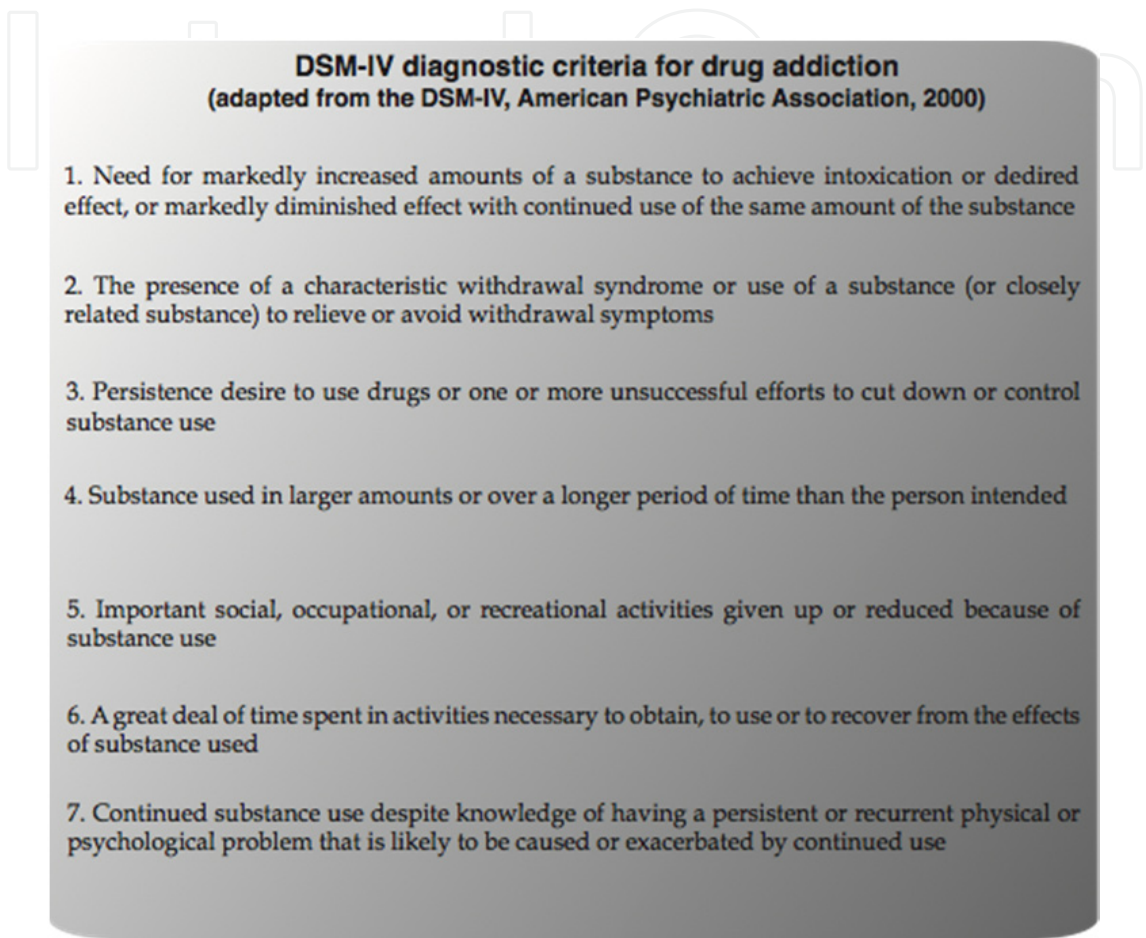


Fig. 3. Clinical features of drug addiction according to the DSM-IV-R (44).

The subject is diagnosed addicted to the substance if they show at least three out of the 7 clinical criteria over the last 12 months.

However, all addicted patients are not equally severely affected and a dimensional addiction severity scale has been developed to assess general behavioural, health and social drug-induced impairments (45-49).

Indeed, drug addicts do not only take drugs, they spend great amounts of time foraging for their drugs, compulsively take drugs, lose control over drug intake, and persist in taking drugs despite the many adverse consequences of doing so, including compromising their health, family relationships, friendships and work. Many drug addicts resort to criminal behaviour to obtain the funds necessary to sustain their compulsive drug use and the great majority eventually relapse to drug use even after prolonged periods of abstinence.

This negative behavioural picture illustrates how drug addiction is not merely a drug taking disorder. Indeed, among the individuals exposed to drugs, and there are many who occasionally drink only a glass or two of an alcoholic beverage, or smoke a cigarette or two, only 15 to 30% overall will switch from casual, 'recreational' drug use to drug abuse and drug addiction (1, 50) (figure 4).

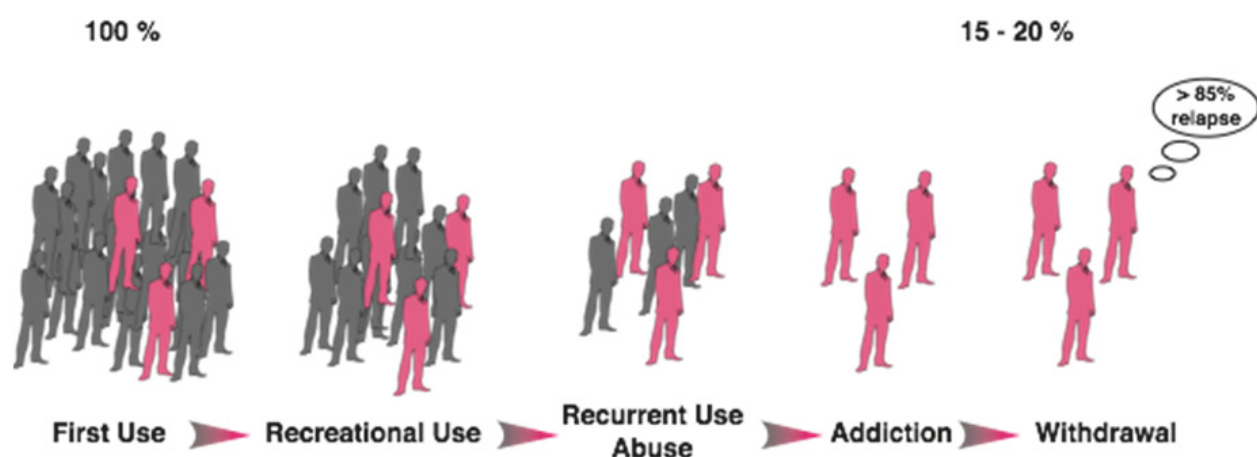


Fig. 4. We are not equally vulnerable to drug addiction

A substantial proportion of the general population experiences drugs at least once in a lifetime. Of the recreational users who control their drug intake, some will shift to more chronic drug use. Only a subgroup of these individuals will develop drug abuse and eventually drug addiction. Epidemiological studies reveal that of the individuals who have been exposed to addictive drugs, 15 to 20 % eventually develop addiction.

Despite considerable research we still do not understand why some individuals develop a compulsive use of drugs nor do we have effective treatments (51) to reduce the substantial social and economic burden (52); for review, see (1) of drug addiction (figure 5). Nevertheless, there is increasing evidence suggesting that drug addiction results from gradual adaptation processes in the brain of vulnerable subjects in response to chronic drug exposure. Not only do these between-systems adaptations trigger an emotional allostatic state (hedonic allostasis) (1, 53-55) characterised for instance by increased anxiety, irritability and depression but they may ultimately lead to a shift in the psychological mechanisms that govern drug seeking and drug taking behaviours, including habits (36, 37, 41, 42, 56, 57) as aberrant instrumental learning mechanisms controlled by Pavlovian cues, altered behavioural control (39, 58-60), decision-making and self-monitoring processes (61, 61).

Similarly, Everitt and colleagues have argued that, during the development of drug addiction, drug seeking is initially goal-directed but becomes habitual, and ultimately compulsive, thereby emphasizing the potential importance of maladaptive automatic instrumental learning mechanisms and their control by Pavlovian incentive processes, so called incentive habits (37, 42), in the emergence of compulsive drug use (35, 37, 42, 59). Additionally, drug-induced adaptations may also facilitate the shift from impulsivity to compulsivity that has been suggested to occur in the development of drug addiction (figure 6) whereby only vulnerable subjects would show a transition from impulse-related recreational drug use to compulsive drug intake (1).

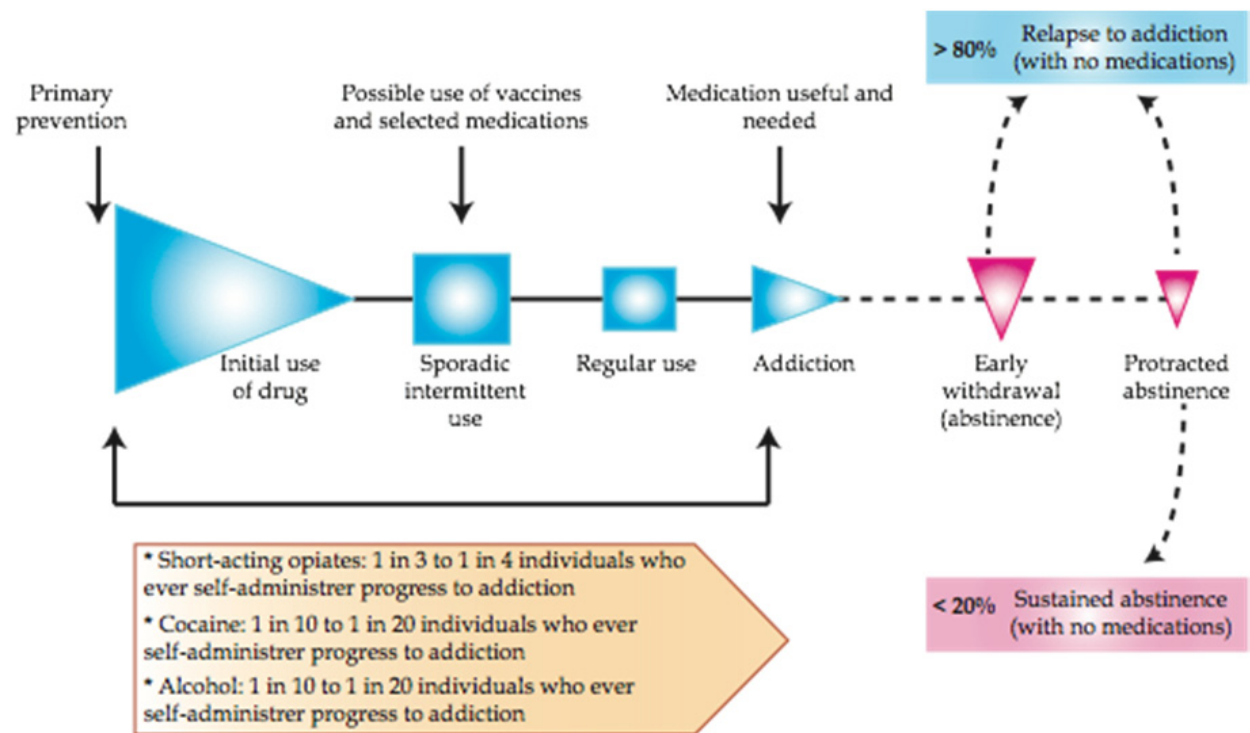


Fig. 5. Strategic targets of therapeutic treatment in the course of drug addiction (reproduced from (51))

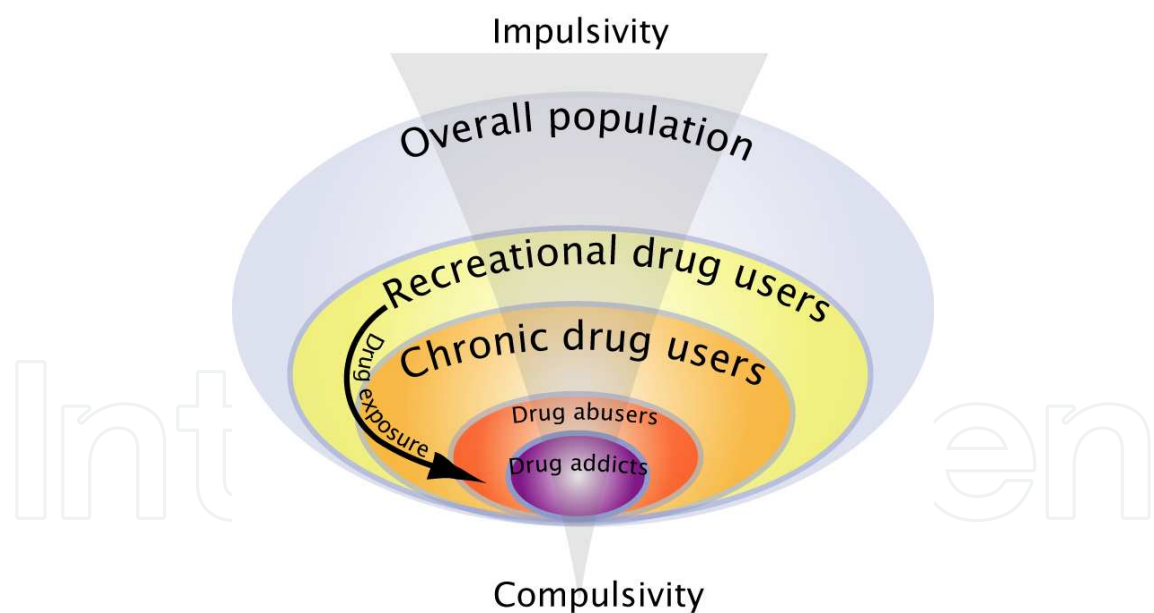


Fig. 6. A progressive shift from impulsivity to compulsivity in the development of drug addiction (42)

2.2 Behavioural and psychological profile of drug addicts

Besides their disinterest for alternative sources of reinforcement and their focus on the drug, drug addicts are characterised by several behavioural and cognitive deficits including impaired inhibitory control (62-67), decision making (68-75) and insight (76-78).



However, major differences can be observed between addicts depending on their preferred drug of abuse. For instance, although opiate and stimulant addicts both display increased sensation seeking (79-81) and impulsivity (82-87), they nevertheless differ in other respects, with heroin addicts showing greater anxiety than cocaine addicts (88), while the latter display higher impulsivity (62, 89, 90).

Thus not only are several personality traits, including sensation seeking, anxiety and impulsivity, associated with increased vulnerability to use drugs (91-94), but different personality traits are preferentially associated with use (95) and addiction to specific drugs (91, 92, 94, 96-103). It is therefore possible that heroin and cocaine addicts may self-medicate different personality characteristics or affective states (104-107), with impulsivity being preferentially self-medicated by cocaine use. However, as discussed in chapter 2 of this book, the relative contribution of a behavioural trait to the choice of a drug does not necessarily predict its implication in the transition to compulsive drug use.

Drug addicts also show several comorbid psychiatric disorders (108-111), as stated by O'Brien (112): «Psychiatric disorders commonly coexist with addictive disorders. These include anxiety disorders, psychotic disorders, and affective disorders such as depression. Although some of these so-called “dual diagnosis” cases are simply a coincidental occurrence of common disorders, the overlap is greater than would be expected by chance on the basis of population prevalences (109)». However, it remains unknown whether comorbid elements contribute to increased vulnerability to drug addiction (113) or whether chronic drug exposure facilitates the emergence of psychiatric comorbidity (for discussion see (112)). Similarly, while some personality, or behavioural, traits are triggered by chronic drug use, there is evidence that personality variables are associated with increased vulnerability to develop drug addiction (92, 114). This rather blur picture not only suggests that several sub-populations exist within drug addicts (115), but it clearly illustrates how little is known about the factors involved in the vulnerability to develop drug addiction.

To date a triadic model of contributing factors has been established that accounts well for both clinical and preclinical literature. Thus, vulnerability to drug addiction is suggested to result from the interaction between a vulnerable phenotype, or personality (being the interaction between genes and history), the drug and the environment (figure 7).

There is clearly a genetic vulnerability to addiction. Genetic factors may contribute up to 40% to the development of drug addiction (51). This estimation gives genetic factors a limited contribution to the vulnerability to drug addiction and highlights the importance of both the drug and the environment in the development of the pathology. There is indeed compelling evidence that life experiences and environments highly influence the effects of drugs of abuse and play a critical role in the transition from controlled to compulsive drug use (116, 117). For instance, drug addiction seems to be more frequent in people living in degraded areas or in people that undergo difficult experiences during their childhood. Such specific environmental conditions at either perinatal, developmental or adulthood stages may alter one's personality construction so that they become more vulnerable to use or abuse drugs (118). On the other hand, positive family relationships, friendships, involvement and attachment appear to somehow protect against the development of drug addiction (119, 120).

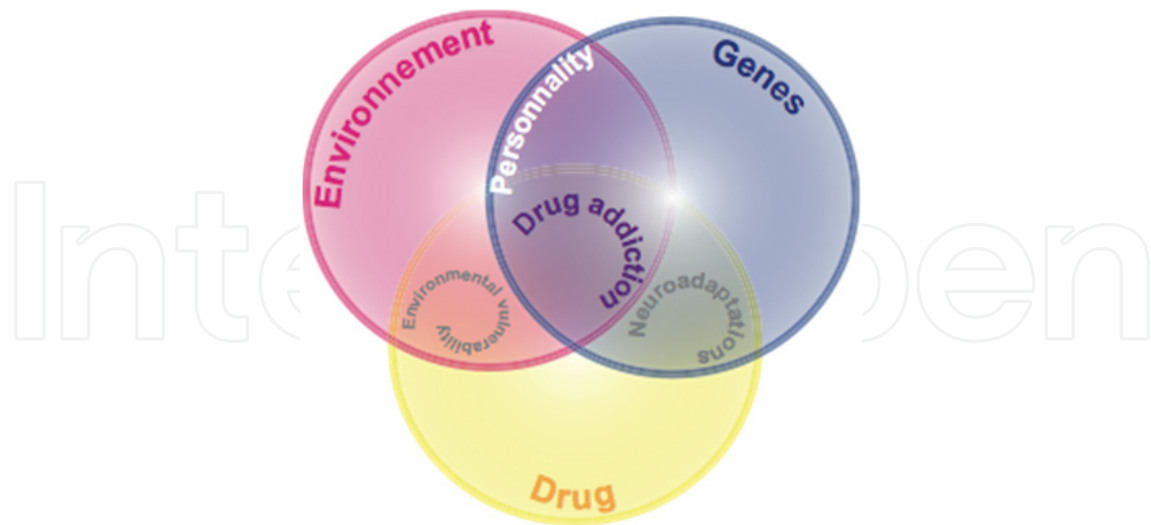


Fig. 7. Triad of influences underlying vulnerability to drug addiction

A number of interacting factors are hypothesised to influence the pathway to addiction, including biological determinants (genes), drug exposure and the environment. Genetic influences may account for up to 40% of the vulnerability for drug addiction

Thus, the present general strategies developed to treat addictions should perhaps be re-oriented towards a more patient-based medication strategy once better insights are gained in the understanding of the etiological and neurobiological substrates of individual vulnerabilities to addictions.

### 2.3 Biological correlates of drug addiction in humans: Insights from imaging studies

An exhaustive synthesis of the neurobiological correlates of drug addiction is beyond the scope of this chapter. Overall, drug exposure impacts both brain structure and function. Thus at the morphological level, drug addicts have decreased grey matter volumes in prefrontal (121-125) and cerebellar regions of the brain (126). Functionally, when presented with drug-related cues that induce craving, drug addicts show abnormal activation of limbic structures including the amygdala (127, 128), the insular (40, 129) and orbitofrontal cortices (39, 130) as well as cognitive prefrontal areas such as the cingulate (127, 128, 131) and dorsolateral prefrontal cortices (74).

Moreover, drug addicts are characterised by decreased levels of striatal D2/3 dopamine receptors (132-134) and reduced metabolism in the orbitofrontal cortex (132). These two alterations are highly correlated (132), thereby providing the orbitofrontal-limbic striatum circuit a prominent implication in addiction (134, 135), even though other networks, including the thalamo-cortical systems, have been identified to be impaired in drug addicts (136).

Interestingly, a growing body of evidence points towards an implication of non limbic striatal areas in the pathophysiology of drug addiction since dopamine transmission is specifically increased in the dorsal striatum of cocaine addicts experiencing craving in

response to presentation of drug-associated cues (137, 138), providing a neurobiological evidence for a progressive involvement of dorsal striatum-dependent habits (139-141) in drug addiction (35-37, 41, 42).

A major limitation of human studies is that the data obtained, though clearly informative, are based on the comparison of current or former drug addicts and drug naive control subjects. Thereby, human studies cannot control for the effects of protracted drug exposure on the brain nor can they define whether the abnormalities observed in drug addicts are a pathological biological adaptation to drug exposure or predated drug use and hence are instead endophenotypes of vulnerability to drug addiction.

This is where the case for animal experimentation in addiction research is revealed compelling. Besides the aforementioned limitations, studies in human addicts are often prone to interpretative issues not least due to inter-subject variability in drug exposure, the frequent co-abuse of several drugs often in combination with alcohol, cannabis and nicotine, the regular occurrence of co-morbid brain disorders such as depression, conduct disorder and attention-deficit/hyperactivity disorder (ADHD) and the difficulty in controlling pre-morbid cognitive and intellectual abilities.

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