

## **Understanding the Pathogenesis of Drug Addiction in Order to Implement a Correct Pharmacological Intervention**

**Icro Maremmani<sup>1,2,3</sup> and Matteo Pacini<sup>1,3</sup>**

### *Summary*

Meaningful therapeutic interventions for addictive diseases should be designed with a hierarchy of targets from the very beginning. The ability to target the core symptoms and the underlying dynamics imply a deep knowledge of the clinical picture, the links between observed behaviours and their psychopathological roots. First of all, a distinction should be drawn between habit and addiction, as the former cannot be considered a target for medical intervention. The identification of craving, loss of control over appetitive behaviour, and relapse proneness are crucial to the singling out of drug addicts within a wider population of drug users. Secondly, addiction should be approached as a relationship between the addict and the substance he is hooked on, as most environmental variables are consequential, and, in any case, aspecific. Effective treatments target the relationship between the individual and the substance from within the addicted patient's brain. Different strategies may be indicated for the disease process, at its different stages, but all available options do share a common psychopathological target. Moreover, treatments should be planned so as to fit the spontaneous chronic course of addiction, that is, as maintenance programmes.

Keywords: addiction, craving, disease, therapeutic programme, treatment options.

Abused substances, regardless of whether they are licit (caffeine, nicotine, alcohol, chocolate) or illicit (heroin, cocaine, amphetamines, hallucinogenic drugs, inhalants), share, to a varying degree, a danger of becoming a means of dysfunctional self-administration practices. This risk depends on those substances' intrinsic capacity to divert human behaviour towards themselves, by repeatedly stimulating a system of cerebral rewards, so allowing substance-seeking drives to get out of control. Though the subjective effects elicited by self-administration vary between different substances, a

common subjective condition, generically referred to as “euphoria” or a “high” can be described, consisting of an enhanced pleasurable perception of any situation. Hence, a pleasurable experience is the event on which future self-administration is likely to be based. A series of pleasurable experiences, together with an awareness that the artifact arose from substance administration, will lead to the substance-seeking drive being reinforced, until administration cannot be postponed or skipped, and control is definitively lost. Unrestrained self-administration is the expression of a neurobiological scenario where the major roles are played by a certain substance and the substrate it acts on, and the crucial feature is the substance’s property of attracting human behaviour towards itself. In Goldstein’s view, “Every abused substance self-administered by humans is self-administered by rats and monkeys as well”; and “surely, a heroin-addicted rat is not a rebel to society, is not suffering from socio-economic difficulties, cannot be said to belong to a dysfunctional family, nor is it a criminal at all. That rat’s behavior is simply a result of heroin’s action upon its brain”. Like abused substances, other means of stimulation are capable of reinforcing the behaviours which first led to pleasurable experiences, until the point of no return is reached (as happens with non-chemical addictions). Therefore, individuals may become committed to work, sexual intercourse, eating, gambling and risk-taking as a priority and with unrestrained urgency.

On neurophysiological grounds, different neuromediators help to produce whatever we perceive as pleasurable. Some neurochemical systems, such as the dopaminergic, gabaergic, and opioidergic ones, have been studied in great detail in connection with the perception of pleasure, and have been found to be closely intermingled. The ventral tegmental, nucleus accumbens, caudate nucleus and substantia nigra have been identified as structures related to these systems. Dopaminergic firing activity mostly corresponds to the ventral tegmental area and the accumbens and caudate nuclei, which, taken together, are indicated as the input branch of the reward system. Gabaergic activity, in the ventral tegmental area, and opioidergic activity, even if briefly, in the substantia nigra and the accumbens, also play a role. Neurochemical events resulting in the phenomenon of behavioural reinforcement, as produced by a group of substances, take place in these central nervous system areas.

Although repeated exposure to the substance is itself enough to allow addiction to develop, addictive dynamics cannot be considered to depend on a single factor. Substance availability is certainly necessary for the onset of addiction, and the market is highly responsive to consumers’ tastes and requests. Social and cultural aspects may be favourable to individuals trying and using substances, as happened in Italy through the 1960s and 1970s. Nevertheless, none of these factors, whether market-related features, personality traits, mental disorders, social or cultural issues, do more than favour the interaction between substances and individuals from the first administration through the early stage of involvement into drug-taking, regardless of whether it will abort or develop into actual addiction. For most would-be addicts, there is an early phase during which the substance is resorted to with the aim of recalling the pleasurable feelings that have been experienced (the honeymoon stage). The development of full-blown addiction implies persisting with substance self-administration over a period long

enough to produce addiction by supporting cerebral changes.

According to the dynamics which lead from the first experience to regular use, before any addiction has developed, one can distinguish between self-medicating drug-users and socially coping ones (those who seek to adapt to a stressful life context). Self-medicating drug-users are not eager to have a “high”, but resort to the substance with the aim of counteracting symptoms of discomfort. Through this practice dysphoric subjects, for example, learn how rapidly and effectively street opiates can soothe their discomfort, at least in the early phase of their involvement. In socially coping drug-users, drug-use looms as a means to resist stressful social, familiar or peer contexts, although this need may emerge from particular personality traits, or environmental factors may increase the probability that particular individuals will try to get hold of substances. However, the vast majority of regular drug-users are bound to reach the ultimate, metabolic stage of drug abuse, that is full-blown addiction, regardless of any further dynamics than that of their prolonged exposure to the substance itself. Likewise, the longer self-medicating and socially coping users persist with substance use, the more likely they are to become metabolic addicts. At this stage, the toxic effect of the abused substances produces enduring alterations in what had previously been an internal balance between the stimulated systems. As far as heroin addiction is concerned, no matter why or how heroin was first used, it takes an average of two years for the appetite for the substance to become unrestrained, and for it to support relapsing behaviour. Short-term therapeutic interventions or self-managed attempts lead to a revolving-door course, characterized by the perpetuation of the detoxification-abstinence-relapse cycle. For some substances, such as heroin, the clinical picture is impacted by withdrawal susceptibility, due to an acquired tolerance to heroin effects. As a rule one effect of repeated exposure to a substance is to make individuals susceptible to displaying reverse symptoms when the stimulation is not renewed for a certain time. This rebound phenomenon is not induced by prolonged exposure to cocaine, metamphetamines and acids, and is milder for cannabis and nicotine. At a later stage of drug-use, the substance’s pleasurable effects are missed, whereas no normal status is perceived unless through self-administration sessions. As time goes on, the subject is more and more likely to experience withdrawal symptoms, or an accidental overdose. Pleasurable perceptions may still be present, but they are not as constant, satisfactory or long-lasting as before. At this stage, snorters may become injectors in order to be able to challenge their heightened tolerance by using lower doses, at still affordable prices.

Nevertheless, withdrawal syndromes also occur, with a different mechanism, for the substances mentioned above, by the same rule of reversal of acute effects. Thus, hypersomnia, hunger and weakness can be expected to follow a sharp interruption or reduction of cocaine use.

Once addiction has set is as an autonomous disease, all addicts fall into the “metabolic” category: the neurobiological structures underlying subjective reward have gone through a process of long-term conditioning, with major short- and long-term impairment of the ability to experience reward by a variety of stimuli, which may include substances.

Like every other disease, addiction is defined by its core-symptoms. Some do not last more than a few days, but are quite intense, and constitute the withdrawal syndrome. Symptoms of opiate withdrawal indicate the recent interruption of a habitual opiate use, but they do not always occur, nor are they enough to justify a diagnosis of opiate addiction. Once withdrawal, if present, has cooled down and been extinguished (both opiate agonists and symptom-targeting drugs can be helpful), addiction is not over; it is now displayed through a crucial, more severe symptom - relapsing behaviour. Thus, drug dependence should not be seen as the crucial issue in addressing drug addiction. In fact, a variety of drugs imply susceptibility to withdrawal when their administration is interrupted, without any behavioural urge to take them again. Abuse-labile substances, on the other hand, can powerfully drive subjects to use the substance again. For example, people chronically treated with betablockers are susceptible to their withdrawal, which may lead to transient tachycardia but can actually be lethal because of acute heart failure or heart attack. However, unlike drug addicts, such people do not miss the drug in an instinctual mode, so that information is required for subjects to avoid betablocker withdrawal, or find a remedy for it by drug-taking.

Thus addiction does not consist in being susceptible to withdrawal, which can be expected to end after a few days. A subtler trend towards loss of control underlies relapsing behaviour, and is displayed during the so-called “post-withdrawal abstinence”. In fact, intervention to achieve detoxification, which focuses on the management of withdrawal, simply restores the baseline tolerance threshold, but fails to provide any long-term coverage against late-onset symptoms, which are called “enduring withdrawal”, “later withdrawal” or “post-withdrawal abstinence”. Addiction is, therefore, basically characterized by a chronic pattern of relapses (a persistent susceptibility to relapses) through involvement with the same substance, or the same set of substances, despite the harmful consequences which the subject is well aware of and is able to evaluate correctly.

After heroin detoxification has been accomplished, with or without medical supervision, discomfort persists as a strange feeling of nervousness, low pain and stress threshold, and an incapability to be “functional” in high- as well as low-priority tasks. The ensemble of these symptoms, first labelled by Martin as “hypophoria” back in the sixties, is related to neuroendocrinological abnormalities, and has equivalent animal models; it arises out of persistent opioid damage due to prolonged fast-acting opiate drugs.

To conceive relapsing behaviour as the crucial aspect of addictive diseases, leads to a relapse-targeting therapeutic intervention. Whatever intervention may be thought of to deal with drug addiction must begin with an early phase of stabilization, followed by a long-term maintenance treatment, so as to hold on the stability that has been acquired. As a rule, short-term intervention interrupts abuse behaviour, but is ineffective as a form of relapse-prevention. Likewise, transient and recurrent abstinence are both quite common in the history of most untreated drug addicts.

Treatment models referred to as standards for the management of drug addiction

have mostly been developed for heroin addiction. The principles of treatment are, however, similar with other substances, alcohol included, as long as the shared core aspects of craving and relapse proneness are focused on, regardless of differences between pictures of acute and chronic intoxication.

Effective treatments for addiction act specifically against a class of substances. No treatment option is currently available to manage the dynamics of addiction, regardless of which substance is involved. Hence, treating someone for drug addiction means employing certain chemicals as anti-craving drugs. Craving is an irresistible drive that supports relapsing behaviour, and anticraving-based treatment models mainly target relapsing behaviour in a preventive way.

Some experts state that drug-addiction should not be approached through the chronic use of other “substances”. In their view, addiction is not comparable with other chronic diseases, such as diabetes or hypertension. Even so, these conditions and drug addiction both display elements of altered physiology, which do not tend to spontaneously readjust. In all chronic conditions, different strategies may be preferable at different stages, to challenge the same pathophysiological substrate at different degrees of abnormality.

The role of pharmacotherapy as an approach to drug addiction may be briefly described as follows: it is indicated in the treatment of withdrawal syndrome and overdose; to improve retention rates in outpatient programmes, so as to limit money spent by the public health system; to offer a variety of ancillary facilities which may help treated patients to minimize their risk of relapse. Moreover, pharmacotherapies may be helpful as long-term options for patients who act functionally as long as they are on the drug, but lose social and productive skills when they are in a drug-free condition.

Expectancies for pharmacologically treated patients must be realistic. The main goal is to diminish the use of the substances involved, alcohol included, as far as possible. Achieving a drug-free condition definitely comes second. The psychopathological symptoms and the general health status of the patient deserve major attention. While under treatment, patients may start or continue working, and improve their family and social relationships. In addition, drug-related criminal activities are likely to be minimized or extinguished.

An anticraving drug should possess two critical features: first of all, it must act as an antidote to withdrawal from the abused substance, in line with the pharmacological property of cross-tolerance. Besides this, it must counteract the craving for the abused substance without inducing a craving for itself. As for the opioid system, an anticraving drug must combine an anti-withdrawal property with an opioid-agonist action. On the other hand, the therapeutic drug itself must not be liable to abuse. In other words, the sensation of well-being achieved by the administration of the drug must not produce a drive to self-administration: that would, in fact, mean perpetuating the dynamics of addiction, either shifting their object from one substance to another, or adding a new one.

Apart from the control of withdrawal, and the anticraving property, on which the substance’s capacity to prevent relapses is grounded, the treatment must restore wha-

tever pathophysiological damage has been done by chronic intoxication. In the case of opiates, for instance, heroin abuse leads to the impairment of the hypothalamus-hypophysis system, and to sexual dysfunction. The former has been shown to normalize during methadone treatment.

Some drugs are commonly mistaken for anticraving drugs. Naltrexone, for example, does not buffer withdrawal, but may elicit it. It has no intrinsic agonist action upon the loop of reinforcement, and may also worsen the opioid function in non-tolerant individuals. Clonidine does control withdrawal, but possesses no opioid agonist property. Neither clonidine nor naltrexone normalize whatever damage has been done by prolonged heroin use. GHB is useful in the treatment of alcoholism because of its anti-withdrawal and anticraving properties, but seems to display some liability to abuse, at least with some patients. In other words, some people display a craving for GHB. Lastly, it cannot normalize the damage done by alcohol intoxication, such as cognitive impairment, but shares the same kind of toxicity. Amphetamines and cocaine are even clearer examples. In fact, amphetamines are effective against cocaine withdrawal, but are almost as liable to abuse as cocaine itself, and share the same toxic effects as cocaine.

Anticraving drugs must, if possible, be administered orally, both for simplicity and for pharmacological reasons. Some substances may be reinforcing when injected, but neutral when taken orally. Injecting makes drugs immediately and wholly bio-available, whereas oral administration results in a slower rise in drug blood levels (T max). Oral administration implies a lower risk of infections and needle pathology. An anticraving drug must have long-lasting effects (over 24 hrs). Among opiates, for instance, heroin is immediately available and traces disappear after 2-6 hours, which makes it highly addictive. An anticraving drug should be safe, well-tolerated and free of toxic effects in the long term. To be considered effective, it must improve the condition of a significant subgroup of patients, not less than 15-20%.

Four therapeutic strategies are currently available to treat craving:

- 1) Maintenance (long-term) treatments by long-acting agonist (cross-tolerant) drugs. This kind of approach is viable when agonist drugs that are neither toxic nor addictive either in the short or long term are available. The property of normalizing the abnormalities produced by chronic intoxication may provide further advantages. This strategy is followed in the agonist-maintenance treatment for heroin addiction (methadone-LAAM-buprenorphine).
- 2) Maintenance therapies with drugs that have some anticraving properties, but do not produce cross-tolerance. These options are currently available for the treatment of alcohol and cocaine abuse.
- 3) Maintenance therapy with substances that block the effects of the abused substances (antagonists). This strategy is viable against substances which act by mainly affecting one receptor system. No craving control is provided. If baseline craving is low, this strategy may be effective, as the lack of reinforcement may gradually detach the individual from the substance. The main example is represented by naltrexone, when used for the treatment of heroin addiction.
- 4) Substances which interfere with the metabolism of the abused substance. Its rejection may be favoured, or its effects altered, so replacing the expected reward with unplea-

sant, aversive effects. Disulfiram treatment for alcoholism is the best example of this strategy.

The first strategy is undoubtedly the most effective. It provides control over craving, which means directly interfering with the reinforcement loop at a drive level. It mends the damage produced by hyperstimulation (by substituting the missing function), and protects against possible overdosing; lastly, it can prolong the acquired benefit for as long as necessary.

Apart from opiates, antidepressant drugs of different categories display some anti-craving properties, especially when alcohol, nicotine or metamphetamaine are concerned. GHB is used for alcohol abuse, and dopaminergic drugs seem to be quite useful in acting against cocaine abuse. Apart from long-acting, slow-release compounds, like clonazepam, there is no scope for the use of BDZs, as these are highly abuse-labile among drug addicts.

On the whole, it can be concluded that pharmacological treatment is an effective approach to drug-addiction. However, no treatment is effective for every patient, nor can any treatment be indicated as “the best”. Different approaches are best suited to different clinical pictures and subgroups of heroin addicts. An accurate clinical evaluation and detailed information about addictive histories is always the first crucial step in matching the patient with the treatment.

## Bibliography

1. Dole V. P., Nyswander M. E. (1965): A medical treatment for diacetylmorphine (heroin) addiction: A clinical trial with methadone hydrochloride. *JAMA*. 193: 80-84.
2. Maremmani I. (1994): Comprehensive treatment of heroine dependence in Italy. Theory of different levels of intervention, i.d. ‘breaking through a wall of prejudices’. *The Italian Journal of Psychiatry and Behavioural Sciences*. 4(2): 95-98.
3. Maremmani I. (1999): Treating Heroin Addicts i.e. “Breaking through a Wall of Prejudices”. *Heroin Add & Rel Clin Probl*. 1(1): 1-8.
4. Maremmani I., Canoniero S., and Pacini M. (2001): *Manuale di Neuropsicofarmacoterapia Psichiatrica e dell’Abuso di Sostanze*, Pacini Editore Medicina & AU-CNSonus, Pisa.
5. Martin J., Ingles J. (1965): Pain tolerance and narcotic addiction. *Br J Soc Psychol*. 4: 224-229.
6. Martin W. R. (1972): Pathophysiology of narcotic addiction: possible role of protracted abstinence in relapse. In C. J. D. Zarafonitis Ed., *Drug abuse*. Lea and Febiger, Philadelphia. pp. 153-159.
7. McLellan A. T., Luborsky L., O’Brien C. P., Woody G. E., Druley K. A. (1982): Is substance abuse treatment effective? *JAMA*. 247: 1423-1428.
8. Tagliamonte A. and Maremmani I. (1995): *Drug Addiction and Related Clinical*

- Problems*, Springer-Verlag, Wien, New York.
9. Tagliamonte A., Maremmani I. (2001): The problem of drug dependence. *Heroin Add & Rel Clin Probl.* 3(2): 7-20.

*Received and Accepted May 18, 2003*