

PHARMACOLOGY AND ADDICTION: YOUR DEFINITIVE, CUTTING-EDGE GUIDE

Unrestrained use of substances is the external expression of a neurobiological scenario, not a moral issue, states Professor Icro Maremmani. He shares the latest scientific findings

“Every abused substance self-administered by humans is self-administered by rats and monkeys as well,” said Goldstein. “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 behaviour is simply a result of heroin’s action upon its brain.”¹²

Abused substances – be they licit (caffeine, nicotine, alcohol, perhaps chocolate) or illicit (heroin, cocaine, amphetamines, hallucinogenic drugs, inhalants) – share a danger of becoming, in varying degrees, a means of dysfunctional self-administrative habits³³.

THE INSTANT-REWARD TRAP.

This risk lies in those substances’ intrinsic capacity to divert human behaviour towards them,

by repeatedly stimulating a system of cerebral rewards, so allowing substance-seeking drives to get out of

control. The effects elicited by self-administration can vary between substances. But a common subjective condition, generically known as a “high” or “euphoria”, can be described, being an enhanced pleasurable perception of a situation^{4,15-17,34-37}.

That pleasurable experience is the event on which future self-

administration is likely to be based. A series of pleasurable experiences, coupled with awareness that they arose from substance use, leads to reinforcement of the substance-seeking drive, until administration cannot be postponed or skipped; control is definitively lost.

Unrestrained use is the expression of a neurobiological scenario, not the playing-out of a moral one.

Like abused substances, other stimulations can reinforce behaviours which first led to pleasurable experiences, until the point of no return is reached – as happens with non-chemical addictions. Thus we see people prioritising work, sexual intercourse, eating, gambling and risk-taking, with unrestrained urgency.

In neurophysiological terms, different neuromediators help to produce whatever we perceive as pleasurable.

THE BRAIN CHEMICALS TO WATCH.

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. Our brain’s ventral tegmental, nucleus accumbens, caudate nucleus and substantia nigra have been identified as structures related to these systems.

Dopaminergic firing activity corresponds mostly to the ventral tegmental area^{5, 11,14} and the accumbens³⁰⁻³² and caudate nuclei¹⁰. Taken together, these 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 behavioural reinforcement, as produced by a group of substances, take place in these central nervous-system areas.

However, addictive dynamics do not depend on a single factor.

Substance availability is certainly necessary for the onset of both misuse and addiction, and the ‘market’ is highly responsive to consumers’ tastes and requests. Social and cultural aspects might be favourable to people trying and using substances, as happened in Italy through the 1960s and 1970s. But 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.

SELF-MEDICATION vs “HIGHS”.

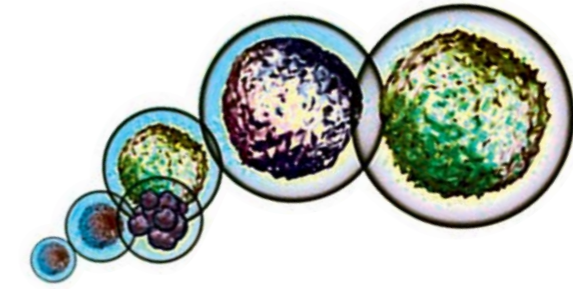
For most would-be addicts, there is an early phase during which the substance is resorted to with the aim of recalling pleasurable feelings: the honeymoon stage. Before addiction has developed, we can distinguish between self-medicating drug-users and socially coping ones, those who seek to adapt to 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 – those who generally feel distressed, the opposite of euphoric – 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 – this need can emerge from personality traits, or from environmental factors increasing the probability that particular users will try to get hold of substances.

The vast majority of regular drug-users can reach the ultimate, metabolic stage of drug abuse, full-blown addictive behaviour, regardless of any current dynamics than that of their prolonged exposure to the substance⁷⁻⁹.

THE HONEYMOON MUST END.

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.



With heroin addiction, 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 treadmill, characterised by the perpetuation of the detoxification-abstinence-relapse cycle⁶.

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 a person display ‘reverse symptoms’ when the stimulation is not renewed for a time. This rebound phenomenon is not induced by prolonged exposure to cocaine, amphetamines and acids, and is milder for cannabis and nicotine.

At a later stage of drug-use, the substance’s pleasurable effects are missed; no ‘normal’ status is perceived unless through self-administrative sessions. As time goes on, the user is more and more likely to experience withdrawal symptoms, or an accidental overdose.

Pleasurable perceptions might still be present, but they are not as constant, satisfactory or long-lasting as before. At this stage, snorters might become injectors, in order to challenge their heightened tolerance by using lower doses at still-affordable prices²⁵.

Withdrawal syndromes can also occur with a different mechanism for the above substances, 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.

When we witness addiction set in 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 might include substances.

MOVE FROM DETOX TO STABILISATION. Like every other disease, addiction is defined by its core symptoms³³. Some do not last more than a few days, but are quite intense, such as the withdrawal syndrome. Symptoms of opiate withdrawal indicate recent interruption of 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 been extinguished – opiate agonists and symptom-targeting drugs can be helpful here – addiction is not over. Rather, it is revealed through a crucial, more severe symptom: relapsing behaviour.

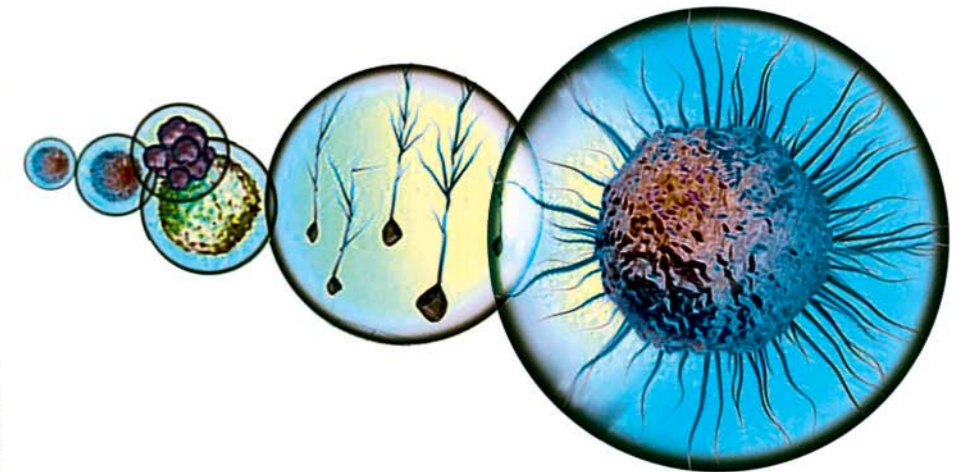
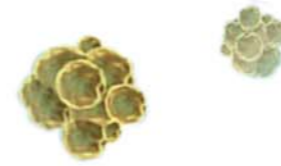
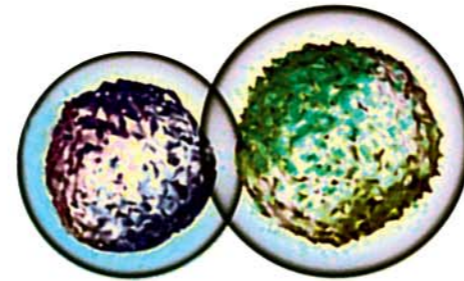
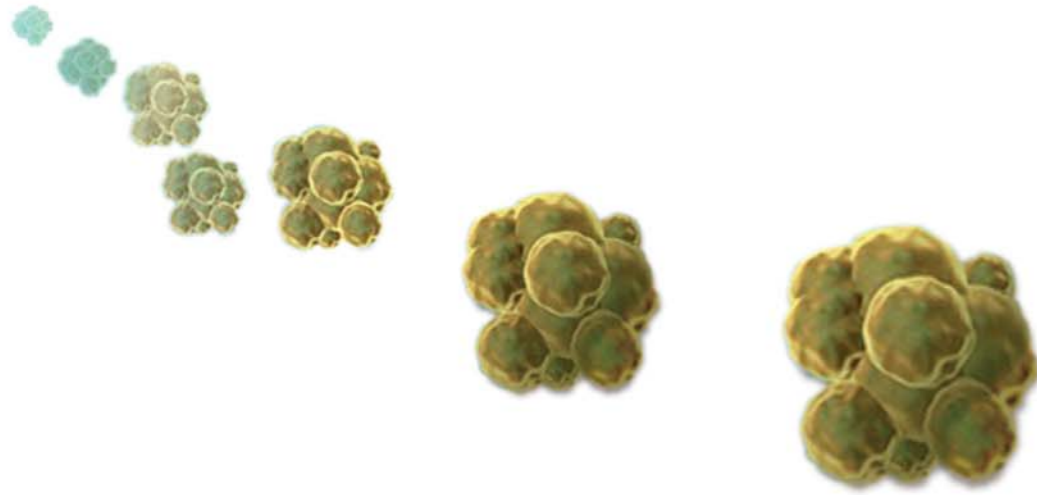
A variety of drugs imply susceptibility to withdrawal when their use is interrupted, without any behavioural urge to take them again. Abuse-labile substances, on the other hand, can powerfully drive subjects to use the substance again. For example, people chronically treated with betablockers are susceptible to their withdrawal. Symptoms can lead to transient tachycardia or even be lethal because of acute heart failure or heart attack.

But, unlike drug addicts, such people do not miss the drug in an instinctual mode. Thus addiction does not consist merely of 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 in so-called “post-withdrawal abstinence”^{26,27}.

In fact, interventions to achieve detoxification which focus solely on management of withdrawal simply restore the baseline tolerance threshold – and fail to provide any long-term coverage against late-onset symptoms. These could be called “enduring withdrawal”, “later withdrawal” or “post-withdrawal abstinence”.

Addiction is thus basically characterised by a chronic pattern of relapses (a persistent susceptibility to relapses) through involvement with the same substance, or set of substances, despite the harmful consequences which the user is well aware of and is able to evaluate correctly.



After heroin detoxification, with or without medical supervision, discomfort persists. There is a strange feeling of nervousness, low pain and stress thresholds, and an inability 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 1960s, is related to neuroendocrinological abnormalities, and has equivalent animal models. It arises out of persistent opioid damage due to prolonged fast-acting opiate drugs^{26,27}.

To recognise relapsing behaviour as the crucial aspect of addictive diseases leads to a relapse-targeting therapeutic intervention. Whatever intervention is used, it must begin with an early phase of stabilisation, followed by a long-term maintenance treatment – be it psychotherapeutic, pharmacotherapeutic or a mix of the two – to hold on the stability that has been acquired.

As a rule, short-term intervention interrupts abuse behaviour, but is ineffective as relapse-prevention. Likewise, transient and recurrent abstinence are quite common in the history of most untreated drug addicts.

THE ROLE OF PHARMACOTHERAPY.

The role of pharmacotherapy as an approach to drug addiction can be briefly described as below.

- It is indicated in the treatment of withdrawal syndrome and overdose.
- It can improve retention rates in outpatient programmes, to limit money spent by the public-health system.
- It can offer a variety of ancillary facilities which might help treated patients to minimise their risk of relapse.
- And pharmacotherapies can be helpful as long-term options for patients who act functionally as long as they are on the prescription medication, but lose social and productive skills when they are “off their meds”.

Treatment models referred to as standards for the management of drug addiction were mostly developed for heroin addiction. But the

principles are similar with other substances, alcohol included, as long as the shared core aspects of craving and relapse proneness are focused on. This is regardless of differences between pictures of acute and chronic intoxication.

Effective pharmacological treatments for addiction act against a specific class of substances. No option can currently manage the dynamics of addiction regardless of which substance is involved. So “treating” someone means using certain chemicals as anti-craving drugs, to help prevent relapse. Craving is a compulsive drive which supports relapsing behaviour; anticraving-based treatment models mainly target relapsing behaviour in a preventive way¹⁸.

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 can be preferable at different stages, to challenge the same pathophysiological substrata at different degrees of abnormality.

Expectations for pharmacologically treated patients must be realistic. In standalone mode, the main goal is to diminish the use of the substances involved, alcohol included, as far as possible. Achieving a drug-free condition is usually feasible only when pharmacotherapies are partnered with psychosocial interventions.

To reduce harms, the psychopathological symptoms and the general health status of the patient deserve major attention. In treatment, patients might start or continue working, and improve their family and social relationships. In addition, drug-related criminal activities are likely to be minimised or extinguished.

ANTICRAVING NECESSITIES.

An anticraving drug should possess two critical features. First, 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 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 wellbeing achieved by the administration of the drug must not produce a drive to self-administer. That would mean perpetuating the dynamics of addiction, either shifting their object from one substance to another, or adding a new one.

Apart from control of withdrawal and the anticraving property on which a substance’s capacity to prevent relapses is grounded, the treatment must restore any pathophysiological damage caused by chronic intoxication. In the case of opiates, for instance, heroin abuse leads to impairment of the hypothalamus-hypophysis system and to sexual dysfunction. The former has been shown to normalise with methadone – although withdrawal from methadone is more painful than from heroin and needs another programme of management when/if necessary.

DISTINGUISH ANTI-CRAVING DRUGS.

Some drugs are commonly mistaken for anticraving drugs.

Naltrexone, for example, does not buffer withdrawal, but might elicit it. It has no intrinsic agonist action on the loop of reinforcement, and in non-tolerant patients can worsen the opioid function^{3,13,21-23,29,38}.

Clonidine does control withdrawal, but possesses no opioid agonist property.

Neither clonidine nor naltrexone normalise damage from prolonged heroin use – but nor do they claim to.

GHB is useful in the treatment of alcoholism because of its antiwithdrawal and anticraving properties, but seems to display some liability to abuse, with some patients. In other words, some

people display a craving for GHB. Also it cannot normalise the damage done by alcohol intoxication, such as cognitive impairment, but shares the same kind of toxicity^{1,2,19,20,24,28}.

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 might 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 hours. 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.

For us to consider it effective, it must improve the condition of a significant subgroup of patients – this would be not less than 15-20%.

FOUR ‘PHARMA’ STRATEGIES.

There are four therapeutic strategies currently available to treat craving .

One is maintenance (long-term) treatments by long-acting agonist (cross-tolerant) drugs. This approach is viable when agonist drugs which are neither toxic nor addictive either in the short or long term are available. The property of normalising abnormalities produced by chronic intoxication might provide further advantages. This strategy is followed in agonist-maintenance treatment for heroin addiction (methadone-LAAM-buprenorphine).

The second strategy involves maintenance therapies with drugs which have some anticraving properties, but do not produce cross-tolerance. These options are available for the treatment of alcohol and cocaine abuse.

The third strategy is maintenance therapy with substances which 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 might gradually detach the patient from the substance. The main example is represented by naltrexone, when used for the treatment of heroin addiction.

Finally, there is a strategy involving substances which interfere with the metabolism of the abused substance. Its rejection might be favoured, or its effects altered, thus replacing the expected reward with unpleasant, aversive effects. Disulfiram treatment for alcoholism is the best example of this strategy.

The first strategy is 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. And it can prolong the acquired benefit for as long as necessary.

Apart from opiates, antidepressant drugs of different categories display some anticraving properties, especially with alcohol, nicotine or metamphetamine. GHB is used for alcohol abuse, and dopaminergic drugs seem to be useful 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. But 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 addicts. An accurate clinical evaluation and detailed information about addictive histories is always the first crucial step in matching the patient with the treatment.

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He is chair of EAAT, the European Association of Addiction Therapy. Readers can meet him at its 4th annual conference: 13-15 October 2008 Convitto della Calza, Florence, Italy. Details at www.eaat.org

REFERENCES.

This article and the 38 research references cited in it can be accessed at: www.addictiontoday.org/addictiontoday/2008/05/pharmacology-an.html

