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The American Psychiatric Association defined drug addiction as an autonomous mental disorder only in its third edition, taking this step as late as 1980. Before that, substance use and abuse was rated as a social, moral and legal problem — possibly even a medical one, but as having nothing in common with a brain disease. Curiously, in that same year the following statement was written in Kaplan & Sadock’s new edition of their textbook of psychiatry, one of the reference books most consulted by all Western psychiatrists: “When used two or three times a week, cocaine does not cause serious mental problems. Daily use of high doses may be the source of minor psychological disturbance. On the whole, chronic abuse of cocaine seldom represents a medical problem.” In later editions of the same textbook, cocaine addiction is described as a clear-cut psychiatric problem.

Advances in basic and clinical research, and the discovery of neuronal circuitry and the molecular mechanisms underlying addictive behaviours were the basis for the new conception of addiction as a brain disorder: among the milestones reached in making such rapid progress were the findings about brain receptors for opioids and other abused substances, endogenous neurotransmitters able to mimic the effects of exogenous substances, and brain pathways that mediate their effects; these discoveries made it possible to devise a pathophysiological model for addictive disorders.

Despite the clear affinities, and the growing clinical and biological analogies or overlap between certain psychopathological syndromes and their pathophysiological dynamics, it can still be stated that the neuroscience of addiction has developed separately from the field of general mental disorders. As a result, current psychiatry nosography has not gone beyond the behavioural description of addiction yet, nor has it accounted for other levels of psychic expression, such as the affective and cognitive settings.
Give the lack of core non-behavioural psychopathological criteria, other psychic symptoms often fall into other categories, which are assessed as additional or associated disorders (forms of comorbidity). Otherwise, the growing evidence derived from epidemiological, clinical and neurobiological research points to the possibility of surpassing a categorical approach to the classification of mental disorders, which can now be replaced by a dimensional view: in this way, distinct syndromes may share symptoms or have multiple categorical expressions, with no further need to multiply apparent diagnostic entities. In fact, the prevalence of double or triple categorical diagnoses, possessing uncertain autonomy, appears to be the rule, rather than the exception, for clinical pictures commonly defined as comorbidity or dual diagnosis; these clinical pictures may be explained more directly as addiction alone. What is more, the categorical approach fails to clarify a substantial part of concurrent clinical situations, so that any diagnoses that may be formulated largely depend on the clinicians’ impressions.
It’s time to admit the existence of a psychopathology of addiction

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Summary

The frequency of the association between substance use and psychiatric disorders is higher than what might be expected as a result of chance alone; the most frequently associated psychiatric symptoms, syndromes and disorders pertain to the domains of mood, anxiety and impulsivity. There are several reasons for taking these psychiatric manifestations into account when evaluating clinical presentations of substance-use disorders. DSM nosology does not seem to grasp the complexity of the interaction between the psychic structures involved, and neurobiological and physiopathological processes activated by encounters with substances of abuse. Based on neurobiological, epidemiological and clinical indications, an integrated, unified perspective explaining the pathophysiology and phenomenology of addiction has been proposed. The lack of substantial changes in the approach to the psychiatric comorbidity of addiction in the DSM V, despite the plausibility of the hypothesis that there may be a close link between addiction and other specific psychiatric conditions, can be explained by the persistent insufficiency of aetiological and pathophysiological evidence which supports that kind of association. The validation of an articulated clinical condition, encompassing part of the grey area of symptomatology that exists between addiction itself and other ‘independent’ psychopathologies, certainly calls for special attention and specific research programmes.

Key Words: addiction; comorbidity; DSM; nosology; psychopathology; mood; anxiety; impulsivity

The presence of symptoms, syndromes or clearly recognizable psychiatric disorders in people with substance use disorders (whether in the form of abuse or dependence) is very high. Studies in the general population indicate that rates of comorbidity are about 50%, involving additional mental disorders in people with a substance use disorder or additional substance use disorders in people with mental health disorders [50, 51], and those with a higher prevalence for addiction than for abuse [51, 65, 87]. Studies conducted in clinical populations indicate a higher prevalence of comorbid psychiatric disorders (up to 95%) in people with substance dependence [26, 52, 67]. The most common comorbid disorders are anxiety, mood and antisocial personality disorder.

The frequency of comorbid substance use and psychiatric disorders exceeds the level that might be expected on the basis of chance alone. It therefore requires a causal explanation. In this connection, there are four key possible explanations that have generated new lines of research:

• Substance use elicits the onset of other mental disorders;
• Psychiatric disorders make people more likely to use drugs, and progress from use to dependence;
• Substance use disorders and psychiatric comorbid disorders have common causes, whether they are genetically determined or acquired;
• Comorbidity is an artefact resulting from the exclusion of psychopathological symptoms that actually belong to the category of dependence,
but are erroneously attributed to other, independent psychiatric disorders.

There is research that supports each of these four explanations. In this article, however, we will concentrate on the last one – the assumption that much of the psychiatric comorbidity observed in clinical presentations can be attributed to the exclusion from the category of substance use disorders of psychiatric symptoms that belong to drug addiction but are wrongly attributed to concomitant mood, anxiety and impulsivity disorders.

In psychiatry, the idea that major diseases concurrently affect various psychological and psychiatric domains is not new. For example, schizophrenia affects mood, thought, volition and impulse control, while mood disorder affects mood, thought and motivations. Despite this, according to current diagnostic frameworks (ICD and DSM), drug dependence is considered to be an exception to this rule. Substance use disorders are, in fact, conceptualized in a similar fashion to the so-called behavioural disorders such as ADHD, the description of which is based solely on observable behaviour.

We will now examine how this situation has emerged in drug dependence with reference to the mostly commonly used diagnostic system: DSM.

1. Evolution of the concept of addiction and its diagnosis in the DSM system

Dependence on psychoactive substances is considered a mental disorder and, as such, it is described in a specific section of the DSM (DSM-IV-TR). This has not always been the case. Advances in our knowledge of the neurobiology, pathophysiology and clinical features of addiction have led to important changes over time in the classification of substance use disorders that have had the consequence of making changes necessary in how they are diagnosed.

In the two earliest editions of the DSM (I and II) [1, 2], drug dependence did not appear to exist except as a symptom of an antisocial personality disorder. Drug dependence was first recognized as a disorder in its own right in DSM-III (APA, 1980), which distinguished between:

- Substance dependence, which is distinguished by the presence of ‘physical dependence’ involving tolerance (the need to increase substance dose to make it possible to continue achieving the desired effect) and withdrawal (signs and symptoms opposite to those of the drug);
- Abuse, whereby drug-seeking and drug use, despite being detrimental to social and personal functioning, were not associated with tolerance and withdrawal (being referred to as ‘psychological dependence’).

This diagnostic framework is consistent with the presumption that the substance is the cause of the addiction. On this view, the development of dependence is correlated with the duration and intensity of drug use. The individual might do no more than passively be a spectator of this transition to dependence, but might otherwise exercise voluntary control over his/her desire to repeat the experience.

In the case of ‘physical dependence’, medical interventions could play a role in facilitating abstinence from substance use, whereas ‘psychological dependence’ was not considered to raise any medical problems.

Over time, this approach was found to be inconsistent with evidence from clinical practice and research which, beginning in the Seventies, had been accumulating: the very high vulnerability to relapse among ‘detoxified’ drug users, which was supported by animal research; the presence of strong forms of dependence on substances such as cocaine of sufficient severity to lead to serious health and social consequences, which, paradoxically, are accompanied by nuanced forms of abstinence or none at all; advances in research, including the discovery of receptors for various drugs of abuse, the molecular correlates of their action on the brain, and neural circuits involved in addiction, but not necessarily in tolerance.

Taken together, these observations indicated that the true basis of addiction was ‘psychological’. With the DSM-III-R [3], the diagnosis changed, and tolerance and withdrawal were no longer prerequisites for a diagnosis of drug dependence. The description of dependence was fundamentally linked with the centrality of the substance in the life of an individual: in other words, it could be applied to those seeking the effects of the drug as the central priority in their personal life. Symptoms such as the disruption of important social, occupational or recreational activities arising from the use of substances, their continued use despite the emergence or exacerbation of psychological or physical health problems caused by the substance, or an inability to control drug use, were viewed as sufficient to warrant a diagnosis of dependence, even in the absence of tolerance and withdrawal.

More recently, with the publication of DSM-IV [4] and the DSM-IV-TR [5], there have been further changes that have not substantially modified the classification of substance use disorders, except for pro-
viding some useful ways for distinguishing some sub-
categories of comorbid disorders on the basis of their
“independence” from drug addiction.

In all editions of the DSM, the psychiatric symp-
toms that do not belong to the strictly behavioural do-
main of the use of the substance remain preliminarily
excluded from the symptomatology of substance use
disorders. To be consistent with the DSM classifica-
tion, the psychiatric symptoms that are present in a
person diagnosed with drug dependence must be kept
separate in other diagnostic categories (such as anxi-
ety disorders and mood). These symptoms may be
causally related to the effects of the substance, but
they are not included as part of the diagnosis of de-
pendence (or abuse).

Despite the longstanding atheoretical approach
taken to mental illness in the DSM, the diagnosis of
drug dependence, starting with the DSM-III, has been
strongly influenced by the bidimensional approach
developed by Edwards and Gross in alcoholism [39].
When adopting this approach, two dimensions can be
distinguished: the first relates to the symptoms of ad-
diction, and the second to the physical, mental and
social consequences of substance use.

2. Advances in neurobiology

Neurobiological research designed to elucidate
the role of brain structures and functions in various
mental illnesses has provided abundant evidence of
the close links between different forms of addiction
(whether substance-related or alternative forms) and
other major psychiatric conditions related to mood,
anxiety and impulse control.

2.1. The psychological effects of drugs and their
impact on the brain

Overall, the acute psychological effects of drugs
of abuse can be seen as the result of interference, due
to their similarity to endogenous neurotransmitters
that act on specific neuronal circuits. Heroin produc-
es relief from anxiety, sedation and heightened mood
through the activation of opioid receptors; cocaine
produces a state of alertness, euphoria and anxiety,
increasing the availability of dopamine, noradrena-
line and serotonin, and so on.

The adaptation of the brain to repeated substance
use is more complex and involves multiple neurobio-
logical processes. In particular, the disruption of syn-
aptic transmission due to substances of abuse leads
to changes at the intracellular molecular level which
result in the modification of gene expression, as well
as the structure and morphology of neurons, creating
a form of neuroplasticity [69, 70]. Early transcription
factors such as CREB, BDNF, and cFOS are involved
in these processes. These and other important chang-
es in specific brain areas can help to explain not just
the ‘core’ symptoms of addiction, but also its associ-
at ed psychopathology.

Addiction results from a complex interaction be-
tween drugs of abuse and their biological substrates
in which the brain plays an active role; this interac-
tion involves inherited, acquired and environmental
predisposing factors. In this interplay, pre-existing
neurobiological factors and those due to the effect
of substances interact with and influence each other,
leading to clinical features that are not simply the sum
of the preceding psychopathology and subsequent use
of the substance.

A brief overview of the main advances in the
neurobiology of addiction is useful in understanding
the contribution of biological processes to the defini-
tion of the pathophysiology of this condition, and in
providing the background information needed to ac-
quire an understanding of the strong ties that connect
addiction with other mental health disorders.

2.2. The current neurobiological framework of
addiction

Considerable scientific evidence has established
the role of the limbic system in the neurobiology of
drug dependence [33, 54]. More specifically, it has
been demonstrated that the self-administration of
drugs of abuse entails, both in the laboratory and in
humans, increases in the concentration of dopamine
in the synaptic space within the limbic region, in a
specific part of the ventral striatum: the shell of the
nucleus accumbens [32, 33, 36, 79]. Through this
action, substances of abuse appear to interfere with
an adaptive biological process that is activated in
response to significant events and motivational in-
fluences. It has, in fact, been demonstrated that the
increased availability of dopamine in the shell of the
nucleus accumbens is associated with the activation
of processes that attribute “salience” to stimuli asso-
ciated with eating behaviour, and with the sexual and
competitive behaviours that are necessary to ensure
the survival and well-being of the individual and the
species. The increased release of dopamine seems
to facilitate associative learning connected with the
stimuli, such as the sight or smell of a food, that sig-
nal the potential for gratification of a primary survival
need [20, 48, 84]. These stimuli that have become salient are stored in the long-term memory. In the case of substances of abuse, this salience seems to be responsible for the impulsivity that is characteristic of addictive behaviour, where the stimuli, events and situations that are naturally or artificially associated with the effect of the substance will become conditioned stimuli capable of inducing craving and automatic responses to seek and use the substance [49].

This learning process is accompanied by persistent changes in the brain that can be observed at the molecular level in areas implicated in memory processes (in animals and humans), such that the presentation of stimuli previously associated with drug abuse can influence behaviour even long after drug use has ceased [27, 43, 64, 69, 82, 88].

In addition to these deep limbic regions, other cortical regions, such as the anterior cingulate and orbito-frontal cortex, are involved in the activation in response to salient stimuli and, more generally, in important functions of inhibitory control on impulsive and addictive behaviour [31, 44, 56, 90, 92, 95, 97]. The pre-frontal cortex controls a wide range of what are known as “executive” and “reflective” functions, including the ability to differentiate between good and bad, good and better, similar and different, and the ability to foresee the future consequences of current activities and to work towards a specific goal. In addition, the prefrontal cortex is involved in “social control”, including the ability to suppress impulses which, if not controlled, can lead to undesirable consequences or illegal behaviour. The chronic consumption of drugs is associated with the presence of functional and molecular changes in these prefrontal areas [14, 15, 17, 98]. Recently, the availability of neuroimaging techniques has made it possible to visualize the correlation between the activation of these areas with the subjective experience of craving in individuals exposed to appropriate stimuli.

2.3. The pathophysiology of psychiatric symptoms associated with drug dependence

The regions and brain circuits involved in the pathogenesis and maintenance of addictive behaviours are normally dedicated to performing physiological functions that relate to survival and quality of life. Among these functions are those involved in the regulation of mood, anxiety and impulse control. We will now examine how closely and in what way the regions and brain systems involved in the process of addiction are also involved in the pathogenesis and maintenance of symptoms belonging to the psychopathological dimensions of mood and impulse control.

2.3.1. Addiction and mood regulation

One indicator of the close relationship between the regulation of mood and addiction is that both involve common brain areas such as the prefrontal cortex and orbitofrontal regions, and limbic areas [11, 34, 77]. Neuroimaging studies conducted in manic patients have shown an attenuation of function in cortical areas within the lateral and medial prefrontal and limbic regions [12, 13, 24, 25, 38, 40, 66]. Other studies have shown a reduction in blood flow and glucose metabolism in the dorsolateral prefrontal cortex, the frontal cortex and medial orbitofrontal cortex [10, 13, 18, 35, 37, 62]—abnormalities that are shared with substance use disorders. In addition, neuropsychological tests in patients with mood disorders have shown similarities with substance use disorders, indicating a common deficit in these cortical regions [45, 55, 80].

Alterations of the dopaminergic system have also been observed in addiction [89, 91, 93] in a way consistent with the mood alterations that are observed in drug users. Of relevance here is the “reward-deficiency syndrome” that has been described in patients who have chronically abused drugs; it is distinguished by reduced reactivity, sadness and anhedonia, and an inability to draw gratification from stimuli that are not drug-related [22]. Dysregulation of the dopaminergic system is also involved in the pathophysiology of mood disorders [19].

The neuroendocrine stress system is heavily involved in anxiety and mood disorders, but also in drug addiction. Dysregulation of this system places the drug user in a fragile emotional state and increases his/her vulnerability to psychological and environmental triggers for relapse and the emergence of other psychiatrically relevant conditions [41, 68, 83, 86, 96].

Among the changes that occur in the brain of the drug user, some involve molecular changes in the areas that control self-administration behaviour, such as the shell of the nucleus accumbens. In this area, molecular processes that have been described include the activation of the 3’5’-monophosphate response element binding protein (CREB). CREB is a regulator of gene transcription, which, when activated, increases the expression of dynorphin. Dynorphin is an endogenous kappa opioid receptor agonist. Its activation leads to the appearance of anxiety, depression and dysphoria. The function of CREB in the nucleus
accumbens has been described as that of a “hedonic thermostat”: increased expression of the CREB increases the transcription of dynorphin which, in its turn, leads to aversive, depressive-like states (dysphoria, anhedonia). Conversely, a reduced expression of CREB reduces the transcription of dynorphin, with consequent elevation of mood [28, 29]. Consistently with the role attributed to CREB in regulating mood, tricyclic antidepressants have been observed to attenuate the activation of dynorphin due to stress [30].

2.3.2. Addiction and impulse control

People with drug problems often have difficulty in making appropriate choices. They tend to prefer a small, immediate reward and avoid the work required to obtain a larger, more stable one. This has been observed in various areas (e.g., money, health) and for a variety of drugs of abuse. In behavioural tests of “delay discounting”, users of nicotine, alcohol, and heroin have been shown to be less willing to delay rewards compared with non-drug-using control subjects [21, 53, 57, 75, 76, 94]. The performance of smokers and users of alcohol, cocaine and heroin in other tests used to measure impulsivity, such as the Iowa Gambling Task and the Stroop test, similarly indicate an increase in impulsivity [21, 42, 53, 57, 75, 76, 81, 94].

As is true of mood regulation, the regulation of impulsivity has been linked with alterations in the brain areas and circuits that are also involved in drug dependence behaviours and other pathologies. These include the limbic regions of the nucleus accumbens, amygdala, the ventral pallidum, and their associated neural circuits, which are part of the “impulsive system” [14, 63]. As observed with the Iowa Gambling Task, damage to these regions may result in loss of the ability to pursue long-term rewards and accurately perceive risks associated with the pursuit of immediate gratification [16]. Another brain region associated with impulsivity is the prefrontal cortex (PFC). People with lesions of the PFC show alterations in decision-making and irresponsible behaviour in a number of areas of social functioning (e.g., family relationships, financial decisions), including substance abuse and other impulsive behaviours.

Research evidence suggests that alterations in the impulsive and reflective systems facilitate the use of drugs and the development of drug dependence. The neurobiological processes that underlie addiction cause further alterations of these systems, leading to further ‘loss of control’ over drug-using behaviour and a more general reduction or loss of behavioural inhibitory control.

3. A longitudinal view of the psychopathology of addiction

Evidence from basic science and clinical research is consistent with a longitudinal view of the psychic structure of addiction, to which different psychopathological components contribute over time. The four key components are: pre-existing psychological and psychiatric conditions; the effects of substances; the addictive processes; and psychiatric consequences. Each of these components has its own unique neurobiological substrate, psychopathology,

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The first component centres on the condition of psychic fragility that precedes the initiation of drug use, and is grounded on the psychic precursors that facilitate use of the drug and the progression from use to abuse and, ultimately, to dependence. Its psychopathological expression consists of temperamental traits, psychiatric symptoms and subthreshold disorders. The corresponding neurobiological substrate involves dysfunctions in the brain reward systems and/or stress in brain areas involved in impulse control and in other molecular changes (e.g. CREB) that relate to the areas and circuits most directly involved in the genesis and maintenance of addiction. The corresponding clinical manifestations include impulsivity, behavioural disinhibition, novelty-seeking, antisocial behaviour, mood instability, temperamental traits (featuring hyperthymia and cyclothymia), other psychiatric symptoms attributable to sub-threshold bipolar disorders, and other disorders classified as externalizing (including ADHD and impulse control disorders) [6-8, 46, 59, 74, 78, 85].

The second component is focused on the use of substances, for which the corresponding neurobiological substrate is determined by the binding of substances with specific neurotransmitter systems and the consequent involvement of specific brain circuits (often sharply different for different substances, but with some overlap). Psychopathological features arise from the acute effects of substances and substance withdrawal that result in symptoms of anxiety, depression, dysphoria, excitement, disinhibition, and so on. The symptoms of intoxication are mostly transitory, but the symptoms of abstinence (involving a prolonged interaction between the substance and the neurobiological substrate) tend to be severe and long-lasting.

The third component comprises the addictive processes. In this case, the neurobiological substrate is marked out by: (i) dysfunction of the mesolimbic dopamine circuit and, more generally, the circuits and areas that are involved in the endogenous reward system, (ii) dysfunction of the prefrontal regions that are involved in impulse control and decision making, and (iii) long-term molecular changes. These changes are determined not only by the direct effect of the substances, but also by their deep and prolonged interaction with the biological substrates mentioned above, which are also influenced to varying degrees by the terms of component 1. The psychopathology comprises two psychological symptoms that are related to the core symptoms of addiction – craving and loss of control. The psychiatric symptoms are more directly related to drug-seeking behaviour, such as continued use despite adverse consequences, reduction or termination of other activities, and so on, but also impulsivity, loss of control, anxiety, instability of mood and dysphoria.

The last component (occurring after the others) consists of the psychiatric consequences, preeminently the clinical exacerbation of symptoms and syndromes in the areas of impulsivity and control, anxiety and mood (craving, impulsivity, loss of control, dysphoria) and can be accounted for in psychopathological terms by the interaction between predisposing conditions (set out in component 1) with the addictive processes (set out in component 3). From a neurobiological perspective, the pathophysiology of these consequences is supported by positive feedback that is triggered by basic neurobiological alterations and abnormalities, and by those that trigger and consolidate the development of drug dependence, while involving the brain regions associated with gratification, impulsivity and the stress system, among others. [73].

4. Where are we going?

Release of the DSM-V is scheduled for spring 2013. This edition of the Manual will provide a major reworking of the section dedicated to substance use disorders, starting with the name. In fact, there has been considerable debate about whether the term “dependence” should be replaced by “addiction”. The use of the first term actually generates confusion between (a) “physical dependence”, which is considered to be the result of a normal adaptive process of the organism, due to tolerance and covering a range of other types of medication (including antidepressants, anti-hypertensives and beta-blockers), and (b) addiction, which is understood as a behavioural disorder. This confusion has impacted negatively on the management of pain because it exposes patients to unnecessary delays in the administration of opioid medications and in the use of appropriate doses arising out of concerns about the risk of developing addiction. A second important point is the inappropriateness of maintaining a division between the diagnosis of (a) abuse and (b) dependence. As mentioned earlier, this division is based on the conceptualization of Edwards and Gross, which does not seem to be supported by the current evidence. Unlike the diagnosis of dependence, which has good/excellent test-retest reliability, the diagnosis of abuse has modest and variable re-
liability [47]. On the other hand, additional tests based on factorial analysis, latent class analysis and response theory have consistently suggested the use of a single diagnostic category with different severity levels based on the number of diagnostic criteria that are applied in each case.

A third important discussion has focused on the inclusion of behavioural addictions in the same diagnostic category as drug dependence. This change would involve shifting these disorders from the category of impulse control disorders to that of dependencies. It is justified by the common neurobiological basis and the pathophysiological, clinical and therapeutic similarities [9, 23].

A fourth proposal for the revision concerned the inclusion of craving in the diagnostic criteria: craving is widely used in basic research and clinical practice (e.g. as a prognostic marker) and is present in ICD-10, but not in the DSM IV.

With regard to comorbidity, the proposals included a more stringent definition of the criteria used to classify comorbid disorders as either dependent or independent [71], and the mention in the text (not including the criteria) of the presence of symptoms of anxiety, mood and impulsivity where these are plausibly linked with drug dependence, but are insufficient to warrant an additional diagnosis [73].

In June 2012, the latest draft of the DSM V released for further review put forward a proposal to eliminate the use of the terms “addiction” and “dependence”. The chapter in question is entitled “Substance use and addictive disorders”. It also proposed the concept of a single disorder resulting from the merger of the criteria for abuse and addiction. The past criterion related to illegal behaviour was removed, and craving was introduced as a new criterion. Eleven criteria were proposed for the diagnosis of substance use disorder. The number of criteria present will determine the judgment of severity of the disease for each individual: mild (2-3 criteria), moderate (4-5 criteria), severe (6 or more criteria).

Regarding the management of associated psychopathology, the absence of significant changes, despite the plausibility of a close link between addiction and other psychiatric conditions, can be explained by the insufficiency of evidence (preclinical, clinical, neurobiological and psychological/psychiatric) in support of an aetiology and pathophysiology that justify the association. Despite the plausibility of a link between mood disorders, anxiety, and impulse control, there is a need for further in-depth research to deepen our understanding of the relationships involved and validate a potential expansion of diagnostic criteria to encompass these psychological dimensions.

Examples of research designed to clarify the specific psychopathological aspects have been published recently [58, 60, 61, 72]. These studies have focused on verifying, with specific reference to addiction, which psychopathological dimensions and symptoms are consistently correlated and are found to cluster together in specific clinical conditions. Another focus of attention has been to what extent these clinical profiles can be considered typical of drug addiction, or whether they are consequences of the pathoplastic effect of addictive processes on pre-existing psychiatric precursors. In this regard, it should be noted that the DSM system includes only two possible causes that might explain comorbidity. In that system, the comorbid psychiatric disorder can be considered only (a) as a consequence of the effect of substances (in which case the psychiatric disorder has been induced), or (b) as an independent primary disorder. The third possibility – that the psychiatric disorder might be the cause of addiction (in which case the addiction has been induced by another psychiatric disorder) – is not even considered.

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Drug addiction: affective temperaments as risk factors

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Summary

The scientific community has recently examined whether correlations exist between affective temperaments and substance abuse disorders. We will try to summarize what is presently known about the nature of these relationships. After reviewing the theory of affective temperaments of Akiskal and Mallya, we will discuss affective temperaments in heroin addicts and alcoholics, with the aim of providing an “at-risk temperamental profile” for the development of substance abuse disorders. A working hypothesis is then formulated to help explain how temperamental profile may promote the initiation of substance use and contribute to the development of addiction.

Key Words: Affective temperaments; heroin addiction; alcoholism; personality; temperaments

1. The Affective Temperaments

1.1. Theoretical construct

The term “temperament”, as well as the noun and the verb “temper”, derive from the Latin verb “temper”, which means ‘to mix’; “temperament” has multiple potential meanings in different theoretical-philosophical contexts. The scientific community has not yet resolved disagreements that centre on the terms ‘temperament’, ‘character’ and ‘personality’. Although several studies have attempted to trace the boundaries between these entities, they are often confused.

In particular, ‘temperament’ refers to the structure (genetic or constitutional) that determines energy levels and the quality of the individual’s mood. ‘Character’ contains all the acquired characteristics that allow the adjustment of the individual to the values and norms of the society in which he/she lives. Lastly, “personality” includes traits that refer to stable ways of perceiving, thinking and relating within the individual and with respect to the external environment.

According to Hippocrates, the Greek philosopher and father of medicine, the four basic temperaments should be considered an expression of the mixture of the four ‘humours’, or body fluids. They lead to a contrast between pairs of qualities: hot and cold, and wet and dry. These qualities also correspond, on one hand, to the major constituents of the universe (earth, water, fire and air), and, on the other, to the four classic temperaments.
According to Akiskal, temperaments are the basic phenotypes that reflect the genetic disposition to bipolar disorders [3, 4]. This model is confirmed by a variety of epidemiological observations. In fact, the family history of people who show an affective temperament is similar to that of psychiatric patients hospitalized for severe bipolar disorder. In addition, one third of monozygotic twins who turned out to be discordant with the other twin, as to the presence or absence of bipolar disorder, manifested severe temperamental disorders. Lastly, a high frequency of affective temperaments is observed in the children of bipolar patients who are assessed during puberty [47, 86].

There are four classically recognized affective temperaments.

The depressive temperament is distinguished by low mood, introversion, low energy, a strong need for sleep, lack of self-esteem and weak confidence in one’s abilities, together with a tendency to ruminate [5, 9, 14, 81].

The distinctive features of hyperthymic temperament are optimistic mood, high energy levels, little need for sleep, high self-esteem and great confidence in one’s abilities. Hyperthymic individuals are equipped with resilience. This is typified by their ability to cope with traumatic events in a positive manner and reorganize their lives positively in the face of difficulties, as well as in their capacity to draw from those difficulties the motivation to attain new goals. Hyperthymic individuals also possess assertiveness; in other words, they have the ability to express their emotions and opinions clearly and effectively without offending or attacking their counterparts. This behaviour ultimately allows a person to defend his or her point of view without excessive anxiety [5, 12, 14, 81].

The cyclothymic temperament includes rapid and continuous fluctuations in mood, energy levels and sleep-wake rhythms. These fluctuations may be spontaneous or be caused by life events that are subjectively perceived as stressful. The reactivity of the individual’s mood to events is a typical feature of cyclothymia, and is often present as a stable trait from childhood. It brings these individuals on one hand to react to favourable events with excessive zeal, enthusiasm and initiative, and, on the other, to collapse in the event of stressful events, expressing deep feelings of despair, sadness and fatigue. Another feature of cyclothymic individuals is their interpersonal sensitivity, i.e. their tendency to perceive themselves as not fully capable of managing relationships with others. This predisposition, strengthened in part by low self-esteem, results in the individual being sensitive to the expression of rejection, judgment and criticism by others [5, 12, 14, 81].

The irritable temperament displays a tendency towards aggression and conflict. Subjects with this temperament are classified as irritable, complain about but react to external events, while showing (in common with hyperthymic individuals) high levels of energy. Considered a mixture of traits belonging to the other types of temperament, irritable temperament is less well defined than the other three [14, 81].

Recently, the construct of the Phobic Anxious temperament has been added to the four classic temperaments. It consists of a high level of sympathetic activity, marked fear of disease, hypersensitivity to separation, difficulty in leaving a familiar environment, need for reassurance, and hypersensitivity to drugs and prescribed medications [77].

1.2. Assessment of affective temperaments and psychometric properties of the TEMPS

In validation studies for the questionnaires designed to measure the temperament traits both of psychiatric patients and healthy subjects, i.e. the “Temperament Evaluation of Memphis, Pisa, Paris and San Diego” (TEMPS), multifactor analysis showed that the hyperthymic temperamental type correlated negatively with scores for the other temperaments, whereas cyclothymic temperamental traits showed positive correlation with depressive, irritable, and anxious temperament scores. This reveals a dichotomy based on the existence of two dominant dimensions. On the one hand there is cyclothymia, which overlaps with dysthymic-dysphoric-anxious dimensions; on the other, there is hyperthymia, an independent entity distinct from all the others [8, 13].

The sample that has allowed the validation of the TEMPS-I, the Italian version of the questionnaire, consisted of 1,010 Italian students aged between 14 and 24. The hyperthymic type of temperament was the most commonly represented in this sample of young people, followed by the depressive and the cyclothymic. Only a few subjects were classified as irritable, suggesting this temperament type is a less robust construct [14, 81].

In evaluating the reliability of the TEMPS-I, the cyclothymic temperament type emerged as the most stable, when we reassessed the various temperament groups within two years of the first evaluation. The total number of subjects with this characteristic rose, giving rise to the notion of ‘stable instability’.
ently with this assumption, a certain number of those originally classified as depressive and hyperthymic temperament types were reallocated to the group with a cyclothymic temperament, while the irritable temperament seems to be less stable, confirming the lower validity of this construct. The best predictor of the stability of the cyclothymic temperament, at least in the Italian population, was male gender [80].

1.3. Affective temperaments among normal and clinical populations

What is the role of affective temperaments? Several authors have tried to answer this question by analysing the temperamental profile of individuals belonging to non-clinical and clinical populations.

In the field of psychopathology, affective temperaments play a dominant role, influencing mood disorders in terms of clinical features, natural history, family history and axis I and II comorbidities. The cyclothymic and hyperthymic temperaments seem to underlie two different variants of bipolar disorder; the first shows rapid fluctuations in mood and emotional instability, whereas the second displays hyperactivity, high levels of energy and emotional intensity. These observations are consistent with the hypothesis that affective temperaments, particularly cyclothymia, can be used as intermediate indicators for genetic susceptibility to mood disorders [10, 26, 79]. With regard to mood disorders, affective temperaments appear to influence the pathogenesis of mixed states, especially when a major affective episode occurs in a person with an opposite temperamental profile (e.g. a manic episode affecting dysthymic temperament, or a depressive episode affecting hyperthymic temperament) [78]. Cyclothymia seems to play a destabilizing role in episodes belonging to either of the two polarities making them responsible for high rates of comorbidity with anxiety disorders and personality. Apart from full-blown cases of bipolar disorder, affective temperaments have allowed the identification of milder forms of bipolar disorder, which are currently considered the most common phenotypical expressions of bipolarity. This explains why, in making any assessment, it is crucially important to assess the behavioural patterns of patients outside their major episodes [3, 5].

In the study of normal populations, affective temperaments have been shown to influence career choices in line with their hypothesized adaptive role [6, 15]. In particular, the depressive temperament has frequently been observed among doctors and nurses. Hyperthymic temperament appeared as the dominant temperamental profile of managers, businessmen, journalists and military personnel, confirming the role played by this temperament in promoting leadership. Lastly, cyclothymia was observed among artists and architects, confirming its association with creativity. Of particular interest is the interaction between affective temperaments and obsessive personality traits, which modulate the impact of temperament on career choices. It has been observed that in the presence of high levels of obsessiveness, hyperthymic individuals have more frequently chosen careers as managers, and cyclothymics as architects. On the other hand, when the obsessive nature of personality is low, hyperthymic individuals more frequently choose a career as an entrepreneur, whereas cyclothymic individuals more frequently choose to be an artist. This suggests that obsessive traits, to the extent they are present, mitigate the expression of creativity in cyclothymic individuals and the appetite for risk in hyperthymic individuals [16, 37]. A clear example of how temperaments influence choice of profession is provided by an analysis of temperamental profiles in the military. Candidates for entry into the Italian Air Force and Navy showed a clear tendency to be hyperthymic [57]. The role of hyperthymia in these individuals seems to go beyond the boundaries of gender differences. In the general population females tend to differ from males in the frequency of their cyclothymic traits [11], but this difference was not observed in this military sample, showing that these women had what is often considered to be a naturally male temperament [56].

Ultimately, it is assumed that the affective temperaments carry out, within the normal range, an adaptive role related to the sphere of aptitudes and aspirations that influence career choices. By contrast, in the clinical realm, temperaments play a role in the pathogenesis of major affective disorders, and milder forms of bipolar disorder, as well as that of anxiety and personality disorders.

By now the correlation between substance abuse and bipolar spectrum disorders has become generally accepted [17, 23-25, 58, 62].

2. Substance Abuse Disorders and their relationship with bipolar disorder

Substance abuse disorders comprise a set of maladaptive behavioural patterns and alterations of the body, termed abuse, dependence and addiction. The term “substance abuse” refers to the uncontrolled
use of substances without any medical supervision, which continues despite potentially damaging consequences for the individual, as a result of the effect of these substances on the system of gratification. Abuse must be distinguished from the use of a stimulant substance, since it involves a first step towards the loss of control over substance use [31, 32, 52, 71].

‘Addiction’, which is often referred to as ‘physical’, involves the progressive adaptation of the organism to the pharmacological action of the substance. This adaptation becomes apparent in the phenomena of tolerance and withdrawal. Tolerance means that, after repeated exposure, a given dose of the substance will produce a milder effect. Withdrawal means that an abrupt and sudden discontinuation of use will result in a withdrawal syndrome. Such homeostatic adaptations are underpinned by a reduced responsiveness of the receptor after over-stimulation for long periods, down-regulation of the receptor itself, and the development of an autonomic response of equal magnitude but of opposite polarity with respect to withdrawal from the substance. The development of addiction is very common for drugs used in chronic treatment (e.g. benzodiazepines, psychostimulants, aminophylline, cocaine, beta-blockers) [31, 32, 52, 71].

Drug addiction (from the Latin “adducere”, meaning ‘slavery’) is a disease characterized by adaptive and long-lasting behavioural patterns. Changes in neuronal circuits of the limbic system (especially those brain functions that regulate emotions and motivation) support drug-seeking, which persists despite the adverse consequences of drug use on the individual’s health and social circumstances (such as family, work and education), even when the capacity of the substance to produce pleasure is lost [41, 45, 46, 69, 70]. Key elements of this drug addiction include drug-craving and the phenomenon of relapse. Craving can be defined as the extreme appetite and loss of control that affected individuals develop towards substance abuse, and is underpinned by the activation of excitatory motor neurons that motivate drug-seeking behaviour. Recidivism represents the tendency to relapse back into uncontrolled use of the substance of interest, despite a strong intention to abstain. It can occur even after many years of abstinence. It is important to note that the pathology of addiction does not necessarily require the establishment of dependence, which emerges only in the case of intrinsically addictive substances such as alcohol and heroin [31, 32, 52, 71] and, in a much milder form, with other types of substances (stimulants and hallucinogens).

The populations that are most vulnerable include young adolescents, probably due to the greater plasticity of their neural reward circuits, and the lower trophism of their corticofrontal inhibitory areas. Heroin addiction is a disease with a high rate of psychiatric comorbidity. At the Psychiatric Clinic of the University of Pisa, we studied our first 90 inpatients with heroin dependence. Many patients had associated disorders. In particular, it is notable that bipolar disorder type I was diagnosed more often than non-bipolar affective disorders (25 patients with bipolar disorder, as opposed to 6 with non-bipolar depressive disorder). Psychotic and anxiety disorders were diagnosed less frequently [63].

In outpatient settings, we studied 40 consecutive patients. In this sample, bipolar and depressive disorders were diagnosed in equal numbers, but the diagnosis of bipolar disorder type II was even higher than that of bipolar disorder type I (16 patients with bipolar disorder and 17 with non-bipolar depressive disorders; among bipolar patients only one received a diagnosis of bipolar disorder type I, compared with 14 patients diagnosed as bipolar II) [55].

If, however, one considers the presence of an affective temperament as a sign of bipolar disorder, the diagnosis of bipolar disorder in heroin addicts increases from 62% to 97%, and only one patient in the consecutive series of 40 showed no affective disorder, family history for affective disorders, or the presence of any affective temperament [55].

When we subsequently investigated the prevalence of suicidal ideation and its risk factors in a sample of heroin addicts requiring opioid therapy, we found a strong correlation between belonging to the bipolar spectrum and the tendency to suicidality. Depression and hostility, as part of the bipolar spectrum, along with social and employment issues, appear to be independently associated with suicidal ideation [61].

Lastly, there is a specific correlation between bipolar disorder and cocaine use, as an attempt to elevate or maintain bipolar individuals’ high levels of arousal [58]. Cocaine abuse by bipolar heroin addicts may serve, in the first instance, as a way of balancing mood to suppress the underlying arousal levels and the related thymus fluctuations. In other words, subthreshold bipolarity, including its temperamental manifestations, appears to initially promote the abuse of heroin, and then go on to expose an overt bipolar disorder, possibly complicated by the onset of a manic or mixed episode, with the possible presence of psychotic symptoms [59]. Something similar seems
to happen with the use of cocaine by alcoholics. The use of alcohol, especially among the young, can be seen as a tool to keep a chronic dysphoric temperament under control. The attempt to induce and maintain a hypomanic state through the use of cocaine is what appears to lead to a full-blown bipolar disorder. In this context, the use of alcohol may encourage the use of cocaine as an antidote to the sedative effects induced by alcohol [74].

3. Can the role of bipolarity in chronic substance abuse be confirmed at the temperamental level?

The affective temperaments have helped to demarcate the edges of the spectrum of bipolar disorders; the resulting knowledge contributes to our understanding of the pathogenesis of attenuated forms, which are now considered the most prominent phenotypical expressions of bipolarity [3, 5].

The correlation between substance abuse disorders and bipolar disorder is widely accepted by the scientific community. As previously stated, in the case of heroin addiction, bipolar disorder type II is the most frequently diagnosed mood disorder in outpatient settings, together with depressive disorders, whereas bipolar disorder type I is the disorder that is most frequently diagnosed during hospitalization [60].

Given the involvement of affective temperaments in the bipolar spectrum, and the correlation between substance use disorders and bipolar spectrum ones, we wondered whether this correlation could be extended from the pathological level to the temperamental affective profiles that we have seen widely represented not only in populations of psychiatric patients, but also in those of healthy subjects [60].

The question that ultimately calls for an answer is the following: is there a temperamental profile that brings with it a high risk of the development of the disease of drug addiction? To be able to answer this question, we studied the temperamental profile of heroin addicts and alcoholics in long-term treatment.

3.1. Temperamental profile of heroin addicts

In a study on affective temperaments among heroin addicts and controls, we found that only the traits of cyclothymic-irritable type show significant differences between the two groups, while no difference exists for the hyperthymic or depressive temperament. This difference does not seem to depend on the presence or absence of a dual diagnosis within the heroin-addicted sample. In fact, when comparing the affective temperaments of heroin addicts with or without psychiatric comorbidity with a control group, the cyclothymic irritable temperament was able to differentiate heroin addicts from controls, but not heroin addicts who had psychiatric comorbidity from those who did not [60].

The importance attributed to drug addiction in psychiatry has been gradually increasing over the years, evolving from a condition considered to be symptomatic of a personality disorder [1] to a distinct class of disorders [2]. The ‘original sin’ of the first two editions of this manual (i.e., in classifying addiction as a symptom of personality disorders) has been that they actually encouraged studies that, in populations of drug addicts, sought for the presence of axis II disorders. If we refer to the diagnostic criteria of the DSM, a large number of patients who were abusing cocaine or heroin showed a set of personality traits that were mostly attributable to cluster B (dramatic trend), with a high prevalence of antisocial and borderline types. The specificity of the diagnosis, compared with that of drug addiction, remains doubtful. In fact, at least one axis II disorder may be diagnosed in 25-91% of drug users, with high variability between studies [18, 27, 66, 84], but with a constant prominence of borderline (5-65%) [18, 49], histrionic (12-64%), antisocial (3-55%) [18], and passive-aggressive features [18, 50]. Even the traits belonging to cluster C (tendency to anxiety) were not a rare observation (28%), especially if patients were of the avoidant and dependent type (35%) [68, 90]. Cluster A traits (indicative of a tendency to eccentricity) were less common, but comorbidity between substance abuse and schizotypal personality disorder is a quite common finding (up to 41%) [18].

On the other hand, even comorbidity with Axis I disorders is very common, particularly with regard to mood disorders; on this relationship there is general agreement in the scientific community [55, 64, 72, 83, 85, 89]. Aspects of personality, as mentioned above, are in line with the profiles of comorbid axis I disorders and they qualify in terms of major mood disorders.

The concepts of temperament and personality, though they are often misleadingly confused, cannot be superimposed. Scales commonly used for investigations of personality such as the “Eysenck Personality Inventory” [36], even if they have been derived from the field of experimental psychology, are not used routinely as tools in clinical practice. Similarly,
some models of temperament, like that of Cloninger [28], are not based upon the classic symptomology of mood disorders. Associations have, however, been established between the temperaments described by Cloninger, and affective temperaments according to Akiskal [54], which show a stronger link with the clinical setting.

The depressive temperament of Akiskal is correlated with the “Harm Avoidance” of Cloninger. Similarly, the hyperthymic temperament is correlated with “Novelty Seeking”. The cyclothymic temperament is correlated with both dimensions. The “Reward Dependence” and “Persistence” dimensions of Cloninger, and irritable temperament of Akiskal, showed no correlation.

The “Sensation Seeking” profile described by Zuckermann [91, 92] looks very similar to the Novelty Seeking dimension [29, 30], and both seem to be related to a propensity to abuse substances [21, 53, 91], in line with their suspected relationship with the mesolimbic dopamine system [19, 39] and the opioidergic system [35, 87]. Our observations are consistent with the published literature, in particular the findings reported by Maremmani et al. [54] on the correlations between hyperthymic and cyclothymic temperaments, on one hand, and Cloninger’s temperamental dimensions, on the other. In a more theoretical vein, the hyperthymic novelty-seekers who do not abuse substances may be over-represented among those who show a high level of personal fulfilment; conversely, a predisposition to a cyclothymic type, with its resultant vulnerability to maladaptive behaviour, is probably associated with low levels of personal accomplishment. Therefore, reviewing the entire population of those who show an affective temperament, we can identify those who embody the “sunny side” of bipolarity and are capable of good social adjustment, and those who embody the “dark side” of bipolarity and show a tendency to instability, anxiety, and antisocial behaviour [10]. In heroin addicts, cyclothymic and irritable traits can be traced to this dark side of bipolarity, which does not necessarily require the presence of a dual diagnosis. Unlike the personality constructs of DSM-IV, which tend to stigmatize heroin addicts, this dark side of cyclothymia is closer to affective processes, and is therefore closely linked with human nature [7, 60].

3.2. The temperamental profiles of Alcoholics

In a study on the emotional temperament of 94 alcoholics and 50 controls, we observed that only the temperamental traits of cyclothymic-depressive type displayed significant differences between the two groups. By contrast, none were observed between alcoholics and controls for the hyperthymic and irritable temperament types. As in the case of heroin addicts, we compared the emotional temperament of alcoholics, whether they had or did not have psychiatric comorbidity, with a control group. The prevalence of cyclothymic-depressive traits allowed the differentiation of alcoholics from controls, but not alcoholics with a dual diagnosis from those without one.

Even in the case of alcoholism, the attention of the scientific community was initially focused on personality disorders, with the aim of finding psychological explanations for aberrantBehavioural styles. Among alcoholics, antisocial personality disorder has been reported as the most common, especially in males [48]. By contrast, comorbidity with Axis I disorders, particularly mood disorders, is widely recognized by the scientific community, although not as commonly as would be expected from a truly independent comorbidity [20, 33, 34, 38, 42-44, 55, 65, 67, 72, 82, 88]. Data from the analysis of the “National Survey on Drug Use and Health” show that alcohol use can be very common even in the absence of a serious mental disorder, suggesting that the risk factors for each personality type may be sufficient to explain the tendency of some people to drink in a problematic way [73]. However, the prevalence of alcohol abuse or dependence has been shown to be much higher among people with serious mental illness. The hypothesis that emerges is, therefore, that there is a risk factor for sub-threshold bipolar disorders, in the form of a specific temperamental profile, which can play a role in promoting the desire for the substance and its use, and worsen Axis I disorders.

Profiles with cyclothymic or with dysthymic temperamental traits, as variants of a dysthymic continuum, actually correspond to the dichotomy between the variants of alcoholism according to Cloninger: an early-onset variant which is genetically determined and a more serious late-onset variant which is environmentally determined, and milder [22, 40].

Lastly, cyclothymia is probably not the only factor that predisposes to alcohol consumption, which is quite typical of healthy hyperthymic individuals [14, 81], but it can be viewed as a key element in promoting the consumption of alcohol in a pathological way [75].
4. Concluding remarks

The correlation between bipolar spectrum disorders and substance abuse disorders is generally accepted. The affective temperaments can be considered attenuated expressions of the bipolar spectrum. In heroin addicts and alcoholics the role of “bipolarity” can be extended from the area of full-blown affective disorders to that of affective temperaments.

What emerges is the central role of cyclothymia, with irritable traits discovered in a group of heroin addicts, and depressive traits in alcoholics. While the cyclothymic temperament qualifies as a real temperamental risk factor for the development of these diseases, irritable and depressive traits, which differentiated these two groups of subjects, may be considered not so much a premorbid condition, but, rather, as a simple association.

Drugs of abuse appear to act on a biological substrate consisting of altered genetic and psychological precursors such as hyperactivity, impulsivity, anxiety, disinhibition, and constitutional dimensions defined as “novelty seeking” and “sensation seeking” [51, 54, 76].

We hypothesize that these precursors belong to the core of the cyclothymic temperament, which appears to function as a premorbid state, promoting the initiation of substance use and the development of drug addiction. More specifically, in cyclothymic subjects the same biological mechanisms that are the basis of stable emotional instability make them particularly at risk of developing an addiction when exposed to highly addictive substances.

In short, the cyclothymic temperament may influence the pathogenesis of drug dependence, promoting a first encounter with the substance at various different levels, by virtue of the unregulated pursuit of pleasure, and later helping to drive the process of addiction, as a result of the increased euphoric effect and gratification perceived by these parties in response to the substance.

When the role of temperamental profiles is viewed from a greater distance, it can be assumed that hyperthymia is the most favorable important condition in the process of adaptation and control, whereas cyclothymia is the most important predisposing factor to behavioral loss-of-control and addiction.

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Drug (heroin) addiction, bipolar spectrum and impulse control disorders

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Summary

In most cases, interactions between the brain and the external environment are controlled by a system in which external inputs tend to satisfy internal inputs, so leading to the extinction of the behaviours triggered by internal needs. In this way, a loss of interest extinguishes the search for pleasure. In some individuals, however, the tendency to seek pleasure, and their hypersensitivity to the increased stimulus, sets up a self-perpetuating circuit where the incoming stimulus fails to satisfy internal needs. In the case of addiction, the search for the addictive substance is constantly repeated, without any equilibrium being reached. The same can be said about individuals with bipolar disorder in whom excitement elicits behaviours that aim to maintain a state of euphoria. Individuals with substance abuse and bipolar disorder share many clinical features, such as the strength and urgency of craving. Behaviours associated with substance dependence are very similar to those of hypomanic bipolar patients, where self-preservation and self-aggrandizement are the common features. In addition to their similar clinical psychopathology, mania and addiction are linked by a common background: excitement and impulsivity. For these reasons, and considering the high frequency of comorbidity, we can assume that the two conditions probably share a common biological substrate with a common reinforcement; substance dependence could then be viewed as belonging to the bipolar spectrum, and impulsivity could be viewed as the ‘bridge’ between these two entities. If so, this would have a major impact on the management and treatment of patients with substance dependence who have other comorbid disorders, raising the probability that opioid medications could have a therapeutic role that extends beyond substance dependence disorders.

Key Words: Drug addiction; bipolar spectrum; impulse control disorder.

1 The pursuit of pleasure. From habit to disease

Even if the WHO and the APA have classified addiction as a “mental disorder” [1], many healthcare professionals remain reluctant to recognize it as a medical entity, and manage it in the same way as other medical conditions, even criticizing the medical approach to the treatment and calling it a “medicalization” of addiction [36]. In patients with opioid dependence, the core of addiction revolves around the cravings that have become hypertrophic. In substance use disorders, the pursuit of pleasure becomes predominant, automatic and can only be achieved through a single form of stimulation, the substance. The excessive feeding of the need for gratification causes an impaired ability to derive pleasure and subjective satisfaction, ultimately leading to an impaired perception of pleasure. The pursuit of pleasure in these individuals reaches dysfunctional levels [53].

The psychopathology of the disease consists of three ‘core’ symptoms – craving, relapse (relapsing behaviour) and the loss of control over instinctive impulses, which are common to other psychiatric disorders. These symptoms allow addiction to be recognized as a distinct entity – not just as a psychiatric
Drug-seeking behaviour that is initially justified by the reward eventually becomes unjustified by the absence of the desired effects that are sought by those using the substance. The loss of pleasure goes hand in hand with a loss of control, and it is at this point that addiction can be said to have developed, after which it is maintained by the memory of how the system once worked. Addiction can be described as an impulse, a stimulus that drives the subject to seek gratification, through addictive substances and through non-chemical means in other disorders [45]. Craving has not been defined as an automatic process [55], but, considering the fact that the pursuit of the substance is caused by a desire for gratification, when drug-seeking is carried out without any expectations, the process can then be said to have become automatic. The emergence of this automatic process marks the transition from the habit to a disease with an irreversible, self-perpetuating disease course. In this last phase of the illness, impulsivity is important and severe. Consistently with this notion, we can consider that the behavioural alterations associated with addiction belong to the sphere of impulse control disorders, and impulsivity can be considered a marker of pre-existing vulnerability to the development of a substance use disorder [57]. The chronic and self-maintaining nature of addiction, which drives vulnerability to the point of relapse, can also be seen in other psychiatric disorders. From a medical viewpoint, drug addiction is a behavioural disorder that develops through prolonged exposure to addictive substances. This disorder is distinguished by the impairment of the individual’s ability to maintain a normal subjective equilibrium, because their pleasure-seeking behaviours have risen to a dysfunctional level [53]. Gratification achieved by use of the substance causes a positive reinforcement, which is maintained even in the absence of craving, resulting in pathological attachment to the substance. This concept can be understood by studying nicotine addiction, in which, despite the absence of a real craving, there is still a positive reinforcement that comes from the gratification derived from use of the substance [54].

The observation that mood disorders are disorders related to substance use was first made by Kraepelin, who demonstrated an increased risk of alcohol intoxication in people with psychomotor agitation [15]. Some years later, the first conceptualization of this idea emerged from the theory of self-medication developed by Khantzian, according to which individuals with a mental disorder will use substances to alleviate their condition. It is misleading to think of addiction as a compulsive phenomenon that is intended to reduce suffering; it is more correct to understand it as a phenomenon that gives pleasure, is ego-syntonic and impulsive. In support of this concept, and the non-applicability of Khantzian’s theory in these patients, there is evidence that individuals continue to use substances both when their clinical condition has improved but also when the mental discomfort associated with the mental disorder has worsened [26]. For Zuckerman on the other hand, substance use is guided by “sensation seeking” and a desire to attain states of well-being, rather than to alleviate pathological conditions [59]. In other words, people use substances because of their capacity to maintain or increase euphoria rather than to self-medicate a depressive condition [18, 20].

2 The bipolar spectrum

The spectrum of bipolar disorders encompasses recurrent disorders of varying intensity, showing mood instability and intermittent or prolonged states of inhibition and excitation of various mental functions such as cognition, mood and psychomotor functions [3]. In addition to mania and depression in bipolar disorder, there are other mood states involved, such as anxiety, irritability, impulsivity, and mood swings [41]. Consideration of bipolar disorder and the bipolar spectrum must take into account all the mood disorders in between unipolar and bipolar disorder that Angst’s unipolar-bipolar dichotomy does not consider [6]; instead, Akiskal has recently conceptualized a “soft” bipolar spectrum [2]. Secondly, we consider the now considerable literature that includes hypomania induced by pharmacological treatment with antidepressants, alcohol or stimulants in bipolar disorder, although the ICD-10 and DSM-IV still deny the status of bipolar to these patients [5]. The co-occurrence of bipolar disorder and other psychiatric disorders, especially anxiety, impulse control disorders and eating disorders, with substance use and personality disorders, is very common; it is also complex, and subject to different pathogenetic interpretations [7, 47].

Patients with bipolar disorder who have multiple episodes of illness and who show the absence of periods free from acute psychopathology are very often cyclothymic bipolar II [4]. The instability of the humoral cyclothymia may be related to impulsivity,
in that both are distinguished by periods of disinhibition, often leading to certain behaviours or thoughts, poor insight and/or ego-syntonicity and marked mood changes that make cyclothymic individuals particularly difficult and problematic. In particular, a cyclothymic disposition is frequently associated with sleep disorder-related anxiety, separation anxiety, eating disorders in women and antisocial-aggressive behaviour in males. These observations are in line with the concept that the cyclothymic temperament is associated with a lifetime personality disorder [4] and, in a high percentage of cases, with anxiety and impulsivity [40]. Cyclothymic temperament could therefore be the common underlying feature in anxiety disorders, mood disorders and impulse control disorders. Impulsivity could be a temperamental trait that characterizes a subset of hyperthymic and cyclothymic individuals. Mood disorders share with addiction the mechanisms of reverberation, self-preservation and positive reinforcement. In bipolar patients, “mood elation” is an enjoyable experience associated with a positive reinforcement that can be produced and continued through the use of stimulants [20].

3 Impulsivity as a bridge between the “pursuit of pleasure” and the “bipolar spectrum”

Impulsivity has been defined as “a predisposition to quick reactions, unplanned in response to internal or external stimuli, which does not take into account the negative consequences that these reactions involve” [32] and it aims to satisfy a desire [16]. It is crucial to consider impulsivity as an individual variable capable of influencing the strength of the relationship between intention and substance use [33]. The link between impulsivity and the use of drugs is well established [9, 10]. Traits and behaviours related to impulsivity include “risk taking”, “sensation seeking” and behavioural disinhibition [35]. There is growing evidence that impulsivity is a stable trait in the bipolar disorder [50] and a “core” feature of the disease [34]. Elevated levels of impulsivity have been found in bipolar disorder during manic phases [51, 52], depression [38] and euthymia [38, 52]. High levels of impulsivity have also been found in all the psychiatric disorders that are marked by “risk-taking” behaviours; in addition to bipolar disorder, these included substance use disorder [32].

A leading distinctive feature of Impulse Control Disorder (ICD) is pathological impulsivity, which can be defined on one hand by its pleasure-seeking orientation and, on the other, by a syntonic state during behaviour of this type. In this sense, ICD can be considered an alteration of object-independent behaviour. In many scientific papers, the term “compulsive” is used to define situations that would best be classified as showing impulsivity [29]. Compulsive behaviours, unlike impulsive ones, are dystonic, are intended to alleviate anxiety and are not driven either by desire or by craving; they therefore do not belong to the category of pleasure.

Patients with ICDs are involved in different types of behaviour (substance abuse, gambling, compulsive shopping, binge eating and promiscuity) that have as their common denominator gratification, through which a single behaviour or a cluster of behaviours are reinforced. The correct definition of ICDs should therefore take into account the role of the alteration of personal gratification in the development and perpetuation of this disease. Impulsivity, as a psychopathological abnormality, characterizes behaviours of addiction, and represents a risk factor for early initiation into substance use. This is why substance abuse can be viewed as a disorder of impulse control and why addiction can be considered a chronic, severe form of impulse control disorder, in which craving replaces desire [22] and is expressed by repetitive behaviours. The fact that impulsivity is not only a fundamental feature of addiction, but also of bipolar disorder, is highlighted by the work of McElroy, which has shown that the comorbidity between bipolar disorder and ICDs is the rule, so that ICDs can be viewed as exemplary bipolar disorders, especially when compared with atypical bipolar cases [27, 28].

Impulsivity is a characteristic feature of states of excitement with a double meaning: on one hand, impulsive behaviour intensifies in manic states; on the other, the manic state is accompanied by a drive towards rewarding objects and situations, and their continual pursuit of these.

As we have seen, addiction, impulse control disorder and hypomania have shared features. It must be added that addiction involves a process that is autonomous and independent, and its co-existence with another mental disorder produces a comorbid condition, which is best defined as “dual diagnosis”. The comorbidity that is often found between the bipolar spectrum and addiction implies the coexistence of different entities, rather than that of psychopathological syndromes that are correlated and derived from distinct processes. In any case, these two conditions share the central nervous system, and have a common anatomical and physiological basis that can be used to
construct a pathophysiological model [58]. Different comorbid psychiatric conditions may have a different impact on the treatment of addiction. Patients with a bipolar disorder differ from their peers in terms of the quality and intensity of the euphoria that is caused by the substance. As a result of their interaction, there is an exacerbation of both clinical presentations; in particular, mood disorders amplify the reinforcing properties of substances, so increasing their use. Although bipolar disorder is more common among addicts than in the general population, and even though 50% of bipolar patients have a history of abuse or addiction in their lifetime [48], in clinical practice these facts are frequently underestimated and misunderstood, because the temperament and hypomanic phases of patients with dual diagnosis are often overlooked. Patients with bipolar I disorder seem to have this type of comorbidity more frequently than bipolar II patients [8]; despite this, the bipolar II disorder is more closely related to alcohol abuse, especially in women [13]. The main epidemiological study that assessed the comorbidity between substance use disorders and bipolar disorders I and II was conducted on a sample of 43,093 subjects, highlighting the finding that between bipolar I disorder and lifetime alcohol use, there is 58% and 38% comorbidity for all other substance use disorders [12]. Of patients with bipolar II disorder, 48% had a history of lifetime use of alcohol or drugs [43]. On the other hand, repeated exposure to psychoactive substances and the continued experience of euphoria led to a new threshold for the perception of well-being, resulting in an imbalance in mood equilibrium [25]. Though most studies have highlighted the specific relationship between bipolar disorder and the use and abuse of stimulants, few have evaluated the question of whether this relationship also subsists with the concomitant abuse of alcohol or heroin. One of our studies conducted on a group of 448 bipolar patients who were being treated for alcohol use evaluated the concurrent abuse of cocaine; it revealed a statistically significant correlation between cocaine abuse and bipolar spectrum. On this basis, cocaine could be viewed a means to maintain “mood elation”. The use of alcohol, however, would act as a tool to cope with dysphoria. In the context of alcohol use and its sedative properties, cyclothymics may use cocaine as an attempt to induce and maintain hypomania, resulting over the long term in the development of “full blown” bipolar disorder [37]. In a group of 1090 patients addicted to heroin, the concomitant use of cocaine provides evidence of a positive relationship with a dual diagnosis, especially one including the bipolar spectrum. If cocaine abuse precedes or coexists with use of heroin, it may serve as a “mood balancer”, weakening states of excitement and mood swings. Subthreshold bipolarity, which also includes the cyclothymic and hyperthymic temperaments, predisposes an individual to heroin addiction, but the craving and suppressed hypomanic state could lead to the use of cocaine and the unmasking of an open bipolar disorder [23]. It has been observed that alcohol, cocaine and cannabis are more frequently abused among bipolar patients than among the general population, although the percentages reported range widely, from 18% to 75% [43]; there is, in fact, no agreement that substance abuse co-occurs with mania or bipolar depression more frequently than with unipolar depression [43]. Both entities are frequently associated with each other; just as frequently, they influence each other. Alcohol use disorders affect the course of bipolar disorder, resulting in an increased occurrence of episodes and more rapid cycling [42]. With reference to patients who are addicted to heroin, mood disorders are the most frequent forms of psychiatric comorbidity: the association of a cyclothymic temperament has been observed in 3.6% of patients [31] and hypomania has been reported in 16% [30] of patients, whereas overt mania seems to be much more rare (below 0.1%). High rates of comorbidity with bipolar disorder among heroin users were found on the PISA-SIA (Pisa-Study and Intervention on Addictions) programme, where 55.6% of 90 heroin users, who had been recruited for a programme of maintenance treatment with methadone, turned out to have a comorbid bipolar disorder I [19]. In the development of abuse among patients with bipolar II, the hyperthymic, cyclothymic and irritable temperaments appear to be prominent [39]. The increase in a propensity to abuse substances is evident across the entire bipolar spectrum, including bipolar I, II, and in patients with a cyclothymic, hyperthymic or irritable temperament. In particular, the cyclothymic temperament is the most common among heroin users and is the only temperament that is able to significantly distinguish “addicts” from controls [24]. Considering the anti-dysphoric properties of opioids, it has been hypothesized that heroin is first taken to try and correct the dysphoria, and that only later does it becomes necessary, as a result of the development of tolerance to these same effects. In any case, dependent individuals retain a memory of the euphoria experienced after taking opiates, and the pursuit of pleasure becomes the main reason why they seek the substance. Many bipolar patients seem to start, to continue or to resume...
the use of drugs because of impulsivity and excitement [17, 18]. The theory of self-medication does not appear to offer a key to an understanding of the dynamics of the phenomenon of “addiction” in patients with a bipolar spectrum disorder; rather, the two most important factors in seeking to understand the use and abuse of substances are “sensation seeking” and an underestimation of the consequences, both driven by (hypo)maniacal excitement, the main phenomenon that can be classified as a relevant major entity [20, 25]. The thesis of “optimal arousal” was initially developed by Zuckermann, in reformulating the original hypothesis that presupposed a relationship between “sensation-seeking” and dysthymia. Zuckermann pointed out that people are attracted to substances because of their power to maintain or increase excitement, rather than their ability to correct depression [18, 59]. As further confirmation of the importance of excitement in addiction, it is easy be noted that craving and repetitive behaviour are commonly associated with phases of excitement [25] and that the use of stimulants increases during mania [11, 20] rather than during depression [49]. Though full-blown mania does not mirror substance abuse in terms of prevalence, a minority of cases show a high level of correspondence; in particular, hypomania and cyclothymia seem to act as ideal substrates for the beginning of addiction and for the recurrence of abuse. The bridge between the two entities is impulsivity [22]. Impulse control disorders, the whole spectrum of bipolar disorders and substance use share a characteristic symptom – dysphoria at the end of the addictive experience, which highlights the change that takes place in the reward system. For bipolar patients who are always looking for a state of excitement, the normal state of mood functions as a sort of dysthymia [46] and when the euphoric state becomes impossible to reach, a state of boredom, dissatisfaction, lack of pleasure and motivation then produce a dysphoric syndrome that is found even in patients with substance dependence during a period of remission or following detoxification [56]. This is the reason why bipolars can be seen as “addicted to mania” and abusers as “addicted to euphoric substances”. In bipolar patients, substance abuse doubles the damage, given that “addiction to euphoria” constitutes an additional element to addiction in perpetuating a system that strikes the same targets in the brain [44].

4 Concluding remarks

The two disease entities are not only mutual risk factors, but also a condition of “double” damage [14]; which is why the authors prefer to look at them from a single perspective. Mood disorders and addiction share the mechanisms of self-renewal and positive reinforcement. Just as one can say that, for a bipolar subject, “mood elation” is an enjoyable experience associated with a positive reinforcement that can be produced and continued by the use of stimulants, the same can be said about the pleasant effect of the substance chosen by drug addicts. Many of the behaviours in the two psychopathological entities can be explained by impulsivity, which thus becomes their common background. If this is correct, we may consider the two entities as belonging to a common substrate, and drug addiction as being a part of the bipolar diathesis. This would have an impact on the treatment of the two disorders, which would be likely to reveal areas of convergence and similarity. In particular, the concept of “dual stabilization” would then assume a leading role. On one hand, antiepileptic drugs tend to act on impulse and on thymic oscillation, while, on the other, opioid agonists with a long half-life may rebalance the endogenous opioid system, in addition to acting directly on mood stabilization [21, 25].

References


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**Contributors**

All the authors equally contributed to, and have approved, the final manuscript.

**Conflict of interest**

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Psychopathological symptoms of heroin addicts at treatment entry

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Summary

Patients with substance use disorder (SUD) show a high rate of comorbidity with other mental disorders, particularly those involving mood, anxiety and impulse control. In addition, an equally strong correlation has been shown between psychotic disorders and substance use disorder (SUD). Application of the classic model of psychiatric comorbidity to the field of drug addiction is subject to limitations: the first is that the high frequency of co-occurrence of these two psychopathological events raises doubts as to their independence; the second is the insoluble problem of disentangling psychiatric symptoms from the heart of the psychopathology of drug addiction; lastly, the overlap between the biological substrates and the neurophysiology of addiction and psychiatric disorders cannot be disregarded. With this in mind, we have theorized that symptoms of mood swings, anxiety and impulse dyscontrol should be considered as constituting the psychopathology of addiction. We put forward the hypothesis that the dysregulation of the opioid system, that is determined by the chronic use of heroin, could give rise to a wide range of psychopathological symptoms that are prominent in distinguish heroin addicts, this being true regardless of the co-occurrence of another mental disorder, factors related to gender, education, history of abuse, the modality of abuse and treatment undertaken by patients in their history. We have considered 5 dimensions: 1. feelings of “worthlessness and being trapped”; 2. “somatic symptoms”; 3. “sensitivity-psychoticism”; 4. “panic anxiety”; 5. “violence-suicide”. Although these symptoms do not always reach the threshold that would qualify them as belonging to a psychiatric syndrome, their impact on a patient’s life must be recognized; above all, these symptoms should be treated as belonging to the context of the treatment of drug dependence.

Key Words: psychopathology of addiction; symptom factors; mood; anxiety; impulse dyscontrol
how these should be classified and their role in the psychopathology of a SUD.

This issue is of vital importance. To be able to resolve the issue of the primacy of substance use with respect to mental illness, we must first resolve the question of how independent the comorbid psychopathological symptoms are from the symptoms that lie at the core of addiction. Application of the classic model of psychiatric comorbidity, in the field of drug addiction, is subject to limitations: the first is that the high frequency of co-occurrence of these two psychopathological events raises doubts as to their independence; the second is the insoluble problem of disentangling psychiatric symptoms from the heart of the psychopathology of drug addiction; lastly, the overlap between the biological substrates and the neurophysiology of addiction and psychiatric disorders cannot be disregarded [41, 49].

With this in mind, we have theorized that symptoms of mood swings, anxiety and impulse dyscontrol should be considered as inseparable from the psychopathology of addiction. Although these symptoms do not always reach the threshold that would allow them to be considered as belonging to a psychiatric syndrome, their impact on a patient’s life must be recognized. Above all, these symptoms should be considered as part of the problem of implementing the treatment of drug dependence [41, 49].

1. **Assessment of symptoms of psychopathology**

The first step in the task of identifying a specific psychopathology of drug addiction is singling out the psychopathological symptoms reported by addicts who have entered treatment. Then it is essential to identify specific factors that describe various dimensions of symptoms. One of the first questions to answer is whether or not there is a correspondence of these symptom dimensions with those typically found in psychiatric disorders [40].

The 90-Symptom Check List (SCL90) can be recognized as the best available inventory of current psychopathological symptoms [13, 14]. The SCL90 is an inventory of self-administration, consisting of 90 items with a score, which varies in intensity from 1 to 5. These items can be grouped into nine factors: Somatization, Interpersonal Sensitivity, Obsessions-Compulsions, Depression, Anxiety, Anger and Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism.

Somatization reflects distress arising from perceptions of bodily dysfunction. Complaints focused on cardiovascular, gastro-intestinal, respiratory and other systems with strong autonomic mediation have been included. Headaches, backaches, and pain and discomfort localized in the gross musculature are additional components, as are other somatic equivalents of anxiety. Obsessive-Compulsive reflects behaviours that are closely identified with the clinical syndrome of the same name. The focus of this criterion is on thoughts, impulses and actions that are experienced as unremitting and irresistible by the individual but are of an ego-alien or unwanted nature. Behaviours indicative of a more general cognitive difficulty (e.g., “mind going blank”, “trouble remembering”) also load on this dimension. Interpersonal Sensitivity focuses on feelings of personal inadequacy and inferiority, particularly by comparison with other individuals. Self-deprecation, feelings of uneasiness, and marked discomfort during interpersonal interactions are characteristics of people showing high levels for this dimension. Feelings of self-consciousness and negative expectations regarding interpersonal communications are further typical sources of distress. Depression reflects a broad range of the concomitants of the clinical depressive syndrome. Symptoms of dysphoric affect and mood are represented, as are signs of withdrawal of interest in life events, lack of motivation, and loss of vital energy. This dimension mirrors feelings of hopelessness and futility, as well as other cognitive and somatic correlates of depression. Several of the items included have to do with thoughts of death and suicidal ideation. Anxiety subsumes a set of symptoms and experiences usually associated clinically with a high degree of manifest anxiety. General indicators such as restlessness, nervousness, and tension are included here, as are additional somatic signs (e.g. “trembling”). Scales measuring free-floating anxiety and panic attacks are an integral aspect of this dimension, and an item on feelings of dissociation is included. Hostility is organized around three categories of hostile behaviour: thoughts, feelings, and actions. Items range from feelings of annoyance and urges to break things, to arguments and uncontrollable temper outbursts. Phobic Anxiety reflects symptoms that have been observed with a high incidence in conditions termed phobic anxiety state or agoraphobia. Fears of a phobic nature oriented towards travel away from home, open spaces, crowds, or public places and means of transport are represented by this parameter. In addition, several scales representing social phobic behaviour have been included. Paranoid Ideation derives from the notion that paranoid behaviour is best
considered from a syndromal point of view. Projective ideation of hostility, suspiciousness, centrality, delusions, loss of autonomy, and grandiosity as cardinal paranoid characteristics are assessed within the limitations imposed by a self-report format. Psychoticism represents florid, acute symptomatology, as well as behaviours typically viewed as more oblique, less definitive, indicators of psychotic processes. Four items reflect Schneiderian first-rank symptoms of schizophrenia: auditory hallucinations, thought broadcasting, external thought control, and external thought insertion. In addition, secondary signs of psychotic behaviour, as well as indications of a schizoid lifestyle, are represented too. Global scores for SCL-90 items are Total SCL-90 score (sum of all items), the number of items rated positively (PST), and the positive symptom distress index (PSDI), which is calculated by dividing the sum of all items by the score for PST.

The administration of the rating scale refers to “normally in the last week” in the experience of the patient, but the timeframe investigated may be decided by the person who is administering the test.

For the composition of the factors reference can be made to Table 1.

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<th>Table 1. SCL90 dimensions</th>
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<tbody>
<tr>
<td><strong>1-Somatization</strong></td>
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<tr>
<td>01. Headaches</td>
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<td>04. Faintness or dizziness</td>
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<td>12. Pains in heart or chest</td>
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<td>27. Pains in lower back</td>
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<td>40. Nausea or upset stomach</td>
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<td>42. Soreness of your muscles</td>
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<td>48. Trouble getting your breath</td>
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<td>49. Hot or cold spells</td>
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<td>52. Numbness or tingling in parts of your body</td>
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<td>53. A lump in your throat</td>
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<td>56. Feeling weak in parts of your body</td>
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<td>58. Heavy feelings in your arms or legs</td>
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<td><strong>2-Obsessive-compulsive</strong></td>
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<td>03. Unwanted thoughts, words, or ideas that won’t leave your mind</td>
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<td>09. Trouble remembering things</td>
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<td>10. Worried about sloppiness or carelessness</td>
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<td>28. Feeling blocked in getting things done</td>
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<td>38. Having to do things very slowly to insure correctness</td>
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<td>45. Having to check and double-check what you do</td>
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<td>46. Difficulty making decisions</td>
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<td>51. You mind going blank</td>
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<td>55. Trouble concentrating</td>
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<td><strong>3-Interpersonal sensitivity</strong></td>
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<td>06. Feeling critical of others</td>
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<td>21. Feeling shy or uneasy with the opposite sex</td>
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<td>34. Your feelings being easily hurt</td>
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<td>36. Feeling others do not understand you or are unsympathetic</td>
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<td>37. Feeling that people are unfriendly or dislike you</td>
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<td>41. Feeling inferior to others</td>
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<td>61. Feeling uneasy when people are watching or talking about you</td>
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<td>69. Feeling very self-conscious with others</td>
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<td>73. Feeling uncomfortable about eating or drinking in public</td>
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<td><strong>4-Depression</strong></td>
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<td>05. Loss of sexual interest or pleasure</td>
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<td>14. Feeling low in energy or slowed down</td>
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<td>15. Thoughts of ending your life</td>
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<td>20. Crying easily</td>
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<td>22. Feeling of being trapped or caught</td>
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<td>26. Blaming yourself for things</td>
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<td>29. Feeling lonely</td>
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<td>30. Feeling blue</td>
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<td>31. Worrying too much about things</td>
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<td>32. Feeling no interest in things</td>
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<td>54. Feeling hopeless about the future</td>
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<td>71. Feeling everything is an effort</td>
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<td>79. Feeling of worthlessness</td>
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<td><strong>5-Anxiety</strong></td>
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<td>02. Nervousness or shakiness inside</td>
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<td>17. Trembling</td>
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<td>23. Suddenly scared for no reason</td>
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<tr>
<td>33. Feeling fearful</td>
</tr>
<tr>
<td>39. Heart pounding or racing</td>
</tr>
<tr>
<td>57. Feeling tense of keyed up</td>
</tr>
<tr>
<td>72. Spells of terror or panic</td>
</tr>
<tr>
<td>78. Feeling so restless you couldn’t sit still</td>
</tr>
<tr>
<td>80. Feeling that familiar things are strange or unreal</td>
</tr>
<tr>
<td>86. Feeling pushed to get things done</td>
</tr>
<tr>
<td><strong>6-Anger-hostility</strong></td>
</tr>
<tr>
<td>11. Feeling easily annoyed or irritated</td>
</tr>
<tr>
<td>24. Temper outbursts that you could not control</td>
</tr>
<tr>
<td>63. Having urges to beat, injure, or harm someone</td>
</tr>
<tr>
<td>67. Having urges to break or smash things</td>
</tr>
<tr>
<td>74. Getting into frequent arguments</td>
</tr>
<tr>
<td>81. Shouting or throwing things</td>
</tr>
<tr>
<td><strong>7-Phobic anxiety</strong></td>
</tr>
<tr>
<td>13. Feeling afraid in open spaces or on the streets</td>
</tr>
<tr>
<td>25. Feeling afraid to go out of your house alone</td>
</tr>
<tr>
<td>47. Feeling afraid to travel on buses, subways or trains</td>
</tr>
<tr>
<td>50. Having to avoid certain things, places, or activities because they frighten you</td>
</tr>
<tr>
<td>70. Feeling uneasy in crowds, such as shopping or at a movie</td>
</tr>
<tr>
<td>75. Feeling nervous when are left alone</td>
</tr>
</tbody>
</table>
2. The use of the SCL90 in heroin addicts. Psychopathological dimensions of heroin dependence

In a recent investigation of ours, the SCL90 was administered to 1,055 heroin users entering treatment in order to verify the correspondence of the observed factors with those used in the mentally ill patients [40]. 77 items, with a weight greater than 0.40, were used to identify 5 dimensions. These dimensions have been renamed on the basis of the items that have greatest weight. The first dimension (Table 2) is a depressive dimension. It is distinguished by feelings of “worthlessness” and “being trapped”. The second includes “somatic symptoms” (Table 3), of which the most important appears to be muscle pain, a sense of heaviness in the arms and legs, and hot flushes associated with chills. The third dimension includes symptoms of “sensitivity-psychoticism”, such as the patient’s feeling that others may be looking at or
brings together depressive, obsessive-compulsive and psychotic symptoms. Treatment-seeking addicts who display depressed mood usually report feelings of uselessness and the feeling of being trapped in a corner. These patients feel abandoned, sad, with no goal or interest; they are excessively preoccupied with difficulties, and report feelings of guilt, while experiencing a low or zero sexual drive, too. Obsessive-compulsive symptoms include difficulties in making decisions, completing a task and concentrating, along with worries about one’s inaptitude, an ‘empty mind’ sensation and an incapacity to dominate one’s thoughts. Other symptoms, such as the need to check actions several times or act slowly so as to avoid making mistakes, are not featured. Compulsions and memory impairment do not appear in any factor. Thought disorders consist of feeling alone even when with other people, the thought that one’s mind is not working properly, while never feeling really close to others. Lastly, these subjects report a feeling of infe-

### Table 4. Items of “sensitivity-psychoticism” dimension, in descending order of importance

<table>
<thead>
<tr>
<th>Item</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling that you are watched or talked about by others</td>
<td>43</td>
</tr>
<tr>
<td>Other people being aware of your private thoughts</td>
<td>35</td>
</tr>
<tr>
<td>Feeling that people are unfriendly or dislike you</td>
<td>37</td>
</tr>
<tr>
<td>Feeling others do not understand you or are unsympathetic</td>
<td>36</td>
</tr>
<tr>
<td>The idea that someone else can control your thoughts</td>
<td>07</td>
</tr>
<tr>
<td>Having thoughts that are not your own</td>
<td>62</td>
</tr>
<tr>
<td>Feeling uneasy when people are watching or talking about you</td>
<td>61</td>
</tr>
<tr>
<td>Feeling very self-conscious with others</td>
<td>69</td>
</tr>
<tr>
<td>Having to check and double-check what you do</td>
<td>45</td>
</tr>
<tr>
<td>Having to do things very slowly to insure correctness</td>
<td>38</td>
</tr>
<tr>
<td>Feeling that people will take advantage of you if you let them</td>
<td>83</td>
</tr>
<tr>
<td>Others not giving you proper credit for your achievements</td>
<td>76</td>
</tr>
<tr>
<td>Feeling uneasy in crowds, such as shopping or at a movie</td>
<td>70</td>
</tr>
<tr>
<td>Having ideas or beliefs that others do not share</td>
<td>68</td>
</tr>
<tr>
<td>Feeling uncomfortable about eating or drinking in public</td>
<td>73</td>
</tr>
<tr>
<td>Feeling pushed to get things done</td>
<td>86</td>
</tr>
<tr>
<td>Feeling that familiar things are strange or unreal</td>
<td>80</td>
</tr>
<tr>
<td>Having to do things very slowly to insure correctness</td>
<td>38</td>
</tr>
</tbody>
</table>

### Table 5. Items of “anxiety-panic” dimension, in descending order of importance

<table>
<thead>
<tr>
<th>Item</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling afraid in open spaces or on the streets</td>
<td>13</td>
</tr>
<tr>
<td>Feeling afraid to go out of your house alone</td>
<td>25</td>
</tr>
<tr>
<td>Spells of terror or panic</td>
<td>72</td>
</tr>
<tr>
<td>Feeling afraid to travel on buses, subways or trains</td>
<td>47</td>
</tr>
<tr>
<td>Faintness or dizziness</td>
<td>04</td>
</tr>
<tr>
<td>Feeling afraid you will faint in public</td>
<td>82</td>
</tr>
<tr>
<td>Feeling fearful</td>
<td>33</td>
</tr>
<tr>
<td>Having to avoid certain things, places, or activities because they frighten you</td>
<td>50</td>
</tr>
<tr>
<td>Suddenly scared for no reason</td>
<td>23</td>
</tr>
</tbody>
</table>

### Table 6. Items of “Violence-suicide” dimension, in descending order of importance

<table>
<thead>
<tr>
<th>Item</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shouting or throwing things</td>
<td>81</td>
</tr>
<tr>
<td>Having urges to break or smash things</td>
<td>67</td>
</tr>
<tr>
<td>Temper outbursts that you could not control</td>
<td>24</td>
</tr>
<tr>
<td>Having urges to beat, injure, or harm someone</td>
<td>63</td>
</tr>
<tr>
<td>Getting into frequent arguments</td>
<td>74</td>
</tr>
<tr>
<td>Thoughts of ending your life</td>
<td>15</td>
</tr>
<tr>
<td>Thoughts of death or dying</td>
<td>59</td>
</tr>
<tr>
<td>Nervousness or shakiness inside</td>
<td>02</td>
</tr>
<tr>
<td>Feeling so restless you couldn’t sit still</td>
<td>78</td>
</tr>
<tr>
<td>Thoughts of ending your life</td>
<td>15</td>
</tr>
</tbody>
</table>

### Table 7. Items not grouped

<table>
<thead>
<tr>
<th>Item</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>01</td>
</tr>
<tr>
<td>Feeling critical of others</td>
<td>06</td>
</tr>
<tr>
<td>Feeling others are to blame the most of your troubles</td>
<td>08</td>
</tr>
<tr>
<td>Trouble remembering things</td>
<td>09</td>
</tr>
<tr>
<td>Hearing voices that other people do not hear</td>
<td>16</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>19</td>
</tr>
<tr>
<td>Crying easily</td>
<td>20</td>
</tr>
<tr>
<td>Feeling shy or uneasy with the opposite sex</td>
<td>21</td>
</tr>
<tr>
<td>Overeating</td>
<td>60</td>
</tr>
<tr>
<td>Having to repeat the same actions such as touching, counting, washing</td>
<td>65</td>
</tr>
<tr>
<td>Having thoughts about sex you bother you a lot</td>
<td>84</td>
</tr>
<tr>
<td>The idea that you should be punished for your sins</td>
<td>85</td>
</tr>
<tr>
<td>The idea that something serious is wrong with your body</td>
<td>87</td>
</tr>
</tbody>
</table>

speaking about him/her” (Table 4). The fourth, “panic anxiety” dimension is marked out by fear of open spaces and roads, and the fear of going out alone (Table 5), and the fifth dimension, “violence-suicide”, is linked with a tendency to scream and throw objects, to feel the urge to break objects and with a loss of control (Table 6). 13 items are not grouped in any factor (Table 7). The main factor (worthlessness, being trapped)
riority, are easily hurt (interpersonal sensitivity), do not like being alone (phobic anxiety) and often feel nervous and upset (“free” anxiety). On the whole, this factor is essentially made up of depressive, obsessive and psychotic features, dominated by feelings of uselessness and of being trapped in a corner.

The second factor (somatization) is distinguished by a number of somatic and anxious elements, which are usually a feature of opiate withdrawal. The patient complains of muscle aches, back pain, heavy legs and arms, weakness and tiredness, loss of sensitivity and paraesthesia somewhere in the body. Hot flushes and cold shivers are possible too, as well as nausea and stomach ache. Sleep is disturbed and broken up, while getting to sleep is difficult. Patients wake up early at dawn and cannot get back to sleep. They report a sensation of choking, or of being breathless; they may tremble, are aware of their heart beating, or even of chest pain. Appetite is low. Interpersonal sensitivity is heightened, so that they are easily annoyed and irritated.

The third factor features sensitivity and psychotism. Patients have the impression that others stare at them and speak about them, may do something against them or exploit them with unpredictable consequences. They think they are not respected by their workmates or are disapproved of because of their own views. They get the impression that others do not sympathize with them or approve of their behaviour, or even show explicit hostility towards them. They feel uneasy when they find other people staring at them or simply in speaking with acquaintances, or may even feel threatened when others are there in the same room. They feel uncomfortable in open or crowded spaces, or when doing things in a group (e.g. eating). These behaviours may be defined as psychotic as long as the patient is convinced that others control or influence their thoughts, in some cases actually being identified as imposed from outside that individual’s mind. Obsessive-compulsive features of a checking type, or taking a lot of time in doing things out of a fear of making mistakes, may also be part of the picture. Lastly, there may be feelings of estrangement and detachment from reality, with the impression that common and familiar things no longer belong to them.

The fourth factor (panic anxiety) can be summed up as agoraphobia, a fear of going around alone, episodes of critical anxiety, fear of travelling by bus, train or subway, sensations of fainting, dizziness or fear of feeling sick or upset in front of other people. Generalized fear is a feature, with the need to avoid certain things, places or activities in order to prevent panicking.

The fifth factor (violence-suicide) includes violent acting outs and features of self-directed aggressiveness. Patients have moments when they cry or throw objects with the aim of breaking them or smashing them into pieces, and suffer from outbreaks of rage. They often get into arguments and feel the urge to push, hurt or beat up others. Side by side with all this, they have suicidal thoughts, or longings for death, are upset, excited or restless, and find it hard to stay seated or lie down for any length of time.

On the basis of the highest z-scores obtained on the 5 SCL-90 factors (dominant SCL-90 factor) subjects can be assigned to 5 mutually exclusive groups. The group whose dominant was “worthlessness, feeling trapped” comprised 14.2% of the subjects, the group with “somatization” as its dominant gathered 24.4%, the group showing “sensitivity-psychotism” as its dominant included 19.4%, the group identified by “panic anxiety” as its dominant comprised 22.3%, and the group whose dominant was “violence-suicide” group profiled a cluster of 19.7% of the subjects. These five groups were sufficiently distinct, and failed to reveal any significant overlap. All these patients showed positive scores in their dominant factors only, alongside negative scores in all the others, the only exception being a small number of patients whose dominant was “worthlessness and being trapped”, who recorded a positive score for the “sensitivity psychotism” factor. This finding was confirmed by the discriminant analysis, which indicated a percentage of correctly classified ‘grouped’ cases as high as 95.26%.

The concept of dimension or “dominant” group allows us to classify subjects avoiding the need to search for a cut-off point above which symptoms would become problematic. To best understand this concept, we can use the analogy of colours. In the specific case of the SCL-90, the five identified dominant dimensions allow each of our subjects to be ‘painted’ in one of 5 basic mutually exclusive colours. Within these colour groups, however, patients continue to have different intensities of colour in so far as the z score is higher in one dimension than another, without necessarily being high in absolute terms. In the case of heroin, this kind of classification of subjects into symptom groups can help in the task of studying the differences that are related to the quality of symptoms rather than to their severity.
3. Relationship between symptom dimensions characterizing heroin addicts and their medical history

The dimensions we have identified in heroin addicts do not show correlations with gender or the length of heroin addiction. The female: male ratio is 1:3.7 for the “violence-suicide” dimension, 1:4.5 for “worthlessness, feeling trapped”; 1:5 for “anxiety panic”; 1:6.4 for “somatic symptoms”; and 1:7.1 for “sensitivity psychoticism”. Younger subjects were preferentially assigned to the dimensions of “violence-suicide”, “sensitivity psychoticism” and “panic anxiety”; older ones to “somatic symptoms” and “worthlessness, feeling trapped” [40].

Among demographic variables, marital status, level of education, economic conditions and living conditions (alone or not) showed no correlation with symptom dimensions; the dominant group “worthlessness, being trapped” comprised a majority of “white collar” individuals [40].

So far, little is known about the demographics of persons in methadone treatment [15]. What is certain is that in at least some parts of the world (notably, Australia) there is a strong correlation between the use of heroin and youth [27], and that those who are employed possess greater human and social capital; this leads to a tendency to avoid the use of psychostimulants [24].

It is no surprise that white-collar workers score strongly in the dimension of “worthlessness, being trapped”, because the psychopathological effects of heroin addiction occur independently of the social adaptation of patients.

In our studies, none of the factors that appear in the Drug Addiction History Questionnaire [32] showed any correlation with the dominant psychopathological dimensions of heroin addicts [40].

By analysing the state of mind of heroin users entering treatment, it becomes clear that lack of insight, alterations of consciousness and memory, the presence of anxiety, depression, eating disorders, suicidality, hallucinations and delusions did not show differences in their distribution patterns between symptom dimensions. Heroin addicts who scored strongly in the “somatic symptoms” dimension showed a higher frequency for a mental state marked out by sleep disorders; the opposite phenomenon was observed for heroin users who scored strongly in “anxiety panic”. Heroin addicts distinguished by “violence-suicide” more frequently presented for treatment in an excited mental state [40].

All dominant symptomatic groups tend to use alcohol, CNS depressants, cannabis, inhalants and illegal methadone as co-drugs of abuse. In a majority of cases, patients that score strongly in the “panic anxiety” dimension also declare using CNS stimulants, while those that have high scores in the “somatic symptoms” dimension tend to avoid hallucinogens. Polysubstance abuse has, in fact, been properly studied in heroin addicts. It is highest in heroin addicts with comorbid anxiety disorders and depression [11]. Combined heroin-cocaine use is found in the psychiatric comorbidity of heroin addicts, but it is inversely correlated with the self-assessment of their condition [2]. On the other hand, psychostimulants can trigger panic attacks [1, 38, 52], but it is also probable that an opiate imbalance can do the same, given that opiate antagonists can induce panic attacks [33] and opiates can exert an anti-panic effect [20].

No correlation was observed with the drug abuse modality, stage of addiction, clinical typology, tendency to self-detoxification, history of treatments and the presence or absence of a dual diagnosis. Stratifying by diagnosis, bipolar patients tend to be better represented among heroin addicts distinguished by “violence-suicidal” and tend to be under-represented among those showing “sensitivity-psychoticism” [40]. Many studies have shown a correlation between heroin addiction and bipolar disorder, not just at the clinical level [6, 10, 28, 30, 31, 35, 36, 39, 41], but at the temperamental level, too [37, 47]. It is, however, our belief that, once established, heroin addiction follows its own path independently of the co-presence of an affective disorder [29, 41, 49]. The use of opioids in patients with dual diagnosis may, in any case, be determined by the anti-depressant [4, 7, 12, 16, 17, 19, 20, 57], anti-manic [20, 42, 48], anti-panic [20] and anti-psychotic [3, 9, 25, 26, 34, 46, 55, 58] properties of opioid therapy. Even aggression is attenuated during opioid maintenance treatment [21, 23, 56]. Consistently with this viewpoint, dual diagnosis heroin addicts require a higher than standard dose of methadone to become stabilized [42].

4. Concluding remarks

Our research data allow us to propose the hypothesis that dysregulation of the opioid system determined by the chronic use of heroin could give rise to a wide range of psychopathological symptoms that are found in heroin addicts at the end of their dependence career, this being valid regardless of the co-oc-
currence of another mental disorder, factors related to gender, education, history of abuse, the mode of abuse and treatment undertaken by patients in their history.

There is, of course, more than one explanation for the presence of these psychopathological dimensions in heroin addicts. On one hand, some symptoms may reflect the severity of the heroin addiction (chronic intoxication) and the concomitant polysubstance abuse of CNS depressants such as alcohol and benzodiazepines; on the other hand these symptoms could be due simply to psychiatric comorbidity, or to polysubstance abuse of other substances. From an alternative viewpoint, the severity of disease could distinguish the symptoms related to intoxication from those related to dual diagnosis. The presence of a strong behavioural disorder seems to be related to dual diagnosis, while the milder abnormalities appear to be due to the persistence of substance abuse. For the mentally ill and those known as “sub-threshold” syndrome patients, substances of abuse may act as amplifiers of discomfort through to the development of a full mental disorder or simply a more severe disease. The combination of a sub-threshold syndrome and amplification related to heroin use could lead to what was once called addictive personality; this combination has mostly been described in patients who had already developed an addiction. We believe that the isolated dimensions have the function of identifying the typical psychopathologies of patients who require treatment with opioids. The hypothesis that mood, anxiety and impulse control disorders are part of the core features and pathogenesis of drug addiction should be considered as equivalent to pointing out the effects of psychiatric manifestations in the development of the phenomenon of drug addiction in general, and heroin addiction in particular [49].

The importance of this topic lies in the need to understand which psychiatric manifestations require additional treatment, and which can be treated as an integral part of drug addiction treatment. In the case of heroin addiction, this line of approach means identifying psychiatric syndromes that are beneficially affected by opiate treatment. Future studies on the psychopathology of addiction could lead to the identification of tools for evaluating the severity of the disease, and the risk of relapse among patients who are in remission but in whom the key psychopathological symptoms of addiction persist.

References


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**Contributors**

IM, PPP, AGIM, MP wrote the first draft. IVB, ET, LR, SB, FR, GP, GG, LdO participated in various research-protocols. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

**Conflict of interest**

Authors declared no conflict of interest. IM served as Board Member for Reckitt Benckiser Pharmaceuticals.
The effects of agonist opioids on the psychopathology of opioid dependence

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Summary

Knowledge about the beneficial psychotropic effects of opiates dates back to the pre-pharmacological era, but the use of opiates has been restricted because of the controversial issue of their liability to abuse, and the potentially lethal effects of accidental or voluntary overdosing. We first review the literature on opiate use and its impact on depressive, anxious, manic and psychotic syndromes, mostly by referring to studies selected from the field of addiction treatment. We then go on to discuss the differences between methadone and buprenorphine in their impact on the psychopathological profiles of heroin addicts. The data gathered by us support the view that some opiates may be regarded as therapeutic not only in the treatment of addictive diseases, but also as candidates for the treatment of certain psychiatric disorders. Such properties are based on their specific activity on opiate receptors, but also on their kinetics, which explain the differences between a destabilizing drug of abuse and a therapeutic agent.

Key Words: Agonist opioid treatment; psychopathology; heroin addiction

1 Psychoactive action of opiates

Since opioidergic receptors and pathways were first described, interest in the psychotropic properties of opiate drugs has increased considerably, in spite of limitations due to the restrictions placed on medical use. Research on inner opioids led to the discovery of peptides with morphine-like effects during the 70’s [18]. Four classes of inner opioids were described: endorphines, enkephalines, dynorphines, endomorphines [23] and three types of classic opioid receptors were identified, and named \( \mu \) (mu), \( \delta \) (delta) e \( \kappa \) (kappa) [42], each characterized by specific related functional parameters [53]. Based on the type of interaction with the mu receptors, opiates were divided into full agonists (e.g. methadone), partial agonists (e.g. buprenorphine) or antagonists (e.g. naltrexone). Full agonists bind to the receptor and produce a maximal stimulation: when challenged by the mass of brain receptors, they produce a dose-dependent increase at tolerated dosages. Partial agonists bind to the receptors, but produce a weaker effect: when challenging the mass of brain receptors, the elicited effect reaches a plateau, so that higher dosages fail to produce any further effect. Antagonists bind to receptors without producing any effect, although effects can be produced when antagonists interact in vivo with the mass of brain receptors in the context of intermingled opioid and non-opioid pathways [55]. Opioids produce their functional effects on tissues and organs directly, or by their interaction with other neuromodulatory systems, including those closely related to the
physiology of pleasure and reward-seeking. Among opioid-related functions we may mention pain control, mood, blood pressure and cardiovascular functions, breathing, thirst, hunger and appetite, sexual arousal and genital functioning [64].

1.1 Short-term effects

For people with no or little tolerance to opiates – a phenomenon found in opiate-naive persons or after the resolution of acute withdrawal – the administration of opiates may produce an acute intoxication syndrome including (potentially lethal) respiratory depression, central nervous system depression, pupillary constriction, itching, nausea and vomiting [45]. Regular exposure to opiate agonists causes the development of tolerance, so that usual dosages become neutral, and higher doses are needed to restore the desired effect. On the other hand, if exposure is not renewed at regular intervals, rebound symptoms develop, which then follow a transient course leading to a gradual return to the baseline tolerance level (indicated as zero tolerance). Rebound (withdrawal) symptoms include anxiety, agitation, abdominal aches, shivers, goose pimples, dilated pupils, and are promptly interrupted by the administration of an agonist at doses over the acquired or residual tolerance threshold. The condition of acquired tolerance and susceptibility to withdrawal is improperly though commonly referred to as “physical dependence” [21].

1.2 Long-term effects

As time goes by, frequent or regular opiate users experience a change in their drug-seeking behaviour: their increasing desire following the first experience overlaps with and is hijacked by craving, an instinctual, appetitive urge which is no longer influenced by reasoning or the intentional planning of safe and rewarding use. For those who decide to discontinue drug use, because of the awareness of drug-related risk or the impossibility of handling drug use in a rewarding and safe way, craving takes the form of a subjective ensemble of drug-related thoughts and feelings leading to relapsing behaviour. Craving-sustained use is referred to as “psychological dependence”, as opposed to the urge to resort to drugs as means of withdrawal buffering [54]. The initial rewarding effect tends to diminish as tolerance to opiates develops: in the presence of craving, the subjects see no choice but that of increasing dosages or the frequency of administration, thus causing tolerance to increase further and withdrawal to become more likely. On the other hand, the natural history of addiction also features recurrent detachment from the drug, which is the only possible alternative to uncontrolled use: thus, the course of addiction is articulated in cycles of uncontrolled drug use, detachments, drug-free periods and relapsing behaviour. Through these cycles, the rewarding, hedonistic component is progressively lost, because it becomes overwhelmed by craving, dysphoria and disruptive behaviour. Likewise, the initial state of hyper-stimulation of the opioid system dwindles to a chronic, not fully reversible state of opioid impairment, subjectively corresponding to a feeling of generalized apathy and dissatisfaction, named “hypophoria” [24, 34, 59].

1.3 Opiate effects and pharmacokinetics

The effects of exogenous opiates vary along their pharmacokinetic profile: in fact, the quality of opiate effects and their longer-term consequences depends on the rapidity of their action on neuronal targets. Fast-acting opiate agonism, which reaches its peak quickly, produces a kind of stimulation that induces longer-term changes in the spontaneous metabolism of the stimulated pathway, beyond the intensity and quality of the acute effect. Slow-acting opiates, on the other hand, have a therapeutic potential in long-term regimens, since they produce neutral, or even beneficial (trophic) effects on the metabolism of stimulated pathways. The same substance may act either as a toxic, destabilizing agent or as a neutral, potentially therapeutic one, according to the rapidity of absorption, release and the mode of administration (intravenous or inhalatory versus oral). The impact of therapeutic opiates, already employed as anti-craving agents, on the psychopathological symptoms of heroin addicts has not yet been fully clarified, although opiate drugs have been known for decades to have potential therapeutic effects in mentally ill individuals [14].

2 Therapeutic effect of opiates

2.1 Opiates and panic

Enkephalin (together with serotonin) is known to modulate the projection originating from the dorsal nucleus of the raphe and leading to the amygdala [26]. Peak anxiety and somatic symptoms were reported amongst buprenorphine and tramadol side effects in a post-marketing surveillance perspective;
they were, however, likely to be part of acute opioid imbalance in subjects with high tolerance levels, because those opiates were insufficient to buffer withdrawal, or actually worsened it due to acute partial agonism (relative antagonism) [56, 62]. In subjects taking effective methadone dosages during the maintenance phase, the emergence of panic attacks and agoraphobia is exceptional. In addition, cases of previously diagnosed panic disorders may achieve apparently spontaneous remission during successful agonist maintenance. In these cases, panic symptoms may return during methadone tapering, which may be favoured by the increase of noradrenergic activity as a correlate of reduction of opioid coverage below the tolerance threshold in panic-prone individuals, despite the absence of classic withdrawal syndrome [36]. In fact, the acute administration of yohimbine shows that heroin addicts who have successfully undergone withdrawal treatment maintain supersensitivity to pro-noradrenergic stimulation [65].

Panic attacks with no link with opiate withdrawal have been reported in non-addicted patients after the administration of naltrexone [27, 33] or k-agonists [20]. On the other hand, naloxone did not produce any panic symptoms in patients already suffering from panic disorders [1], which suggests a likely difference between acute opiate antagonism and enduring antagonism, the latter being effective in eliciting pathological anxiety.

2.2 Opiates and depression

Starting in the 1950s and until legal restrictions were placed on their medical use, opiates were used in the treatment of mood disorders and aggressiveness, due to the feature of the rapid onset of their antidysphoric action. Undoubtedly, endorphins are highly concentrated in the limbic system and hypothalamus, and their metabolism is intermingled with that of monoaminergic pathways. Long-acting opiates were indicated as effective in enduring depressive syndromes displayed by detoxified heroin addicts. Such observations, together with the discovery of inner opioids, converged to suggest that the endogenous opioid system plays a role in the pathogenesis of depression itself. Also, electroconvulsive treatment was found to produce improvement in mood parameters, which was linked to the increase in levels of beta endorphin [8, 48]. During the Eighties, opiates were regarded as potential candidates for the treatment of dysthymia, as a new class of antidepressant drugs [10]. In particular, buprenorphine was tried on a group of depressed patients who had shown they were resistant or poorly responsive to common antidepressant treatment, with promising results [3, 4, 9]. Buprenorphine was particularly interesting as an instrument to probe the effects of opiate receptor stimulation, due to the combination of partial mu agonism and k-antagonism [47]. The effect of k-antagonism of buprenorphine was studied using, at same time, naltrexone and buprenorphine, so as to counterbalance mu-agonism and leave k-antagonism as the sole mechanism of action: authors found significant improvements in dysphoria, depression, irritability, anxiety, asthenia, nausea and painful symptoms, in comparison with previous results from experiments with naltrexone or in a drug-free regimen [13, 57].

Depression at treatment entrance is among the negative predictors of one-year retention in naltrexone maintenance, together with psychosis and aggressiveness [35]. The incidence of thoughts of death and of ending one’s life are considerably greater during naltrexone maintenance than during methadone or buprenorphine maintenance, regardless of treatment response; this finding suggests an independent impact of opiate antagonists on the mental status of inactive heroin addicts (personal unpublished data). Nevertheless, naltrexone-induced dysphoria is exceptional during the first three months of a low-dose (50mg) naltrexone programme [11, 44], but may be more common at doses of 100 mg or more, and/or in the long term [6, 28].

2.3 Opioid anti-manic effect

Agonist maintenance may be effective in stabilizing heroin addicts with comorbid bipolar disorder I. One study of ours shows, in a naturalistic manner, that heroin addicts with additional psychiatric diagnosis may display similar outcomes to those with no additional diagnosis, as long as their stabilization dosage is maintained at a high level, approximately 150% of the average for uncomplicated addicts. In other words, the two groups displayed similar 3-year retention rates and outcomes to those of dual diagnosis addicts, who mostly displayed axis I bipolar disorders, as long as their stabilization was achieved through the prescription of unusually high methadone dosages [41]. Dual diagnosis patients, followed for 8 years, showed better retention in treatment of peers without dual diagnosis [37]. Moreover, the time taken to achieve stabilization was longer for dual diagnosis addicts; this did not just depend only on the longer time needed for induction into higher dosages.
In heroin addicts hospitalized for acute psychosis or psychomotor excitement, mostly corresponding to major manic or mixed states, subjects who had their methadone dose increased or were being started on methadone were less often given a prescription of antipsychotics and anti-manic drugs at discharge, although the duration of hospitalization was similar [49]. It was noticed that methadone-maintained heroin addicts are less subject to mood swings, whether on the depressive or on the manic side [60].

Naltrexone was reported to have anti-manic properties, which may be recuperated by counter-balancing the rise of endorphine levels, which is the source of euphoria and elation states [67]. However, manic relapses were not prevented during naltrexone maintenance [66], and mood disorders quoted as a negative predictor of retention in a naltrexone programme [35]. Naltrexone may be a partial obstacle to the display of certain manic symptoms (manic euphoria), without blocking the onset or the course of psychomotor excitement, so that the resulting dysphoric mixed mania or mixed states will increase the likelihood of treatment discontinuation.

2.4 Antipsychotic effects of therapeutic opioid

Opiate agonists are known to induce acute neuroleptic-like effects on the endocrine system, such as hyper-prolactinemia and the suppression of surrenal activity. Sedation may also take place when the tolerance threshold is overcome during the induction phase [2, 15]. On neurochemical grounds, typical antipsychotics and opiates both act on the same neuronal targets and interfere with dopaminergic transmission, though they move along different molecular pathways [5]. Buprenorphine has shown it is active against hallucinations and delusions over a time-span of four hours in a small group of heterogeneous psychotic patients [61]. Selective k-agonist receptors (such as pentazocine), on the other hand, have psychotomimetic properties [17, 19]: this toxicological property is in line with the finding that the levels of the endogenous selective k-agonist dynorphines are related to the severity of symptoms in schizophrenic subjects [16].

Methadone maintenance treatment can be credited with preventing relapses in psychotic subjects with a previous history of psychotic episodes [25]. The subtraction of methadone treatment may be followed by psychotic relapses [25, 63]. Although the emergence of psychotic symptoms is uncommon as a feature of heroin withdrawal, the abrupt interruption of methadone from a tolerance level far higher than that achievable by regular heroin use may produce a major late-onset dopaminergic rebound.

In heroin addicts hospitalized for an acute psychotic episode, the increase in methadone dosage or the initiation of methadone treatment was effective in achieving control of psychotic symptoms even when applying lower rate of treatment doses of antipsychotics and anti-manic drugs, while the duration of hospitalization itself remained unchanged [49]. The profile of psychotic heroin addicts at their first treatment attempt displays a higher level of global symptom severity, though coupled with less severe addictive symptoms and a shorter duration of addictive history, with respect to their non-psychotic peers. It may be speculated that the presence of a psychotic background underlying opiate use leads to an early worsening of global mental status through fast-acting opiate use; it is therefore likely that agonist treatment will favour opiate stabilization. Apart from the resolution of the withdrawal-related exacerbation of psychotic symptoms, the positive impact of opiate agonism, which may have been the reason for transition to regular heroin use, may be recovered by slow-acting, stable dose agonist treatment, but in a re-stabilizing way, rather than a de-stabilizing one [29]. In other words, the long-term use of opiate agonists may be effective in the treatment of psychotic symptoms in former psychotic patients who later became heroin addicts through a self-medication practice [22, 29]. Psychotic heroin addicts may be represented among those who resort to street methadone as a regular practice before entering treatment, which should be regarded as a self harm-reducing behaviour rather than a poly-abuse pattern. In fact, those patients may have an independent motivation for seeking treatment earlier and staying in treatment longer, which may overcome addictive ambivalence and improve compliance [38]. In evaluating the psychiatric diagnosis of patients who are entering treatment, we attempted to distinguish between patients who had started heroin use after the onset of psychiatric disorders, and those who had suffered from psychiatric disorders after the onset of their drug-using habit. Among the former, psychotic disorders and anxiety disorders were better represented, and were linked to the trend towards less severe addictive symptoms. The latter group mostly consisted patients suffering from mood disorders, who have more severe addictive symptoms. Although the time sequence is not a definite proof of self-medication dynamics, it is somewhat consistent with the idea that some disorders, rather than others,
may lead to heroin by a self-medication route [30]. The same patients would then suffer from an early worsening of their psychiatric disorders, due to acquired opiate imbalance, when the severity of their addictive disease is still at a low level; they will benefit more directly from the opiate-balancing effect of agonist treatment [32]. Methadone dosage would work partly as a psychotropic stabilizer, regardless of addictive symptoms, so that the eventual stabilization dosage will be higher than in non-psychotic heroin addicts. Once both psychopathological grounds (addictive and psychotic) have been neutralized, psychotic heroin addicts may reach a positive outcome, unlike what could be expected in the absence of treatment [43, 58].

Opiate antagonism was also considered in relation to psychotic symptoms. For instance, naloxone administration did produce an improvement of symptoms in selected schizophrenic patients, but the results were not homogenous [67]. Subjects who were suffering from independent psychotic disorders were more likely to drop out of naltrexone treatment by the first year [35]. The negative impact of opiate antagonism on psychosis is indicated by the evidence that psychotic symptoms worsen during long-term naltrexone treatment [66]. Thus, the predictable interaction between opiate antagonism and certain psychotic disorders, when combined with opiate addiction, is unfavourable.

3 The impact of methadone and buprenorphine on the psychopathology of opiate addicts

Evaluation of the psychological profiles of substance abusers is particularly awkward, especially at the time of treatment entrance, because of the heterogeneity of psychic disorders, which may be attributable to pre-existing psychiatric disorders, or to transient or persistent substance-induced cerebral changes, or else to psychosocial conditions associated with addictive lifestyle, or, lastly, to the cerebral changes that run parallel to the process of addiction onset and its worsening [46]. The current official nosography (DSM-IV TR) only accounts for those features that can be objectively attributed to one specific clinical picture, out of all the theoretical configurations that are possible.

As mentioned above, drug addicts display an array of psychopathological signs that act as one direct cause of their psychosocial competence and health status. According to the DSM-IV TR perspective, such features belong to the sphere of comorbidity. Nevertheless, such a psychopathological ground is closely related to, when not actually overlapping with, the development and self-maintenance of addiction upon a specific cerebral substrate, as an autonomous process. Some authors have outlined a pathogenetic mechanism by which drugs of abuse may interact with the underlying substrate, whether this is expressed by temperamental traits or subthreshold psychopathological patterns, which themselves represent a risk disposition for engagement in experimental substance use or a process of transition to intensive use. Thus, such conditions, by their influence on the frequency and variety of drug use, would also indirectly favour the onset of addiction as an autonomous, enduring substance-induced process. On this view, symptoms belonging to the dimensions of mood, anxiety, and impulse control should initially be considered as intrinsically related to the addictive process, and as mirroring addiction severity and activity [51].

Depressive symptoms were reported to be a positive 3-month predictor of retention and opiate use during buprenorphine treatment [12]. By contrast, the MMPI depressive dimension proved to be a negative predictor of retention [52]; similarly, Symptom Checklist-90 (SCL-90) [7] depressive and paranoid features were predictive of dropout [50]. We assessed treatment-entering opiate addicts by means of a rating scale for the screening of general psychopathology, the SCL-90: our aim was to measure the impact of agonist treatment on the baseline psychopathological profiles of patients. When applying a dimension-oriented analysis, significant and generalized improvement is seen both with methadone and with buprenorphine treatment [50]. Although SCL90 is not a screening instrument for addictive symptoms or drug use-related psychopathology in its 9 different dimensions, we did manage to describe a typical 5-dimension profile for heroin addicts entering treatment [39].

In a later paper we ascertained the quality of life in methadone- or buprenorphine-treated opiate addicts at a 12-month follow-up by selectively enrolling those who had survived the early 3-month attrition, in order to equalize the post-treatment status of addictive symptoms [40]. On the whole, successfully treated heroin addicts showed improvement on all grounds with either agonist treatment regimen [40, 50]. In a recent paper we presented the results of a psychopathological analysis of 1055 treatment-entering opiate addicts, again by applying the SCL-90, and attempting to classify heroin addicts according to their dominant dimension. We were able to distinguish 5
subgroups with the following dominant dimensions: (1) depressive symptoms, including feelings of hopelessness, and a perception of being trapped in a corner, as might be expected with patients who had applied for addiction and/or psychiatric treatment, (2) somatic symptoms that might turn out to be predictable in relation to ongoing withdrawal, (3) interpersonal sensitivity and psychotic symptoms, (4) panic symptoms displayed as agoraphobia, (5) violence and suicide, including impulsive acting-outs, self-directed aggression and assaults, non-violent impulsiveness. The groups did not differ by sex or disease duration. A younger age was a feature of patients belonging to groups 3 and 5, whereas patients belonging to groups 1 and 2 were older [39]. We used this five-factor psychopathological classification to determine whether psychopathological dominance at treatment entrance may be regarded as a predictor of the differences in therapeutic impact of the two agonist treatment regimens. Patients entering with dominant depressive, somatic and panic-agoraphobic symptoms benefit from either treatment to a similar extent. On the other hand, patients with dominant sensitivity-psychoticism do better when matched up with a methadone regimen, whereas those mostly featuring violence and suicide items are more likely to be retained in treatment when assigned to a buprenorphine regimen. This is the first study on a large sample that has provided evidence of a link between dimensional psychopathology and the differences in impact of agonist treatments, which were found to be separate from the effectiveness of addictive symptoms, with direct patient/treatment-matching implications [31]. In order to minimize the possible impact of fast induction on high buprenorphine doses, we observed a smaller group of dual diagnosis patients entering methadone or buprenorphine treatment, with a flexible dosage regimen starting from anti-withdrawal dosages and moving on to anti-craving and stabilization dosages, on a clinical basis, over a 6-month period. Diagnostic subgroups were similar between groups, while the need for additional psychotropic medications as safeguards for various psychopathological targets was higher in the buprenorphine group, especially as regards anti-psychotic medications (personal unpublished data). Although less sound, such data are consistent with the stronger impact of methadone on comorbid psychosis as a psychopathological dimension.

4 Conclusions

Evidence from the literature and suggestions from clinical practice converge in indicating solid grounds for the proposal of using opioidergic drugs as primary psychoactive drugs, and determining the need to reconsider their therapeutic potential separately from the issue of abuse liability and adverse events. In fact, opioidergic drugs should not be considered merely as anticraving agents, or, more exactly, their anticraving action against opiate addiction should be regarded as only one of their possible therapeutic targets. Opioidergic drugs loom as new candidates for the treatment of psychosis, mood and anxiety disorders, because they offer a different mechanism of action from the already available classes of psychotropics. Addiction is accompanied by a desensitization of the endogenous opioid system, enduring throughout the reversible aspects of tolerance, which is a long-lasting consequence of repeated exposure to fast-acting opiates such as heroin. Some subjects do initially benefit from the anxiolytic, mood-regulating and thought-controlling effects of opiates, but they eventually develop a psychopathological inadequacy, due to the resulting functional hypotrophy of the overstimulated circuitry. The opioidergic deficit that develops through fast-acting opiate use has a twofold nature: on one hand, there is the addictive component, and, on the other, the component related to pre-existing psychopathology. In the case of dual diagnosis, this appears to result in double damage, depending on the combination of the psychopathological component with generic addictive damage. In the case of uncomplicated addiction, a lower level of opioid agonism may be enough to create a narcotic blockade, to compensate for the opioidergic dysfunction. Otherwise, in the case of an independent psychopathology, a greater level of opioidergic dysfunction can be expected, from two independent but synergic sources, so that the restoration of a normal opioid function would require unusually high levels of agonism with respect to the treatment of uncomplicated addiction.

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Intentional self-poisoning versus other methods of suicide in illicit drug users, according to gender

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Summary

Monitoring of the association between suicide and drug-related deaths (DRDs) in illicit drug users is not carried out consistently in many European countries. In our study, we evaluated DRD suicides unrelated to alcohol in Slovenia during the years 2002-2007, and compared suicide methods between males and females. Out of 356 cases of DRD, 106 (64 males and 42 females) were DRD suicides. Of these, 69 (65.1%) were due to intentional self-poisoning by drugs, 30 (28.3%) were due to other methods for committing suicide, and 7 (6.6%) utilized intentional poisoning together with another method. Females were older than males; self-poisoning with benzodiazepines was more frequent in females and, in our study, no females were self-harmed by hanging, by suffocation, or by firearms. In females, age was tested as a risk factor that has proved to be more important than suicide modality, but the use of benzodiazepines in female illicit drug users should be considered a critical issue with increasing age.

Key Words: drug-related deaths; suicides; heroin use; intentional self-poisoning by drugs

1. Introduction

Suicide is one of the top 10 leading causes of premature death in Europe, although the incidence of suicide has been falling since 2000 in the 27 EU countries [14]. Slovenia is a Central European country that is marked by high rates of suicide and of liver cirrhosis [12]. Both annual rates have exceeded 30 deaths per 100,000 of the population in some years in the latest decades, and alcohol-related psychiatric disorders are the best predictor of the regional suicide rate (SR) [11]. In the years 2000-2007, between 25 and 30 deaths due to suicide were recorded in Slovenia [14]; thus Slovenia is still a country that, among the EU group, has one of the highest SR figures, along with two other new member states, Lithuania (28.9) and Hungary (23.2) [14].

Studies on suicide in the general population have shown that there are significant gender differences; males commit suicide more frequently than females, and males are more likely to employ violent methods (e.g. hanging and shooting), whereas females are more likely to employ non-violent methods, such as poisoning with drugs [4]. In the case of Slovenia, survey results show that, in the general population, males commit suicide 3.5 times more frequently than females, and that two-thirds of those whose death was due to suicide decided to hang themselves (males more frequently than females; almost three quarters of the male suicides and over half the female ones) – a result that is peculiar to Eastern Europe countries [13]. The mean age of those whose death is due to
suicide is just under 51 years, 20 years less than the mean age for deaths from natural causes, but the suicides recorded in Slovenia for women aged at least 65 show a very high SR (in 2003 the SR for Slovenia was ranked first in the world) [19].

The risk factors for suicide in the general population have been properly researched worldwide, whereas less is known about suicide in heroin users [3,4]. Gender, psychopathology, family dysfunctions and social isolation have been recognized as risk factors for suicide in the general population, as in heroin users, too, but there has been a higher prevalence among the latter group. Heroin users are exposed to additional risk factors related to drug use [3,4]. They run a higher relative risk for suicide compared with the general population; in particular, figures for an age-specific standardized suicide mortality rate for heroin users were reported at levels up to 14 times higher than in matched peers [3,4].

The tradition of monitoring the association between suicide and alcohol use in Slovenia is well established, and has involved attentive studies, but a possible association between suicide and illicit drug use has never been scientifically explored; to date, no studies on this topic have appeared in the literature. The reason lies partly in the fact that the epidemic presence of heroin addiction in Slovenia only started in the early 1990s. Considering the facts mentioned above, and the high SR in the Slovene population, we could expect suicide among the population of heroin addicts in Slovenia to be present but under-reported, due to the WHO rules for selecting and encoding the underlying cause of death. Suicides among drug users are recorded in the General Mortality Register (GMR) when death is the outcome of self-directed poisoning, with a fatal concentration of illicit drugs in the body, but not, for instance, when a drug user commits suicide by hanging. The aims of the present study are to analyse DRD suicides among illicit drug users (without any relation to alcohol) in Slovenia during the years 2002-2007, and to compare the use of various suicide methods between males and females.

2. Methods

2.1. Source of data, data collection, definition

For the purpose of retrospective study, data on people who committed suicide in Slovenia in the period 2002-2007 were obtained and extracted from two sources, the GMR and the Special Mortality Register (SMR), both run by the National Institute of Public Health. In the meantime the SMR has been terminated, the latest data being those for 2007.

The data on the deceased and their causes of deaths are collected on the “Medical Death Certificate and Civil Death Certificate (DEM-2 form)” and stored in the GMR. The causes of deaths are encoded according to the WHO International Classification of Diseases, 10th Revision (ICD-10). Among all the different causes of death appearing in the GMR, the DRDs include cases where the underlying causes of death are: mental and behavioural disorders due to psychoactive substance use depending on opioids, cannabinoids, cocaine, other stimulants, hallucinogens or multiple drug use (F codes), or poisonings that are accidental, intentional or of undetermined intent (X and Y codes) due to the substances included under the heading of narcotics (T40.0 - T40.9) or psychostimulants (T43.6) [7,8].

The SMR comprises the data collected from a variety of data sources: data from the GMR, those from the Institute of Forensic Medicine in the Medical Faculty of Ljubljana and those from the General Police Administration of Slovenia. The SMR forms were filled in with the demographic data for the deceased person, the underlying causes of death, and the manner of death, e.g. a traffic accident, violence, or the effects of illicit drugs in body fluids, if present. For the analyses, cases were selected in which death was due to fatal poisoning by accident, or suicidal intent, a consequence of homicide, or death with undetermined intent. In all these violent deaths, one of a set of illegal drugs of abuse had to be involved [7,8].

Among all DRD deaths, these due to suicide (intentional poisoning and intentional self-harm) were studied.

2.2. Statistical analysis

Comparisons between male and female cases were made using univariate T-test and Chi-square (Fisher exact). Variables found to be significantly different at the p<0.05 level were used in a logistic regression analysis to predict gender as a criterion. We used the statistical routines of SPSS, version 20.0.

3. Results

In the time period 2002-2007 in Slovenia there were 356 cases of DRD, including 106 (29.7%) cases of suicide (but excluding alcohol-related suicide). Of these suicide victims, 64 (60.4%) were male and 42 (39.6%) were female. Mean age of death for females
was 48±21 (95%CI 41-54); mean age for males was 37±13 (95%CI 34-40). Mean age at death for males was significantly lower than that for females (T=-3.25 p=0.0008).

Among all cases of suicide, slightly fewer than 2/3 were due to intentional self-poisoning by drugs, and over 1/4 were due to other methods of committing suicide by inflicting intentional self-harm; the remainder were due to a combination of self-harm and self-poisoning (Table 1).

Regarding the use of drugs as a way of committing suicide, it was found that the majority of victims died due to self-poisoning by narcotics and psychodysleptics, drugs obtained at an illegal market or prescribed by a physician. The second largest group consisted of antiepileptic, sedative-hypnotic and anti-Parkinson drugs; in a third group, accounting for a share of less than 7%, psychotropic drugs not classified elsewhere were involved, followed by diuretics and other unspecified drugs, medications and biological substances.

Narcotics and external causes were also involved in seven cases attributed to a combined manner of committing suicide.

External causes were involved in 1/3 of these deaths; the most frequent was suicide by hanging, followed by jumping from a high place, self-poisoning by the inhaling of exhaust gases from vehicles, and self-harm by other means or by the discharge of unspecified firearms.

Regarding gender, females more frequently used intentional self-poisoning as their way of committing suicide, whereas males mostly relied on other methods. Between men and women there were differences in the groups of drugs used for committing suicide, but also in the violent manners of death that were

### Table 1. Causes of suicide according to gender (Slovenia 2002-2007)

<table>
<thead>
<tr>
<th></th>
<th>Total N=106</th>
<th>Males N=64</th>
<th>Females N=42</th>
<th>Chi (df)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of suicide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-poisoning</td>
<td>69 (65.1)</td>
<td>34 (53.1) a</td>
<td>35 (83.3) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other methods of suicide</td>
<td>30 (28.3)</td>
<td>24 (37.5) a</td>
<td>6 (14.3) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other methods plus poisoning</td>
<td>7 (6.6)</td>
<td>6 (9.4)</td>
<td>1 (2.4)</td>
<td>10.26 (2)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Underlying cause of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisoning by narcotics and psychodysleptics [hallucinogens]</td>
<td>37 (34.9)</td>
<td>22 (34.4)</td>
<td>15 (35.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisoning by antiepileptic, sedative-hypnotic and anti-parkinson drugs</td>
<td>26 (24.5)</td>
<td>10 (15.6) a</td>
<td>16 (38.1) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisoning by diuretics and other or unspecified drugs, medications and biological substances</td>
<td>6 (5.7)</td>
<td>2 (3.1)</td>
<td>4 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poisoning by psychotropic drugs, not classified elsewhere</td>
<td>7 (6.6)</td>
<td>6 (9.4)</td>
<td>1 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No intentional poisoning</td>
<td>30 (28.3)</td>
<td>24 (37.5) a</td>
<td>6 (14.3) b</td>
<td>13.77 (4)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Manner of suicide – external causes of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-harm by motor vehicle crash</td>
<td>3 (2.8)</td>
<td>2 (3.1)</td>
<td>1 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-harm by hanging, strangulation and suffocation</td>
<td>8 (7.5)</td>
<td>8 (12.5) a</td>
<td>0 (0.0) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional injury-sharp object</td>
<td>3 (2.8)</td>
<td>2 (3.1)</td>
<td>1 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-poisoning and exposure to other gases and vapours</td>
<td>6 (5.7)</td>
<td>5 (7.8)</td>
<td>1 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-harm by jumping from a high place</td>
<td>7 (6.6)</td>
<td>4 (6.2)</td>
<td>3 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-harm by jumping or by lying down in front of a moving object</td>
<td>2 (1.9)</td>
<td>1 (1.6)</td>
<td>1 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-harm by other means and discharge of unspecified firearms</td>
<td>6 (5.7)</td>
<td>6 (9.4) a</td>
<td>0 (0.0) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-harm by drowning and submersion</td>
<td>2 (1.9)</td>
<td>2 (3.1)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional self-poisoning</td>
<td>69 (65.1)</td>
<td>34 (53.1) a</td>
<td>35 (83.3) b</td>
<td>15.59 (8)</td>
<td>0.049</td>
</tr>
</tbody>
</table>
chosen. Men frequently performed hanging, firearm discharge and self-poisoning by exposure to carbon monoxide. On the other hand, the most frequent form of violent suicide chosen by women was jumping from a high place; conversely, females did not inflict harm on themselves by hanging, strangulation or suffocation, or by the use of firearms.

Among the intentional poisonings, a close examination of the specific type of drug used, including consideration of the combined use of poisoning with other methods of suicide, revealed that intentional self-poisoning by benzodiazepines was the method most frequently chosen; it was even more frequent in females than in males. This method was followed by making use of the group of substances comprising morphine, heroin and opium, where men prevailed, followed by methadone and other or indeterminate drugs (Table 2).

Of all 69 cases where suicide was due to self-poisoning, the largest group (26 people) had used benzodiazepines; in many other cases, psychotropic drugs and non-psychotropic drugs were the cause of lethal poisonings, whether they were used alone or in combination. Considering now the involvement of narcotics, in 7 cases the use of narcotics was reported together with a violent cause of death: in 3 cases self-harm by other means or by the discharge of an unspecified firearm was combined with narcotics; in 2 suicides who had jumped from a high place, narcotics were found in their body fluids; in one case of suicide by hanging and in another case of drowning and submersion, narcotics were found, too. Considering all the cases of reported poisoning, half of these subjects used narcotics, but the majority used prescribed drugs, and only 13 cases involved illicit opioids (heroin, opium).

Using gender as a criterion and age at death and suicide modalities as predictors, logistic regression analysis showed the importance of age at death for females. Passing from self-poisoning plus other methods of suicide to other methods, or to self-poisoning alone did not add predictive value (Table 3).

### 4. Discussion

In our analysis it was found out that 29.7% of DRDs were cases of suicide, with a male to female ratio of 1.5:1. When committing suicide, women were on average 11 years older than men. The majority of suicides were an outcome of self-poisoning, irrespective of what drugs had been prescribed by a physician or obtained from an illegal market. Furthermore, one quarter of suicide victims died in a violent manner, and a minority died from a combination of drug use and violent death. In comparing the situation for men and women, there was a difference in the groups of drugs used for suicide and also in the violent manners of death chosen. Only the factor “age at death” identified a significant difference between men and women.

The data analysed in the present article were obtained from the SMR; those data had been prepared in a way that implemented the recommendations of

| Table 2. Intentional self-poisoning by specific drugs, class of drugs |
|---------------------------------|-------|-------|---------------|-------|
|                                | Total | Males | Females       | Chi (df) | p     |
| No poisoning                   | 30 (28.3) | 24 (37.5) | 6 (14.3) | b      |
| Morphine, heroin, opium        | 24 (22.6) | 14 (21.9) | 10 (23.8) |         |
| Methadone                      | 9 (8.5) | 5 (7.8) | 4 (9.5) |         |
| Benzodiazepines                | 26 (24.5) | 10 (15.6) | 16 (38.1) | b      |
| Other or undetermined          | 17 (16.0) | 11 (17.2) | 6 (14.3) | 10.31 (4) | 0.036 |

| Table 3. Backward stepwise logistic regression. |
|---------------------------------|-------|----------------|
| Criterion: gender; predictors: age and suicide modality. | B | Exp (B) | 95% CI for EXP (B) |
|---------------------------------|-------|----------------|
|                                | Min | Max | p     |
| Age                            | 0.03 | 1.03 | 1.01 | 1.05 | 0.031 |
| Suicide modality                |     |     |      |
| Other methods plus poisoning vs other methods | 0.46 | 1.60 | 0.16 | 16.31 | 0.065 |
| Other methods plus poisoning vs self-poisoning | 1.57 | 4.78 | 0.53 | 43.25 | 0.692 |
| constant                        | -2.78 |     |      |
the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). The aim of merging the data gathered from three data bases was to include as many DRDs as possible that had occurred in Slovenia in the period 2002-2007. The quality and reliability of the data obtained were safeguarded by searching for additional information whenever basic data were missing.

In interpreting data for DRDs in Slovenia, it should be borne in mind that the deceased are usually heroin users. Various studies have pointed out that suicide proves to be an important component of mortality among heroin users; with these subjects, the proportion of DRDs that is due to suicide ranges from 3% to 35%, most frequently lying in the 3-10% range [3,4]. As in the general population, heroin users who committed suicide are predominantly males (1,17), while those who attempt suicide are predominantly female [2,3,5,18]. Studies on suicide among heroin users have rarely reported gender-specific data in methods used for suicide [3,4]. A majority of these cases of suicide are take the form of poisoning, hanging and gunshot wounds, and, due to the predominance of males among the deceased, violent methods are the most commonly reported means of suicide, while poisoning with substances such as drugs constitutes a small minority of male fatalities, but as much as a half of female deaths [3,4]. The almost 30% suicide rate among all DRDs, the male to female ratio and the methods of suicide found in our study are in agreement with the results reported in the literature.

Studies reporting methods for committing suicide used by heroin users indicate a much higher proportion of fatalities that relied on self-poisoning with substances than in the general population; drug overdose was the means of suicide in at least half of these cases [3,4,16]. In short, as is true too of the general population, among heroin users suicide committed in a violent way is common, especially because of the high proportion of males, but self-poisoning by drugs is a predominant feature of completed suicide [4]. Although drug overdose is a major cause of suicide in heroin users, it is non-opioid prescribed pharmaceuticals that constitute a clear majority [3-5], and, in the opinion of some authors, this could also be applicable to studies that have merely reported a substance overdose without further specification [3,4,16]. One paradox that emerges is the low proportion of suicides that are due to an overdose of heroin. The relationship between heroin overdose and suicide is a controversial one [4], because heroin overdoses constitute only a small proportion of completed suicides [5]; some authors have hypothesized an association between heroin overdose and suicide [15,18], whereas others have expressed doubts about this association [5,6,9]. On the other hand, heroin overdose is the most common cause of DRDs, which are usually accidental. Heroin overdoses are over-represented in males (with frequencies that exceed 80%), but it is striking that in 80% of cases involving heroin addicts, in spite of this finding, the deaths that are due to suicide do not directly involve heroin [3].

With reference again to the literature mentioned above, the second section of the results reported in this our study are likewise coherent with earlier studies. Females mostly died as a result of intentional self-poisoning by drugs, and not a single female was self-harmed by hanging or suffocation, or by firearms. By contrast, the suicides of males were most frequently carried out in ways that differed from those chosen by females, and took a violent form, especially self-harm by hanging, self-harm by the use of firearms or revolvers, and intentional self-poisoning by inhaling carbon monoxide.

The most frequently used class of drugs, utilized by one third of the deceased, was the group of substances comprising narcotics and psychodysleptics, followed by the use of one of the group of antiepileptic, sedative-hypnotic and anti-Parkinson drugs, which were involved in one quarter of cases. Referring now to the specific types of drug most frequently used in committing suicide through intentional self-poisoning, benzodiazepines were resorted to in one quarter of these cases; the higher frequency found in women compared with men was statistically significant. Benzodiazepines were followed by narcotics (morphine, heroin and opium), which were used in one fifth of these cases, and methadone by less than one tenth. It should also be noted that in a half of all cases narcotics were used too, whereas in the other half no narcotic prescription drugs were involved. For these cases, with a few exceptions (notably, methadone) ICD codes do not specify individual drugs, as the codes are structured in a way that groups drugs and drug classes together. No information was available either on whether prescription drugs had been prescribed to drug users or had been acquired from an illegal market. Although suicides caused by an overdose of heroin only accounted for a small proportion of suicides, an overdose of a substance belonging to the larger group comprising all narcotics was present in almost one half of these cases.
5. Conclusions

In cases of DRD suicide, death occurred ten years earlier than the average recorded for cases of suicide in the general population. The mean age of female suicide victims has been higher than that of male ones over the last ten years. In addition, the percentage rate of women who committed suicide has been very close to that for men, which is not the case with other forms of DRD. Drug users are endangered, especially because of the risk of suicide due to intentional self-poisoning by drugs; in these cases, females run a higher risk than males.

Both suicide as an outcome of depression, and suicidal behaviour or other psychopathological tendencies should be prevented by interventions that aim to achieve early detection, together with appropriate and effective treatment for addiction and other mental disorders. As cases of heroin overdose due to the intention to commit suicide seem to be rare, and prescription drugs were the most frequent choice in carrying out intentional self-poisoning, special attention should be dedicated to prescription drugs. The data certainly indicate the need for caution in prescribing practices for this group, particularly with respect to benzodiazepines.

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The Italian Manifesto for the treatment of heroin addiction. The mixed care model

A proposed layout for a new healthcare system for citizens with heroin addiction

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What is the point of writing a Manifesto about addictive diseases? The appearance and profiles of patients and their addictive diseases have inescapably gone through changes as the years have passed. Going back to the 1960s, sexual revolution was the ultimate frontier, whereas nowadays social media are the main challenge. What was once restricted or prohibited has become acceptable and available, to an extent which former promoters of change themselves consider excessive. Everything seems to have evolved and changed its array, everything but heroin addiction.

What has not changed, though, is the unrelenting stigma that afflicts men and women who fall ill of addiction, and extends out to their families and children, their environments and hopes.

“You are nothing but a junkie” – that is, more or less, what a lot of patients repeatedly get to hear as an immediate judgment given by their employers, friends and significant ones. This may be taken as a dramatic example of how this category of ill people is denied the right to be normal. On the other hand, it may also sound like a denial of the social duty to have these people cured, just like any other category of patients.

Although we are the ones who have been committed throughout our lives to explaining such medical platitudes, on a topic very similar to the normality of illness or the equal status of various diseases, we cannot disregard the persistence of a stigma as deep as this one.

This explains why a Manifesto about Addiction,
written with the aim of improving society’s ability to deal with addictive diseases, has been prepared as the most balanced way of portraying the thoughts we share as a group of scientists. This constructive document, which was originally proposed during the Addiction Medicine Expert Forum that was held in March 2013 in Pietrasanta, Lucca, Italy was thus intended as a structured, unified way of expressing, precisely and concurrently, a request for a change in the status quo of opiate addiction healthcare standards and trends.

As any Manifesto is supposed to do, this document aims to formulate and illustrate rules and principles put forward from the perspective of challenging the criticisms that have been made by experts, patients, their families and – why not? – those who are neither directly or indirectly involved in addiction-related issues.

None of us hope our children will have to live in a world where ignorance and prejudice can easily prevail over skill and knowledge. Had we that in mind, we would probably have resigned from any commitment to the understanding and treatment of addiction, rather than dedicating most of our professional lives to it, and would have chosen any other field of interest and occupation.

In line with this feeling, our keenest wish is that this “Italian Manifesto for the Treatment of Addiction: a mixed model” may become a milestone upon which a new integrated model of intervention can be developed.

1. **Addicted patients today: changes in drug use trends and drug-related environments in the last 30 years.**

   *By Isabella CECCHINI*

GfK-Eurisko is to date the most important Italian agency for market surveys, and it has the capacity to adequately cover the various aspects of social life and market dynamics as far as purposes, fields and sectors, methods and procedures are concerned, across a large number of nations worldwide. It has also developed sound expertise in the field of addiction research over the last decades. This research sector has included dozens of qualitative and quantitative investigations, and thousands of interviews held with both physicians and patients, so attaining the objective of a thorough analysis of the whole statistical universe of addiction-related topics. Out of this substantial body of data, one statistically significant finding has always emerged: the fact that the profiles of addicted patients and their drug-related lifestyle have gone through radical changes more than once over the years.

A recent study on a sample of 100 physicians working in addiction treatment units within Italy, and 378 addicted patients receiving agonist treatment in those same treatment units, sheds some light on the current approach to addiction and the role of available treatment in Italy.

It appears that the stereotypical addict no longer has to face a condition of isolation, social marginality or degradation of general living conditions. Patients with addiction can now count on agonist treatment, they often have a job, lead a normal social life and are able to maintain social ties. The Gfk-Eurisko survey described above, which was carried out during the Spring of 2011, portrays average addicted patients as work-competent, despite their history of drug addiction (around 50% of interviewed patients were currently employed), with at least a secondary level of school education (almost 50% had a high school diploma), and a stable social and family environment (one out of three was married or was living with their partner, one out of four had children, almost 80% were mainly living with relatives, a partner or friends). Younger patients are more frequently female than older ones (34% vs. 18%), had a higher educational level (54% had a high school diploma vs. 34% among older ones), but were less often employed.

Heroin consumption is typically the latest step in a substance use career that starts quite early: tobacco smoking and drinking during adolescence come first, running parallel to a variety of risk behaviours, to be followed by experimentation with amphetamines, LSD, ecstasy and cocaine (on average, before the age of 18). Younger patients have a more complex history, marked by a higher number of abused substances and heavier drinking. As a rule, patients are informed, motivated to enter treatment, show that they appreciate and feel grateful for what is offered by the healthcare system, and declare their full satisfaction with the treatment provided by addiction treatment units. They have usually have heard about different treatment options, and younger ones are more likely to have heard about newer medical drugs. Two patients out of three receive methadone, one out of four buprenorphine-naloxone, and 13% buprenorphine. Patients declare they are satisfied with their on-going treatment, and regard it as the way they have successfully used to break away from their previous drug-related lifestyle and environment, and so manage to get back to a normal lifestyle.
From this viewpoint, it is positively striking that as many as 71% are allowed take-home supplies (although each dosage is only enough to cover a few days, usually a week). In this way they reach a higher level of autonomy in the management of their therapeutic regimen, so that they are no longer obliged to attend treatment units on a daily basis to be able to receive supervised drug administration. On one hand, the chance of take-home supplies favours patients’ social life and ability to do their job competently; on the other, it strengthens the therapeutic alliance with the physician, who shows he/she can rely on the patient to deliver the ‘prize’ of satisfactory compliance with treatment rules and objectively positive results, while entrusting the patient with the task of taking increasing responsibility for their own treatment instrument.

Thanks to agonist treatment and psychological support, patients are able to attain a good level of mental and somatic health (61% subjectively evaluate their health status as good) and feel that their condition is stable (as many as 80%). In this context, local addiction treatment units play a crucial role: addiction physicians have a long-term career in the field of addiction (24 years, on average), are highly skilled in agonist treatment (with 19 years of experience, on average), are in charge of a high number of patients (each has 124 patients taking an agonist treatment, on average). Patients have a good opinion of the physicians who are in charge of their case and of the therapeutic efforts being made on their behalf by the staff: almost all patients report that they are definitely satisfied with their therapeutic experience.

Another outstanding datum is the demand by physicians for measures designed to promote and favour access to agonist treatment: the availability of safer drug formulations (a lower liability to abuse and to the risk of diversion would favour take-home practices), the implementation of dedicated facilities and resources, the development of an active network of addiction specialists, and, not least, the simplification of legal restrictions on treatment delivery.

2. The changing role of families in the treatment of heroin-addicted patients.

The story of Elizabeth and Gail.

By Elizabeth BURTON-PHILLIPS and Gail PITTS

The family history of Elizabeth Burton-Phillips and Gail Pitts, founders of Drug-Fam exemplifies what cognitive changes took place in the families of drug addicts during the last 20 years. These two mothers each lost a child due to drug addiction. Elizabeth’s son (Nicholas) committed suicide in 2004, and Gail’s son died in his sleep after binging on abuse drugs, in 2007. Through their own painful experience, these two mothers learned that heroin and cocaine addiction is a chronic, complex and lethal disease. Elizabeth also concluded that patient recovery is only possible when medical intervention is performed by applying certain technical rules, and significant family members are involved in the therapeutic process. Since their sons’ death, these two mothers have been travelling around the UK and other European countries to tell their stories, and highlight the importance that an active role played by families can have against addiction – a role born out of the victimization of families that is caused by addiction itself. As a general rule in the UK, but to a lesser extent in other countries too, the needs of families with drug-addicted members have been neglected or underrated. This customary neglect is in contrast with the potentially leading role of families in the management of addiction, namely as far as recovery is concerned. A UK-DPC (UK Drug Policy Commission) study indicated that some 1,500,000 people have either a son or daughter, or a significant other, suffering from drug abuse-related problems; other studies, though, estimate that number at a level as high as 8 million. It can, however, be stated that a great number of families is involved, daily, in taking care of drug-addicted relatives, and struggling to improve their quality of life. Evidence from research does clearly indicate that addiction treatment is more likely to be successful when parents, relatives and partners are engaged in the therapeutic and rehabilitative process together with therapists. The experience of Elizabeth, who lost one child but succeeded in saving the other, has helped us to understand that the support of families and friends is a crucial factor in winning the struggle against alcohol and drugs, and that a happy family life must be considered as one of the basic objectives of social life. Elizabeth and Gail learned that an addicted person must be determined, resilient and keep on struggling to reach one clear-cut goal: to break free of past addictive behaviours. Nevertheless, rehabilitation, to be understood in the broad sense of recovery, is a long path forward, on which patients proceed and have to face upcoming obstacles, may need to stop for a while, as well as go through slips and actual relapses. Although this process is part of one’s personal history, the patient must be supported by, and form alliances with, other
social forces in order to stride forward and avoid surrendering. Families, friends, social operators, support groups and health professionals must make their contribution to improving treatment outcome. Elizabeth and Gail have learned that when parents support their children on their way towards change, treatment initiation is favoured, as well as the stability of their new lifestyle. Guidelines highlight that families and significant ones are a major resource to include within treatment programmes; of course, this can only be done while fully respecting the patient’s wishes. In many a programme run by humanitarian organizations it has been noted that over half of all drug abusers indicate their mothers as the main source of help in achieving the move towards rehabilitation.

In the UK, an individual’s social wealth is made up of the ensemble of resources one can count on through the management of one’s social ties (for instance, families, partners, children, friends or peers). Moreover, families can rely on the main intrinsic resources for the recovery of patients: a home, money, values and ideals. The help produced by such resources is vital in ensuring a wider range of possible choices to be made for rehabilitation, to improve information about possible solutions and to provide oneself with independent resources in one’s way out of drug-related impairment.

The attitude of families is going through changes, too. Satisfactory recovery depends on the network of support that patients can count on, and family members are usually the spinal column of this network, whereas social facilities and social operators play a central role in planning the steps towards recovery. However, the pathway to recovery is likely to be a long one for anyone who enters treatment; it is often hard to move forward, progress is made difficult by obstacles and challenges, and discomfort arises from the feeling that an addict will always bear the stigma of addiction in the views of others.

This is a heavy burden to share, and it poses a critical challenge for most families. Needless to say, we cannot expect that families will be likely to find their normality restored as soon as their addicted members ask for help. Elizabeth’s and Gail’s experiences warn us about the need to keep families informed, where “families” should be taken to include non-addicted members. Elizabeth, founder of Drug-Fam, a family-support organization, clearly stated that “Prevention in schools by spreading information about drugs is surely important, but the acknowledgement of families is the same as crucial. Parents must understand the powerfulness of this disease and what damage drugs of abuse can do”. The time has come to take the issue of addiction even more seriously than we may have done so far, while accounting for the role of the family, independently of feelings of shame and while being careful to keep at a distance from any stigmatizing view [1].


By Gaetano DI CHIARA

After nearly 50 years of experience, it has been soundly established that methadone maintenance treatment is effective in limiting the negative impact of heroin addiction by curtailing rates of mortality, drug consumption, criminal acts, and the spread and severity of blood-borne infectious diseases, along with the global improvement of somatic and mental health, and psychosocial adjustment.

In the last twenty years, though, buprenorphine treatment has been available too as an alternative to methadone treatment. Randomized controlled and observational studies have shown that, for those who are retained in treatment, buprenorphine is as effective as methadone in controlling heroin use. Nevertheless, buprenorphine treatment as an option is hampered by a higher rate of treatment dropout [21]. This dropout rate varies between single studies and according to the methodology used, but in observational studies it has been reported at as much as twice the value it has in methadone studies [29]. The higher frequency of dropout among buprenorphine starters is not caused by lower dosages, since it is constant above 8 mg, nor is it due to slower induction procedures, since it occurs in a later phase in the course of treatment [29]; it is, rather, related to buprenorphine’s mechanism of action and the way it interacts differently with patients’ baseline features. Buprenorphine is a high affinity (<1nmol) partial agonist of opiate receptors, so that it occupies most brain opiate receptors (80-92%) even at an oral dose as low as 16 mg [9]. Its profile differs sharply from that of methadone, which only occupies 22-35% of available receptors at an equipotent dosage (30-90 mg) [13].

At dosages that are equally effective in preventing heroin use, a key difference is that methadone acts only as an agonist, whereas buprenorphine also acts as an antagonist (and to a greater degree, on phar-
Harm reduction is a low-threshold therapeutic strategy, which may also bring with it a therapeutic advantage [26]. This kind of intervention aims to reach out to out all addicted subjects, in order to give them a chance to improve their health status and control the risks related to drug use (infections, crime, social impairment). In other words, harm reduction is focused on the basic needs of addicted persons, rather than aiming to achieve the extinction of addictive behaviours.

Candidates for harm reduction are individuals who have not got in touch with healthcare facilities yet, and those who are going through relapses after periods of treatment or are suffering from a severe form of addiction. Its purpose is to reach out to subjects before they apply for treatment themselves, or to categories of patients who are at risk of never doing so, in their natural environment (street, home, jail, meeting points).

The principle of harm reduction is to ensure minimal healthcare levels, without imposing any conditions, that is, even on those those who are unwilling to enter any treatment. Harm reduction aims to offer people survival, and the preservation of human dignity, regardless of the stage of their disease or their possible motivation to become detached from the substance.

Taking care of people dwelling in such troublesome conditions makes it possible to establish a straightforward human alliance between addicts and healthcare operators, as a preliminary stage of the therapeutic alliance, so favouring the development of new motivations and the access of addicts to treatment facilities.

Running parallel to harm-reducing interventions, integrated treatments focus on the core aspects of the disease, aiming at the objectives of detachment from habitual use, antagonism to the compulsive relationship with drugs of abuse, the reduction of craving intensity and the prevention of relapses [6, 25, 28]. For treatment responders, recovery from social impairment and the extinction of maladaptive behaviours can be achieved by the stable control of craving and of drug-seeking behavioural automatism. From this point of view, integrated treatment is expected to positively affect the level of global health of patients, by limiting overdose events and infective risks, and further reducing the harmful potential of drug abuse practices. While the improvement of health status and the lowering of infective risks can reasonably be expected with responders to integrated treatment, harm reduction does not enable drug addicts to win control over their cravings and it has no impact on the natural course of addiction [19, 34].

Harm reduction measures appear to be patient-centred, whereas integrated treatment is directly focused on the disease, but the two types of interventions can be intermingled in a complementary way. The outreach potential of harm reduction paves the way for a prospective patient’s request to undergo detoxification or apply to join a therapeutic programme, and will help to raise patients’ to level of awareness of health priorities.

Prevention and rehabilitation are surely to be included in a treatment plan for heroin addiction; nev-
etheless the general principle of treatment is to resort to different strategies, according to the stage of disease. Different pharmacotherapies may be employed for the same patient during the phases of induction, stabilization-maintenance and treatment withdrawal at the end of the therapeutic process. Obviously, a lot of patients may be approached in the street, where counselling and harm reduction should be mostly effective.

However, any treatment, regardless of its distinctive features should stick to the basic principle of preserving patients’ health, starting from their dignity, their quality of life and the value of their social ties. The truth is that winning control over the urges to seek drugs and then use them is crucial to achieving this objective, since it results in the extinction of drug-induced conditioning. It is also important to bear in mind that health-preserving measures are relevant, too, because they help patients by favouring normal life expectancy, good nutritional support, the quality of home life, hygienic standards, and chances of social re-integration. In this connection, health-enhancing interventions envisage a pyramid of integrated and sequential objectives, foremost among which is stable detachment from addictive behaviours and improving the quality of life [15].

Regrettably, harm reduction and integrated treatment have been regarded as two alternatives, both on cultural and political grounds. In many countries they share the same budget with each other – a fact that typically creates a situation where they are forced to compete with each other. In countries that have chosen the strategy of complementary interventions, instead of creating opposition between the two modalities, a sound and reliable patient-intervention matching procedure has established that:

With severely ill patients, for whom the priority must be to lower the level of individual and social harm, harm reduction is preferred, even if this means resorting to pharmacological means; the dosages prescribed are kept low enough to avoid antagonizing the effects of self-administered heroin, while allowing patients limited autonomy in determining their own actual dosage from day to day.

For patients who may respond to high-threshold interventions, and achieve a stable disease remission, usually starting from a low level of global impairment, the treatments to be preferred should aim for the patient’s complete detachment from heroin; the leading examples are methadone, buprenorphine and naltrexone treatment.

Thus harm reduction and integrated treatment can be reasonably combined, although they are based on different methods and resources, and may be used with different patients or at different stages of a patient’s addictive history.

It should be remembered that patients undergoing treatment, even when they are not responding satisfactorily, do display a lowered risk of HIV seroconversion when compared with patients who are untreated and are not in touch with healthcare services. Moreover, it should be pointed out that antiretroviral drugs, which are crucial in controlling HIV epidemics, are particularly effective on patients who stably follow effective treatment programmes.

Harm reduction interventions are useful beyond any doubt: in fact, when only high-threshold facilities are available, severely ill patients are neglected and therefore get left behind, losing any chance of even having their discomfort relieved (which is unacceptable in any civilized country). On the other hand, when harm reduction is the prevalent mode of intervention, heroin addiction no longer has any chance of actually being treated. The adoption of harm reduction means that heroin addicts may avoid most of the social and health consequences of their addictive behaviours; even so, harm reduction fails to control their behavioural disorder, which inevitably remains as the source of severe personal, relational and professional impairment.

All in all, it seems reasonable to conceive of harm reduction as the implementation of a wholesome therapeutic strategy, rather than an alternative to treatment. The Narcotic Control Board (INCB), which supervises drug-related phenomena and regulations, publicly took a stand in favour of harm reduction programmes, as long as they are not performed as the sole mode of intervention and are not a way of giving up the aim of lowering the demand for drugs of abuse, but are actually linked to therapeutic objectives, rehabilitation and recovery.

5. Change or evolution? Are drug addicts really different from mentally ill patients, and is it possible to conceive of the treatment of addicts within mental health departments?

By Icro MARREMMANI and Fabrizio STARACE

Until now, non-scientific approaches to the problem of addiction have been prevalent, influencing both clinical judgments and treatment solutions.
Gradually through the years, addiction has been recognized simply as a chronic relapsing brain disease, and its treatment has become handled more and more according to common medical principles.

The guidelines developed by the European Opiate Addiction Treatment Association clarify that [8]:

- Opiate addiction must be regarded as a disease with a chronic, relapsing course;
- Detoxification from opiates is neither the essential nor the primary mode of treatment, since it exposes the patient to a heightened risk of overdose, besides failing to provide the patient with any form of relapse prevention;
- There is no scientific evidence to indicate that addiction treatment needs exceptional medical principles or non-medical ones;
- Addicted patients should be treated as normal patients, in order to avoid useless and counterproductive stigmatization;
- Long-term treatment should be started immediately after the patient has asked to enter treatment, and should be based on methadone, buprenorphine, or a buprenorphine-naloxone regimen at adequate drug dosages;
- Drug dosages should be tailored to each patient’s case, and dose-splitting may sometimes be required in order to achieve a better response and stabilization;
- For patients who cannot tolerate traditional treatments, other opiate agonists may be employed;
- Treatment programmes must meet the patient’s needs, whether medical or non-medical, and the place of treatment should be close to the patient’s life environment;
- Polydrug use is not an exclusion criterion for enrolment into agonist treatment programmes.

The separation of addiction treatment centres from the rest of healthcare structures is no longer acceptable, as long as integration with other medical facilities looms as an impending need. The attitude of neglect shown by general psychiatrists towards commitment to addiction treatment and research is no longer endurable. There are sound, simple reasons for regarding the science of addictive diseases as a branch of neuropsychiatry. Moreover, apart from the involvement of psychiatrists in traditional roles (case management, pharmacological treatment, psychosocial interventions, psychotherapies and residential treatment), a priority of increasing urgency is the need to handle cases of dual diagnosis (including interactions between the drugs used to treat the two diseases). Lastly, research data seem to indicate the existence of a psychopathological syndrome running parallel to the presence, staging and current severity of core addictive symptoms [16, 17, 20].

Psychiatrists are certainly used to acting as good case managers: besides treating patients, they also take care of them, listen to them and give hints in the form of counselling or psychoeducational sessions, since the patient’s cognitive array is not functional to treatment. Psychiatrists also plan rehabilitative interventions, considering that psychiatry was itself born with rehabilitative aims, in the pre-pharmacological era. In any case, psychiatrists end up being called upon to participate in the management of addiction, because of the high prevalence of dual diagnosis. No one but a psychiatrist is competent to deal with mood disorders, anxiety disorders, psychoses, personality disorders, and aggressive or suicidal behaviours that may become manifest during the course of addiction in over half of these cases.

If research should confirm the existence of a specific psychopathological syndrome running parallel to addiction, that newly acquired knowledge would necessarily become part of the skill of anyone who managed cases of addiction as a psychiatrist. These being the premises, what differences are left to be accounted for between the technical skills of an addictionologist and those of a psychiatrist? Addiction medicine could simply be regarded as a branch of psychiatry, similar to adolescent psychiatry, geriatric psychiatry, psychiatry of affective disorders, psychiatry of chronic psychoses, or whatever.

In a future perspective, addiction science should intermingle with general psychiatry not only as far as university studies are concerned, but for everyone who is active in the field of addictive diseases, at any level. Patients should then find their ideal place of treatment there, once integration between mental health structures and neuroscience departments comes to incorporate addiction-related services.

6. Change or evolution? The point of view of a physician working in local Addiction Treatment units

By Lorenzo SOMAINI

In the latest years we have witnessed a continuous evolution of addictive phenomena. Healthcare institutions have been asking themselves about the best strategies to: facilitate access to treatment for new patients, who are becoming younger and younger; to improve conditions and perspectives for those who
are already in treatment; and to refer patients who have been abstinent and stable for a long time to general practitioners. Nowadays, the objectives of heroin addiction treatment are not merely to be understood as the reduction and extinction of substance use and the prevention of drug-related mortality, but primarily as the achievement of optimal adjustment, in terms of both somatic and psychic health. Obviously, objectives should be tailored according to the distinctive characteristics of each patient and planned according to the current grade of disease severity. As a result, the therapeutic programme should be designed to achieve the best results attainable on the basis of each patient’s features and needs. In this connection, we shall account for some variables which are expected to influence both the prognosis of addiction and the outcome of treatments. The best known are:

- years of active addiction;
- concurrent psychiatric disorders;
- polydrug use.

As far as the duration of addiction is concerned, neurobiological evidence indicates that the changes induced by heroin in intracellular transduction systems become more and more stable through relapsing and ongoing substance use. As a result, patients who start treatment as early as possible after the development of addiction have the best prognosis. Criteria for enrolment into methadone and buprenorphine programmes have changed over the years in response to that knowledge: very restrictive criteria dating back to the 1960s have gradually been modified until now the only safety criterion left is that of avoiding iatrogenic addiction. Patient profiles have also changed, from the stereotype of selective heroin injectors, who were started on a single-drug treatment regimen, to the current prevalent profile of polydrug users, who are under multidrug treatment regimens, possibly due to concurrent psychiatric disorders and/or infective diseases. This evolution has brought an increasing need for different specialists to collaborate, but also for general practitioners to be in charge of the surveillance of the patient’s global health status.

On the basis of all these considerations, we should reasonably revise the concept of therapeutic objectives, so as to fill the gap between the objective outcome results we expect from agonist treatments (extinction of drug use, extinction of craving, mortality reduction, and so on) and the subjective rating of the patient (which should account for improvement in life quality, coping with treatment-related stigmas, opportunity to lead a normal life, and so forth). This gap corresponds to the room for personalized objectives, to be achieved according to the patient’s individual features, and as a function of the level of treatment implementation. A two-phase intervention system may be hypothesized, to be enacted in a way similar to what is available for other illnesses: the first phase corresponds to the level of specialized addiction treatment units (which is exactly what an Italian Ser.T is) mainly engaged in the achievement of symptomatic disease control and monitoring, together with behavioural stabilisation; and a second level, corresponding to general practice, to which patients may be referred in a second phase, once stabilization has been attained, in order to simplify the management of stable, long-term treatment prescription and delivery. Obviously, synergy between the two levels is needed, as well as a dedicated study pathway to develop and update addiction treatment skills at both levels.

An integrated model, which has been called “Shared Care Model” or “Hub-Spike Model” in some countries, could ensure benefits both to the patient and to the healthcare system it is developed within. Supposedly it is likely to favour treatment access for new patients and avoid the stigmatization of the treatment process in all its elements, by creating a web of intermingled facilities at the heart of the healthcare system. It might also promote the return of stabilized patients to the levels of basic care, so increasing available resources for patients who need intensive care and/or specialized skills, or display more complex clinical pictures.

7. Change or evolution? The point of view of General Practice

By Alessandro ROSSI

As long as General Practitioners have to hold their practice according to the blinkered prerogatives indicated by the Healthcare System (Ministry, Regional Authorities, Local Healthcare Units), GPs are simply excluded from playing any role in the management of addicted patients. In fact, the priorities of the healthcare system are basically:

- Chronicity (Chronic Care Model)
- Continuity of care (H24, AFT, UCCP, etc.)
- Limitation of costs

On the other hand, addiction scenarios involve new types of drug users that reflect new patterns of consumption. The epidemiological standards of addiction are those that have been subject to the greatest changes, both in terms of the social features of patients (comprising a phenomenon of social leveling) and the type of addiction (e.g. polydrug use,
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gambling). New drug users are more and more often employed and socially integrated, and may not tolerate wearing the badge of addiction that arises from attending specialized centres. Moreover, addicts who do not inject (such as smokers and inhalers) and those who suffer from non-chemical addictions would hardly regard themselves as addicts, sometimes not even as patients.

From this standpoint, the challenge to be faced by General Practitioners is that of winning a role in intercepting those patients as a category of subjects affected by a chronic disease (consistently with the prerogatives of chronicity indicated by the healthcare system) which definitely represent a major public health issue.

The Italian Association of General Practitioners (SIMG), based on its experience lasting two decades in the field of formation, publishing and carrying out research on the issue, has put forward some proposals. The first is to build up a nationwide network of GPs, on a voluntary basis, which would have the advantage of building bridges between single participants, and providing them with professional and logistic support, so allowing them to share the management of selected cases with specialized centres. Patients who have already been stabilized, and show a clear motivation to recover, may be then be assigned to a new professional figure, the “GP with a special interest in the field of addictive diseases”, following the British model (GPwSI), or following the Italian model that is already operative for the management of chronic pain, as indicated in “Law 38”. Such GPs would:

- Limit the costs of and curtail the need for specialist consultations, by allowing GPs to become consultants within their own general practice, and, whenever possible, extending their knowledge to their collaborators.
- Organize workshops to acknowledge and train colleagues in order to spread the skills of addiction treatment among GPs, by integrating the views held at the level of general practice with addiction medicine as a speciality.
- Optimize the provision of treatment, by favouring access to health facilities, reducing delays and allowing treatment administration at home.
- Improve the standards of patient care by integrating the addiction-focused care provided by specialists within a holistic approach, the patient being considered as a whole, while utilizing the typical know-how of General Practice.

We should then develop the figure of the GP who has a particular interest in addictive disease (GPwSI) within the Italian health system, by adapting the corresponding British model. Such a figure would be a GP who has gained specialized knowledge and skills about the prevention, diagnosis and treatment of addictive diseases, and may become a referee among his/her peers for field formation, peer-to-peer consulting, and referring patients to dedicated health facilities.

Those participating in the GP network would then have the following prerogatives:

- Prevention and early diagnosis
- Treatment
- Relationships with families

As far as early diagnosis is concerned, we need to refer to a shared basis of knowledge about the patterns of risk factors, in order to be able to identify vulnerable groups, families and single subjects in need of preventive interventions.

Treatment would certainly be limited to a subgroup of addicted patients, namely those who have already been stabilized both on clinical and psychosocial grounds. At this stage, some of the available medical treatments may be handed over to GPs, depending on the laws that regulate prescriptions, and pharmacological features and risks. That is to say, buprenorphine-naloxone treatment has been shown to be feasible in a general practice setting, due to its low abuse liability and the simplicity of its administration; as such it looms as the optimal therapeutic instrument around which to favour the development of a hybrid network between GPs and addiction specialists.

7. Change or evolution? The point of view of humanitarian institutions and organizations

By Massimo BARRA

The objective of treating drug addicts – all drug addicts – is a core health concern for the government of any country. If it is true that a drug addict, apart from being an ill person, may also be dangerous to others, untreated drug addicts, those not yet reached by the healthcare system and left to their natural destiny, are far more likely to be dangerous to society, and – to a greater extent and in many different ways – be responsible for drug-related crime and a source of infectious diseases. A government that takes decisions in the interest of its community should therefore develop a public healthcare system that is capable of contacting and reaching out to the highest possible number of addicts. To do so, therapeutic interventions should be multidisciplinary and integrated, and
enhance the work of whoever, within a private or public context, works systematically to produce beneficial effects against addiction at any level, from the encouragement of initial contacts with health and social operators to the actual therapeutic overpowering of the core addictive mechanism. Instead of engaging in ‘holy wars’ between methods that claim to be able to heal drug addicts in a thorough and definitive way, we had better regard all the efforts made towards the therapeutic engagement of addicts with equal respect, and be able to provide each intervention with adequate funding.

To illustrate, we may distinguish between interventions that are “high-threshold”, “intermediate-threshold”, “low-threshold” and “very-low-threshold”, the first three corresponding to different levels of active compliance by the patient with the treatment, running in parallel to a proportional underlying motivation. A request for help, especially when the aim is the avoidance of withdrawal, to be followed by detachment from the object of craving, is, as a rule, accompanied by an ambivalent, dilatory and hesitant attitude. For many addicts in this predicament, the prospect of living without their drug of abuse is feared as viewed suspiciously as an intolerable frustration.

A typical static addiction treatment centre is open for patients to come and ask for help, but it automatically selects those whose illness is mild enough to leave room for the addict’s capability to take action and apply for treatment. Although the request for treatment may be deceitful, and have the underlying aim of obtaining other advantages, or simply be feeble and unstable, it is up to therapists to turn an ambivalent, weak motivation into a structured and constructive motivation to be admitted to long-term treatment. It is, in any case, unacceptable that healthcare policies should ever leave behind or exclude those who feel it awkward to even begin asking for help, because of the high level of their disease severity.

If those applying for treatment must be approached as ill individuals, those who cannot even imagine any alternative to continuing to live an addict’s life, even if they feel it is contrary to their ideal plans, must be twice as seriously ill. Those patients are the ones to whom we should dedicate the greatest attention, instead of regarding them with scorn and avoiding them, as do those doctors who go no farther than looking out for ‘ready-made’ treatment responders as their reward.

Hence we decided to try to build up a network in the urban area of Roma, back in the 1970s. It was called the Metropolitan Integrated Anti-drug Web, and served as a beacon for all those who wished to mediate between patients, wherever they had met them – possibly even in the streets – and treatment centres to refer them to. According to each patient’s presumed level of motivation, and the resources and skills of the referee, the patient was referred to a range of facilities, going from high to very low threshold ones.

From this perspective, no contradiction should arise between agonist and non-agonist treatment regimens and residential treatment of any kind, or between general practitioners and addiction specialists, since each of these may act in synergy to get the patient moving forward on the long-lasting path to recovery. Indeed, the longer the patient has been working with health operators, the better the results. A patient may choose a physician to be his/her case-manager, – a choice that should not be limited by territorial rules, which Olivenstein indicated as the “new feudalism of mental health”. A figure like this must be able to formulate a diagnosis and plan a therapeutic programme, with a second-choice or second-line option to resort to in cases where the previous strategy fails or is no longer feasible, so as to prevent the patient from the harmful consequences of dropping out and relapsing. As long as treatment is a long path, it is crucial to always have a rescue plan, without which the risk of treatment failure is an impending threat, with the possible consequences of causing individual and social damage.

8. Economic viability of Care Models for heroin addiction

*By Lorenzo MANTOVANI*

In Italy, the costs of drug use are estimated to be as high as 2% of the National Annual Income, which was 31 billion euros in 2011. Related health costs have been estimated to be slightly over 5% of total State expenditure. In Italy there are 1,630 dedicated treatment units, 563 corresponding to territorial addiction treatment centres, and 1,067 therapeutic communities of different kinds. Addicted patients in need of treatment are estimated to be just over half a million; if this figure is correct, the 170,000 treated subjects cover only about one third of the total number of addicts. An investment of as little as 1 Euro in the treatment of addiction generates a benefit of as much as 6 Euros [30]. As far as heroin addiction is concerned, appropriate treatments have reliably proved to be cost-effective as a means of patient management, even in the Italian context. They are cur-
rently recommended by several agencies of Technology Assessment in Scotland, Wales, the UK, Canada and Australia [4, 10, 24, 33]. Shared or Mixed Care Models may help to fill the gap between the estimated total population of addicted subjects and those currently on treatment, in a highly cost-effective way, to the point of actually reducing the comprehensive cost of heroin addiction [23]

9. Addiction and the network of territorial facilities
By Pier Paolo PANI

Addiction is one of the diseases that have the strongest social impact. Dole and Nyswander, in the first article ever published on the effectiveness of methadone treatment stated: “With this medication, and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. … This treatment requires careful medical supervision and many social services. In our opinion, both the medication and the supporting program are essential” [7]. Many years later, the work of Thomas McLellan proved the effectiveness of psychosocial intervention within methadone maintenance programmes [22].

In some contexts an integrated approach is more feasible, due to the complex interactions between health and social factors, whereas single interventions, when they are kept separate, may be a failure or even cause damage, as long as specialists work on single aspects rather than exchanging information about their experiences [27]. Some Cochrane reviews by the drug-and-alcohol study group evaluated the effectiveness of psychosocial interventions combined with agonist treatment for opioid addiction [2, 3] or case-management for the coordination and continuity of care [11]. Despite this, the advantages and costs of integration practices need further clarification.

In the public Health System, the gold standard of integration should be backed up by a clear-cut matrix system, where each treatment unit is at the same time part of a District (which is responsible for the necessary integration between services and institutions) and a Department (which looks after the scientific quality and adequacy of interventions). If such a model can be properly implemented, Addiction Treatment Services will follow a hub-and-spoke mode of functioning, which consists in deriving all general functions (operative planning, coordination, clinical activities) from a common pole (the “hub”). Other nodes and spots within the network (the array of “spokes”), spread out over the territory, would then serve as peripheral centres and receive treatment requests (from territorial treatment units; substance-specific treatment units for alcoholism, tobacco dependence, and so on; but also from general practices, mental health centres; family support centres, social services, and so forth). A system constructed on this model can be expected to guarantee the uniformity of treatment practices and give patients access to dedicated skills at any level and at any point of the network, thus avoiding any need for them to be transferred from one treatment centre to another just to perform ordinary treatment programs. Transfers could then be correctly limited to special cases or to the transition between different phases of treatment.

The arrangement of any such network may start with the implementation of spontaneous pilot projects, as has happened in other countries [31], with the involvement of institutional healthcare structures and other related services.

Further interventions may be addressed to encouraging virtuous trends in terms of the promotion of integrated treatment. Currently, our public health refunding mechanism does not account for the economic value of integration and coordination, and fails to offer any incentives to promote collaboration between different levels of intervention. We may also look forward to the inclusion of continuity of care among the essential care levels, with a corresponding economic evaluation.

The organization of a care model of this kind, able to provide continuity and integration of treatment, implies the drawing up of regulations that will help to dismantle barriers, whether to horizontal integration (between institutions, services and operators playing medical and social roles) or to vertical integration (between institutions, services and operators at a basic [GP], specialist, and inpatient level), in terms of prerogatives, logistics, treatment administration practices and refunding.

10. A glance at the near future: the Mixed Care Model
By Icro MAREMMANI

In the near future, healthcare measures for heroin addiction may, reasonably, be updated to suit current clinical pictures and therapeutic options. As in other medical areas, healthcare measures should be arranged at different levels, in accordance with guidelines elaborated by Europad and WFTOD (World
Federation for the Treatment of Opioid Dependence, NGO with Special Consultative Status within the Economic and Social Council (ECOSOC))[8]. There is no scientific evidence to support the omission of general medical principles from the treatment of addictive diseases (criterion J), so that addicted patients should be treated as normally as possible, with the aim of avoiding the need for shunning any stigmatizing special regulations (criterion K). Level 1 (the first level of intervention) is represented by GPs; level 2 (second level of intervention) corresponds to local addiction treatment units; lastly, university centres correspond to level 3 (third level of intervention). GPs may provide an active link between the general population and specialized centres; these latter may function as an outpatient practice and arrange for inpatient treatment to take place in therapeutic communities or clinics (first level of inpatient treatment), or directly in hospitals, within which addiction centres should be physically located (second level of inpatient treatment). University centres can provide third-level facilities, both in the form of out- and inpatient treatment, and make available training and skill-developing activities, including dedicated teaching within degree courses in medicine, nursing, psychology and sociology; the teaching of these subjects should also be included in postgraduate specialization and updating courses (figure 1).

Actually, it is just a matter of reproducing, in the Italian setting, a model that already exists in other parts of the world; it is usually called the “Shared Care [or Hub-Spoke] Model”, or else the “Mixed Care Model”.

By now it is clear that this is the only feasible way to enhance the treatment of addictive diseases, while minimizing stigma-related obstacles.

When a group of physicians decided to found the “Progetto Comunità Aperta” (‘Open Community Project’) in Pietrasanta, back in the 1980s, they put into practice the idea of handling heroin addiction directly within the heart of the town community of Pietrasanta, placing the centres in one of the main shopping areas, with the most crowded streets, where patients would be able to mix with tourists and common citizens [18]. This initiative – a tough one – as it may appear visionary rather than far-sighted, aimed to abolish the barrier that was keeping addiction treatment communities out of urban health centres.

Pietrasanta’s daily Centre was based on the on-site integration between psychosocial and pharma-
logical interventions, and was intended to prevent and reject the stigma that afflicts addicted patients who take the steps needed to get their condition treated. Integration was, indeed, the concept that inspired the project, which still stands as an example for setting up a model of integration between different therapeutic approaches within the natural environment in which addiction first occurs and to which patients should be readapted, in order to be regarded as ‘healed’ and as having truly recovered. Keeping the patient apart from his/her natural context may be wrong-headed as a method, since it is likely to make re-adaptation traumatic or unpredictable, and be followed by fatal relapses, during the spontaneous chronic course of addiction itself.

Pharmacological interventions alone cannot be the fulcrum of any new philosophy for the treatment of addictive diseases: when pharmacotherapy for depression was introduced, for instance, it seemed obvious that such an approach would favour the recovery of the patient’s working ability, soften the impact of depressive symptoms on relationships, and allow patients to remain within their social context while under treatment. This line of reasoning was not proposed again either in psychiatry or in the field of addiction treatment.

Given the advances made recently in neuroscientific knowledge, can we now move forward on the way to integrating pharmacological and psychosocial treatments, so as to avoid the segregation of therapeutic programmes for heroin addicts and combat cultural stigma?

For the time being, we should ask ourselves whether isolation from the company of addicts – at least of addicts who have been stabilized – has any social, let alone therapeutic, meaning. Is such isolation expected to bring any advantage to society or to patients themselves? The news is that “Martians walk among us”, since the latest generation of addicts consists of fathers, employed people, and children belonging to socially integrated families.

It would be a therapeutic milestone to be able to treat addicts while they are living in their homes, or keeping or finding their jobs. From this perspective, we look forward to being able to count on an integrated network of various healthcare and social resources, coordinated by two key figures: the physician specialized in addiction medicine, and the general practitioner.

References


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