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(2) to enhance the provision and quality of services to drug abusers and their families, especially heroin addicts;
(3) to promote a better understanding of methadone treatment by the general public and its elected representatives and officials;
(4) to promote collaborative research and to provide a European research centre;
(5) to work with the American Methadone Treatment Association to promote support for methadone treatment worldwide;
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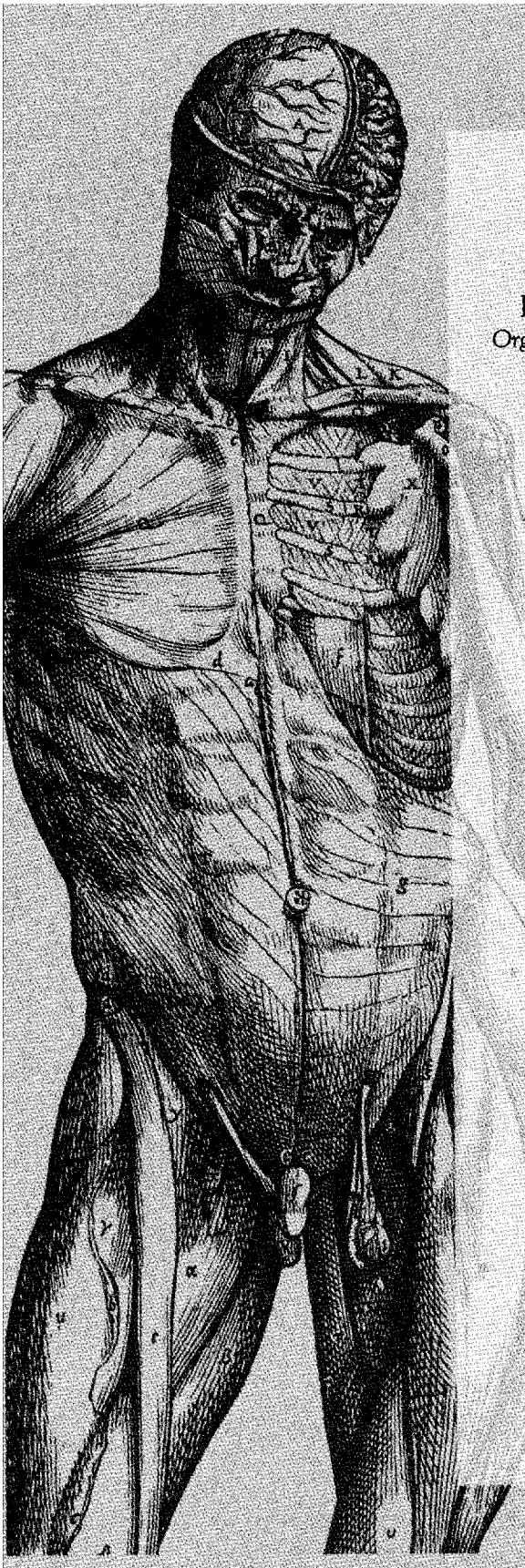

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Heroin Add & Rel Clin Probl 2003; 5(2): 7-98 **Overview Article**

Dual Diagnosis Heroin Addicts. The Clinical and Therapeutic Aspects

Icro Maremmani[1,2,3], Matteo Pacini[1,3], Sonia Lubrano[1] Mercedes Lovrecic[4] and Giulio Perugi[1,3]

Summary

Addiction and other mental disorders interact in various ways. Substance abuse tends to exacerbate psychiatric symptoms, and to induce a more chronic course with fewer and shorter disease-free intervals. It also often prevents the effectiveness of psychoactive therapies. At the same time coexisting mental disorders worsen the course of addiction itself. Mentally ill abusers tend to have a turbulent lifestyle and be prone to risky behaviours. Lastly, the risk of relapse is often heightened to the point of discouraging any therapeutic intervention. In this paper we focus on particularly important aspects of maintenance treatment and delineate guidelines for clinical practice. The authors have taken part in a collaborative effort to develop the field of comorbidity and this paper is built on literature surveys and clinical experiences in their own treatment centre. We suggest that dually diagnosed addicts should first be treated for their addictive disease by using adequate methadone dosages, which can be expected to be higher than those required for the treatment of uncomplicated addicts; stabilization should be considered a medium-term goal. Some dually diagnosed patients may benefit from treatment that targets their addictive problem while taking into account their mental disorder. Apart from their anticraving activity, opioid agonists should be reconsidered as psychotropic instruments for the treatment of mental illness, especially mood, anxiety and psychotic syndromes. Lastly, dually diagnosed addicts are expected to benefit from facilities offered within integrated programmes to the same extent as uncomplicated addicts, once programmes are based on adequate dosages for a sufficient length of treatment.

Key words: Dual Diagnosis - Heroin Addiction - Clinical Aspects - Therapeutical Aspects

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Introduction

The first step in structuring an effective treatment for dual diagnosis patients is the definition of a correct psychiatric diagnosis; this is not always easy, because there is an overlap area between outbursts of primary psychiatric disorders and drug- or alcohol-related psychopathology.

Psychiatric illness and substance use share several features: substance use may elicit or else mask a concurrent but independent psychiatric symptomatology, thus making it difficult to discriminate between them. Viewing the question from another angle, the acute or chronic use of substances generally causes such a wide variety of psychiatric symptoms that almost any known psychiatric syndrome may be mimicked (Table 1). The clinical severity, duration, and typology of psychiatric features has been shown to be correlated with the quantity and duration of underlying substance abuse. The use of alcohol or other drugs may bring forward the onset of psychiatric disorders for which an independent proneness already exists, exacerbate symptoms of current psychopathology or favour relapses into major syndromes. Conversely, mentally ill individuals may resort to substances in order to soothe psychiatric symptoms or to counter the side-effects of administered agents. Withdrawal of substances can be another cause of psychopathology. Addictive disorders may also coexist side by side with independent psychiatric disorders, as autonomous entities.

Lastly, there is significant overlap between the behaviours that accompany some types of psychiatric disorder and drug-related behaviours. In some cases, maladaptive behaviours of the kind commonly displayed by drug addicts may be mainly due to concurrent psychiatric disorders.

When psychiatric disorders are complicated by alcohol abuse or other drug-use disorders, clinicians may incorrectly conclude that the original disorder has been resolved. On the other hand, comorbid psychiatric disorders are likely to condition the patient's attitude to, and compliance with, any treatment programme or rehabilitative intervention. For instance, anxiety or phobia may make subjects unable to participate in self-help activities. Interpersonal relationships may be hampered by the bizarre behaviour which characterizes manic or psychotic syndromes. This impairment may be misinterpreted as a sign of relapse into substance use.

When two independent medical disorders affect the same subject, the term 'Dual Diagnosis' can be used. In the fields of psychiatry and addictive diseases, the term has taken on the meaning of "the coexistence of a psychiatric disorder with a substance use disorder". From now on, we will use the acronym 'DD' to indicate dual diagnosis. The most frequent diagnostic combinations are: cocaine abuse with major depression; panic disorder with alcohol dependence; schizophrenia with alcohol dependence and the abuse of other substances; borderline personality disorders with intermittent polyabuse. It is not uncommon to assess the same individual for more than two disorders; in that case the same considerations hold as with dual diagnosis.

DD patients must be evaluated in terms of case severity, chronicity, and the degree of functional impairment. A wide range of different clinical conditions call for specific

Table 1.
Substance abuse and psychiatric symptoms

Psychiatric symptoms	*Substances of Abuse*	*Clinical features*
Delirium	Alcohol and sedatives Amphetamines and cocaine Hallucinogens and PCP Inhalants Opioids	Intoxication and withdrawal Intoxication Intoxication Intoxication Intoxication
Psychosis	Alcohol and sedatives Amphetamines and cocaine Cannabis Hallucinogens and PCP Inhalants Opioids	Intoxication and withdrawal Intoxication Intoxication Intoxication and flashbacks Intoxication Intoxication
Amnestic Disorder/ Dementia	Alcohol and sedatives Inhalants	Persistence Persistence
Mood disorder	Alcohol Sedatives Amphetamines and cocaine Hallucinogens and PCP Inhalants Opioids	Intoxication Withdrawal Intoxication and withdrawal Intoxication Intoxication Intoxication
Anxiety disorder	Alcohol and sedatives Amphetamines and cocaine Caffeine Cannabis Hallucinogens Inhalants	Intoxication and withdrawal Intoxication Intoxication Intoxication Intoxication Intoxication
Sexual disorder	Alcohol and sedatives Amphetamines and cocaine Opioids	Intoxication and withdrawal Intoxication Intoxication
Sleep Disorder	Alcohol and sedatives Amphetamines and cocaine Caffeine Opioids	Intoxication and withdrawal Intoxication and withdrawal Intoxication Intoxication and withdrawal

particular interventions, but there is a trend for patients to be clustered round certain treatments instead of others on the basis of which clinical features are prominent. For instance, methadone-maintained populations include many addicts with comorbid personality disorders. Schizophrenic alcoholics tend to be treated in hospital in-patient units or local mental health services, or within homecare programmes.

Mentally ill subjects run a high risk of developing substance use disorders, and, conversely, substance abusers are likely to be future psychiatric patients. Approximately one third of all psychiatric patients abuse substances, a frequency which is twice that found among the general population. Over 50% of substance abusers report symptoms of psychopathology, though these are mostly interpretable as substance-induced rather than as due to any independent mental disease.

In cases of dual diagnosis, there is a clear trend towards greater chronicity and severity, and more serious somatic, social and psychological problems, than in cases of uncomplicated addiction. Moreover, relapses into substance use are more likely; this, in turn, causes psychiatric symptoms to become exacerbated, so setting up a vicious circle. DD patients take longer to complete any treatment successfully, are likely to undergo several critical phases over time, and tend to recover more slowly.

When psychiatric illness and substance abuse coexist, the medical approach to the patient is inevitably awkward. This is due both to the patient's psychiatric condition and abuse behaviours, and to a cultural context which does not favour a scientific approach to mental illness in general, or, more emphatically, to addictive diseases. On one hand, depression and doubts about effectiveness are unlikely to hold patients back from resorting to medical services. On the other hand, environmental issues interfere with a correct medical intervention: patients are unlikely to know what kind of treatment is provided by which service; some kinds of facilities are only available if paid for; and some kinds of service, though effective, are only available in some areas, so that addicts in some parts of a country face disadvantages.

Usually, when DD patients apply to local services for the treatment of their addiction, acute psychiatric syndromes are often mistaken for substance-induced alterations, or, conversely, withdrawal or intoxication phenomena are misinterpreted as psychiatric illness. In the latter case, patients are usually referred to psychiatric services. Paradoxically, the same happens with psychiatric patients who apply for treatment at psychiatric centres, if they are also current substance abusers. The intensity and frequency of psychiatric symptoms and substance-induced symptoms usually fluctuate. So, it may be that the need to buffer intermittent acute variations on a basis comprising a chronic psychiatric illness and an addictive condition catch the clinician's attention more than the need to control the independent aspects of the case, which will be psychiatric, addictive and social. The end result may be that the health system becomes an obstacle to patients seeking treatment, rather than a way of providing them with adequate health facilities. Currently, a correct approach to DD patients requires not only attention to the specific issues of each case, but also an awareness of the continuing divergence between the health system, as it is implemented now, and the needs of dual diagnosis patients.

Several categories of operators work together in psychiatric services: psychiatrists, psychologists, social workers, counsellors, and others. Treatment strategies vary from one service to another and within the same service. It is crucial for psychiatric patients to be provided with integrated treatments, comprising counselling, case management, hospitalization, rehabilitative and residential programmes, so as to satisfy the needs

arising from both acute and chronic conditions. In some cases psychotropics are used to treat psychiatric disorders and, simultaneously, substance use disorders. The frequency of psychotropic abuse among general psychiatric patients is low, whereas dual diagnosis patients tend to abuse otherwise innocuous agents, such as sedative tricyclic antidepressants. Trouble may therefore follow from the incautious prescription of psychotropics to abuse-prone patients. This is why psychiatrists should broaden their knowledge of substance-related medical issues, while physicians who deal with drug addicts should also be knowledgeable about psychiatry, especially the use of psychotropics. As in the field of general psychiatry, a variety of therapeutic solutions are available for the treatment of substance use disorders (short- and long-term detoxification programmes, agonist maintenance, therapeutic communities and self-help programmes), which often apply divergent basic principles and may be incompatible with each another. In fact, some programmes require a drug-free condition as starting point, whereas that condition is simply the long-term end result of other programmes. Some programmes, such as methadone maintenance, do not invariably aim at the complete elimination of heroin use. Controlled heroin use may be acceptable, when no evolution towards abstinence is feasible, as long as methadone maintenance ensures satisfactory personal and social readjustment.

As is true of treatment for psychiatric patients in general, teams working in addiction medicine units comprise physicians, psychiatrists, psychologists and counsellors. Other operators may also be involved, offering a variety of adjuvant skills. A biopsychosocial approach, comprising and integrating various professional skills, should lie at the core of any service for addictive diseases.

Psychotropics are currently used to treat whatever complications may follow substance abuse (overdose and withdrawal), but some of them, especially disulfiram, naltrexone and methadone, are effective on addiction too. Addiction physicians are often knowledgeable about psychotropics, but a prejudice exists that any psychotropic is quite likely to induce dependence. Many addiction physicians therefore avoid prescribing psychotropics, whereas they should be able to decide when to resort to them and what category is required for specific psychopathological conditions. Unless dual diagnosis patients are provided with effective treatment for their psychiatric illness, the risk of relapse is bound to remain high. Self-help associations, such as Alcoholics Anonymous and Narcotics Anonymous, may have much to offer to other types of treated patients. Self-help interventions should not be viewed as alternative treatment options, but be made part of integrated treatment programmes. On the other hand, unfounded fears and misinformation may spread within self-help contexts, as long as participants only report opinions and views based on strictly personal experiences. Specific self-help programmes for dually diagnosed patients have recently been developed in the USA; these do indeed focus on the improvement of patients' compliance with psychopharmacological therapies.

Dual diagnosis patients frequently get in touch with their GPs, but they usually win little attention. Moreover, GPs are likely to deal with cases of dual diagnosis by

prescribing generic psychotropics, such as antidepressants and anxiolytics, or abuse-targeting agents, such as disulfiram and naltrexone, which should be included in integrated treatment programmes. GPs are the category of physicians most likely to prescribe anxiolytic drugs, especially benzodiazepines, which are those most likely to be abused. Generally speaking, GPs show they are most concerned about the side complications of addiction, such as withdrawal, overdosing or somatic issues, rather than aiming for a specific intervention directed at the core of the addictive disease.

Traditionally, the public health system has always given patients the responsibility of seeking treatment, as if that was a sign of their motivation to be cured. More recently, the same issue has been raised in connection with what is called 'case management'' (CM), considering that most patients with additional psychiatric illness are reluctant to resort to services or are not capable of taking advantage of available facilities. CM may be a crucial resource in dealing with addiction, when the aim is to start patients on treatments and favour retention in treatment. CM may also be valuable in attenuating the negative results of dropping out of treatment. Conversely, programmes lacking a CM approach are more likely to be hampered by psychopathological crises and hospitalization episodes, while the most severe cases are unlikely to be successfully handled. The broad aim of CM is to encourage reluctant patients to enter treatments, and limit the negative impact of treatment failures on the personal history of subjects. Dual diagnosis patients need to be followed up for both their conditions, applying strategies devised to fit their individual condition. Physicians and patients should share the responsibility for treatment. At present, patients who deny the presence or minimize the severity of their condition are treated with excessive severity by physicians. Dually diagnosed patients require a completely different approach in order to be persuaded to enter and comply with treatment programmes. It is advisable to avoid confrontation with patients whose conditions are particularly severe, such as psychotic ones, because they are unlikely to comply with the rules of the programme until the severity of their condition has been at least partly improved. Too often, addictive diseases are regarded with a 'here and now' attitude by physicians themselves, who also tend to overrate the background aspects of associated psychiatric disorders. Substance abuse tends to be interpreted as symptomatic of a previous psychic trauma, rather than as an independent condition. Too often treatment strategies focus on the resolution of some evolutional problem, in the mistaken conviction that addiction will achieve remission once its background has been readjusted. So far, the main outcome of this attitude has been a perpetuation of the vicious circle of addictive behaviours.

Some treatment programmes require patients to be drug-free as a condition for admission. In most patients with a severe dual diagnosis condition (such as schizophrenics), a drug-free state should only be thought of as a possible long-term outcome of adequate methadone maintenance. On the other hand, a drug-free condition may be useful for patients suffering from depression or panic disorder, in order to allow an earlier, better-defined diagnosis, and, later, a correct therapeutic plan. For dual diagnosis patients, the requirement of a drug-free condition as a preliminary to programmes

actually functions as an obstacle. We therefore suggest that the concept of a "drug-free state" be redefined as a therapeutic goal to be approached step by step along a route mapped out by an adequate treatment programme. Homeless patients, who dwell in highly drug-polluted environments, cannot be expected to be brought to a drug-free condition by any deadline, especially an early one.

The sequential model is the first to have been applied and to date has been the most frequently employed. According to this, the psychiatric disease and the addictive disease are approached in two different stages. Some clinicians reckon that the addictive disease should always be approached first, and that it only makes sense to treat the comorbid psychiatric illness once any abuse has been halted. Others argue that specific treatments for the psychiatric illness may be feasible even when there is ongoing substance use, before any specific intervention for addiction has been started. Another view is that the decision on treatment priority should take into account the severity of each condition, the preference going to the condition most urgently calling for intervention. To exemplify all this, we could select the case of a dual diagnosis depressed heroin addict who seeks treatment at a mental health service when still suffering from depression, and also attends a specific programme for substance abuse to cure recurrent alcohol binges.

On the parallel model, the patient is enrolled in two programmes simultaneously, the first targeting the psychiatric illness and the second focusing on substance abuse. A twelve-step programme, such as those provided by AA, may, for instance, be combined with psychiatric treatment under the supervision of mental health operators. As with the previous (sequential) model, this model too consists in a combination of already running programmes. Psychiatrists deal with the psychiatric illness, and addiction physicians or operators manage the addiction-related issues.

The integrated model couples psychiatric treatment with intervention against substance abuse within a single programme, specifically planned for dual diagnosis patients. Theoretically, two distinct categories of physicians and skills should be involved, together with a twofold CM approach, so as to allow patients to overcome both psychiatric and addictive relapses.

Each of these treatment models has pros and cons. Requirements for treatment adequacy vary with different states of comorbidity, symptom severity and global functioning impairment. In fact, the sequential and parallel models may be those that best fit severely addicted patients who also suffer from a minor form of psychiatric disease. The main drawback to these approaches is that patients may be given contradictory information in the two different settings they attend. Conversely, when a CM facility is available, and is embodied in a single operator possessing two sets of skills in a specific setting, patients get the benefit of a homogeneous treatment approach.

The Clinical and Therapeutic Aspects of Personality Disorders in Addicted Patients

Addiction and symptoms of psychopathology

Drug-related psychopathological symptoms have been investigated using a variety of psychometric scales. Along the MAACL (Multiple Affect Adjective Check List), heroin addicts display high levels of anxiety, depression, hostility, anedonia (i.e. inability to feel pleasure in response to a variety of physical or interpersonal stimulations) [135; 184; 266]. One result of an evaluation by the Tennessee Self Concept Scale (TSCS), which assesses self-esteem, was that heroin addicts had a mainly depressive self-conception [289]. By contrast, when the same dimension was assessed by the California Psychological Inventory and the Eysenck Personality Questionnaire, no differences emerged between addicts and controls with respect to depressive symptoms in general, or to low self-esteem in particular [48; 196; 227; 306]. Moreover, depressive symptoms were not a norm among heroin addicts. Data gathered by the Beck Depression Inventory (BDI) show the presence of depressive symptoms in less than half of all the heroin addicts examined. Such symptoms are reversible, as a rule, by methadone treatment [93; 241] . The depressive features emerging from an examination by the Profile of Mood States included lethargy and weariness as long as addiction endures, while patients entering methadone treatment show high levels of aggressiveness and acting-out [353].

As for sexual life, several studies reported no difference in sexual identity and orientation, except for the greater drive towards heterosexual intercourse that is found in heroin addicts [70].

Anxiety symptoms are moderately featured during methadone maintenance, and they benefit from environmental and rehabilitative interventions [77- 80; 135].

According to data gathered by the PISA-SIA (Study and Intervention on Addictions) Group (Figure 1), heroin addicts entering treatment, as examined by the SCL90 (Symptom Distress Check List 90), mainly display symptoms of depression, somatic concern, obsessiveness and compulsiveness [154]. Otherwise, psychopathological symptoms seem to be mild during all kinds of treatment (therapeutic community, TC; psychopharmacotherapy, PD; psychotherapy, PT; methadone detoxification, MD; methadone maintenance, MM; naltrexone maintenance, NLT). If significant psychopathology does emerge, this should, in fact, raise doubts that an incorrect therapeutic choice has been made, or that there has been therapeutic misconduct [215].

Addiction and psychopathological dimensions

Apart from single psychopathological items, the personality of addicted patients was also investigated as a profile along the Minnesota Multiphasic Personality Inventory (MMPI). Anxiety traits, together with other kinds of abnormal personality features, are far better represented than psychotic traits [48; 96; 277- 279; 308]. Pathological personality traits are common (Psychopathic Deviance scale), including a tendency towards isolation and loss of self-management capability (Depression scale) [298], which may all be the direct consequence of addiction itself. MMPI-based studies, however, do not define a

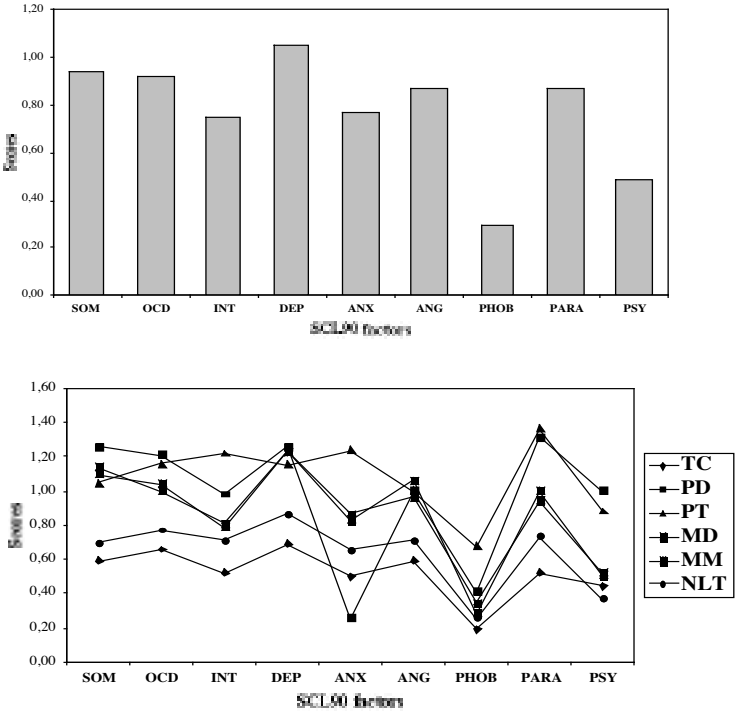

Figure 1. Psychopathological symptoms in 326 heroin addicts during various kinds of treatment (from Maremmani & Daini, 2000)

constant personality profile for addicts, or any specific personality trait. Addicts' personological deviance spreads over all dimensions, except for virility-femininity and social introversion [70]. As to the global weight of deviance, addicts seldom turn out to be highly deviant (addicts' grade of deviance falls within +1SD in eight scales out of nine), and the average score rises above the +2SD threshold only on the Psychopathic Deviance scale. A more detailed analysis makes it possible to distinguish between two MMPI clusters: the type I profile is characterized by low deviance on dysthymia, generic discomfort and thought disorders; the type II profile, by contrast, is characterized by high deviance only on the Psychopathic Deviance (Pd) scale. Moreover, the MMPI can discriminate between heroin addicts and alcoholics: the former record high scores on the Hysteria scale (Hy), whereas the latter have high scores on Pd, Mania (Ma), Hy and Psychoasthenia (Pt) [114]. Personality traits vary according to gender: female addicts are typically impulsive, whereas the personality profile of male addicts is centred on traits of dependency, self-criticism and shyness [70].

As regards thinking style and interpretation of reality, like the "locus of control" (LOC) orientation, it has been suggested that addiction builds on the need for outer objects as a source of reassurance. That attitude seems to reflect the idea that it is the environment that controls life-events, rather than one's will. According to the LOC theory, having an internal LOC implies being insensitive to reinforcement, whether positive or negative, so that behavioural orientation develops without accounting for harm avoidance or reward seeking, and life events are faced with unchanging expectations. On the basis of the definition given above, internals are those individuals who think they will be able to control events, whereas externals face events as inescapable and outside their control, denying any importance to learning from experience [199]. Against expectations, heroin addicts proved to have an internal LOC. The LOC of addicted patients may fluctuate in response to environmental changes, but on the whole stays stable. Untreated addicts tend to display an external LOC, whereas an inward shift is observed as methadone treatment proceeds. Thus, treatment tends to restore the previous personality structure, in line with the LOC orientation.

In conclusion, it can be stated that there are personality features that constitute a norm among addicts, and are peculiar to them as a category. These are aggressiveness, dysphoria and irritability, hypercriticism towards others, and socially troublesome conduct. However, there is little sense in assessing antisocial behaviour in untreated addicts, as that must mostly be read as the outcome of drug-related financial troubles and habitual involvement in crime. Though they are complex and inconsistent, the data from the literature appear to agree on some basic points: 1) depressive features are frequent, and are usually sensitive to methadone treatment, which makes addicts indistinguishable from controls, for instance in their self-esteem and introversion/extroversion; 2) anxiety features are frequent both before and during methadone treatment; 3) psychotic features are quite rare.

Addiction and Personality Disorders

The issue of a relationship between substance use and personality has long been discussed. This hypothesis probably arose from the observation that most addicts have unsteady relationships and display an unstable identity, or antisocial behaviours which lead to their involvement in crime. At present, addictive diseases are no longer classified as types of personality disorders[102], but they are often linked with some personality disorders. Addictive behaviours may carry diagnostic implications, as in the case of borderline and antisocial personality disorders (DPAS) [51; 122; 166; 182; 298] .

Before DMS came into use [1], diagnostic criteria were only available for antisocial personality disorder. That made it seem as if DPAS was the only personality disorder to be linked with substance use disorders. As some of the traits that are typically included within the picture of antisocial personality disorder, such as impulsiveness, were found in other personality profiles too, it was logical to expect that the overlap between personality disorders and substance use was wider than previously thought.

Clinical studies have recently been performed using semi-standardized and semi-

structured questionnaires, in order to assess the axis-II comorbidity pattern of substance use disorders. The results showed that a significant percentage of substance abusers have at least one personality disorder, and that antisocial personality disorder is not the only one to feature prominently; others, such as borderline personality disorder, are common too.

Between 25% and 91% (according to which study is chosen) of addicted patients display at least one personality disorder [13; 60; 244; 349]. Borderline and Histrionic personality disorders are those most often featured, with a rate of 5-65% [13; 171] and 12-64%, respectively [13]; Antisocial (3-55%) [263] [187]and Passive-Aggressive follow [13; 179; 189]. DSM C-cluster is also frequent, with a percentage as high as 28%, mostly due to dependent (35%) [13; 263; 409] and avoidant profiles. Although A-cluster usually appears as the least frequent, the prevalence of schizotypical personality disorder is not negligible (up to 41%) [13].

The vast majority of clinical studies — there are few exceptions [349] — examined samples of heroin addicts who had spontaneously applied for admission to hospitals on substance-related issues, so that personality disorders were assessed while substance use was necessarily taken into account.

Generally speaking, when diagnoses of borderline personality disorders have been revised by leaving out the substance-use criterion, a high proportion of patients are no longer labelled as borderline [95]. This incongruence may be bypassed if patients are only enrolled after previous assessment for personality disorders, without knowing their substance abuse status [349]. Despite this complication, the incidence of lifetime personality disorders was similar to that of current personality disorders: this evidence suggests that personality disorders among substance abusers are not actually overrated as a result of substance abuse itself being used as a criterion [349].

As regards comorbidity for personality disorder in relation to the kind of abuse — alcohol or cocaine — it was assessed that personality disorders are more frequent both among alcoholics and cocaine-addicts than among controls [405], and more frequent among cocaine-addicts than among alcoholics. Other authors report a similar prevalence of personality disorders among alcoholics and among drug addicts who are off alcohol[349] .

Among cocaine addicts, B cluster is prominent, followed by C and A, which comes last. Among alcoholics, B (borderline profile, in particular) is prevalent, followed by C and A, which again comes last. By contrast, C is the first cluster among controls. When the Millon Clinical Multiaxial Inventory (MCMI) is applied, a narcissistic personality profile turns out to be very prevalent among heroin addicts, whereas alcoholics more commonly display schizoid and/or borderline features [349]. On the personality side, alcohol and sedative drugs appear to be those most abused by individuals with personality disorders [95].

Some clinical features appeared to be linked with comorbid personality disorders in addicted patients. Substance use starts earlier, and overall functional level is lower. The relationship between personality disorder and earlier substance use can be explained in

one of at least two ways: subjects who develop personality disorders may have early psychosocial problems which favour their contact with substances; alternatively, the early use of substances leads to chronic behaviours which are later labelled as personality disorders. When personality disorders are concurrent, overall functioning is poorer, but no greater duration of substance use has been documented. In other words, addicts with personality disorders display greater impairment at treatment entrance, but, despite this, they are thought to have as good a chance of remission as the others [349].

Antisocial Personality Disorder (APD)

Several epidemiological, clinical and forensic studies have so far confirmed the strong link between APD and substance use disorders (SUDs) [129; 167; 297]. As many as 20-40% of subjects with SUDs displays APD, and rates are higher among polyabusers [14; 206; 307]. For no other personality disorder has such a high occurrence of SUDs ever been documented as for APD [28]. Moreover, SUDs, when diagnosed according to the DSM-IV, are linked with APD more strongly than with any other axis I disorder [167]. No other clinical condition is so strongly linked with APD as SUDs, especially alcohol use disorders [28]. In fact, for 93% of those taking APD abuse substances, and 90% of antisocial abusers, alcohol is the only abused substance, or is one of the abused substances [407]. The highest odds are those recorded for the association between APD and alcohol, with psychostimulants coming second[389]. However, no specific link appears to exist between alcohol and APD. Some authors report that APD is more frequent among cocaine abusers than among alcohol abusers [405]. On the whole, it can be stated that subjects with APD are well-represented among alcohol abusers, though they constitute a minority of them. In other words, alcohol abusers are frequent among antisocials, rather than the reverse.

Antisocial alcoholics display a type-II alcohol dependence, typical of male alcoholics; it is characterized by early initiation, a quick transition to regular use, antisocial behaviour, familial history and low insight [10].

The novelty-seeking dimension, which, like APD, is commonly associated with SUDs, is a feature that distinguishes antisocial alcoholics from their non-antisocial peers. Moreover, in alcohol abusers, there is a link between novelty-seeking behaviour and type-II features, which, as noted above, are typical of antisocial alcoholics. Thus, APD and novelty-seeking seem to overlap, at least partly, with a convergence on substance use [145]. Single APD features correlate with alcohol abuse, even when a full-blown APD cannot be diagnosed: one study investigating the relationship between personality and patterns of alcohol use in a sample of alcohol users reported a correlation between heavy drinking, hypophoria and low levels of submissiveness [242].

Individuals with APD also have a record of abusing substances other than alcohol, opiates included. APD is a risk factor for opiate use in alcoholics. In fact, APD turned out to be common among former pure alcoholics, who later became alcohol-opiate polyabusers or opiate-abusers. By contrast, alcoholics with no APD seem to be at lower risk of opiate abuse. Moreover, as a rule (in over 90% of all cases), antisocial opiate-addicts have a history of alcohol abuse forerunning opiate use. It is not, however,

known whether APD is a risk factor for opiate-use in subjects with no past or present history of alcohol abuse [206].

Several studies suggest that Conduct Disorder (CD), the underage equivalent of APD, is also involved in the relationship between APD and SUDs. The likelihood of alcohol abuse among children with CD is the same as that of antisocials, but children with CD are also at risk of nicotine and cannabis abuse. CD is predictive of future APD, and it also looms as a risk factor for substance use [32; 307; 389].

Family studies report that family-positive alcoholics are more likely to display antisocial traits [10; 14]. The family history of alcohol dependence does not overlap with the family history of APD. In other words, in many cases alcoholics do have alcoholic relatives, but no antisocial ones. Children of alcoholics commonly display personality profiles which comprise: hyperactivity and attention deficit disorder, impulsiveness, aggressiveness, affective instability, gregariousness, intellectual impairment, verbal expression deficit with alexithymia, abstraction deficit, and, eventually, antisocial traits [14].

Personality and the etiopathogenesis of addiction

The self-medication hypothesis for addictive disorders

The psychopathology of addiction is characterized by a feeling of desire, better defined as craving, which includes a positive component, the pursuit of a pleasant effect, and a negative component involving a withdrawal-related discomfort or a fear of withdrawal symptoms to come. Once patients have undergone detoxification, addiction is not over: a form of withdrawal does, in fact, persist — known as secondary, protracted, or psychic withdrawal. This features only the positive component of craving. Only that component is left after detoxification, while the negative component dwindles as the resolution of acute withdrawal proceeds. During secondary withdrawal, addicts seek drugs as if driven by positive craving, and not by physical withdrawal, which corresponds to negative craving. That positive drive becomes more crucial and persistent after the latest episode of drug taking. It can be hypothesized that this residual craving is nothing but an expression of what preceded drug use, that is, the substrate upon which drug use developed. On this hypothesis, secondary withdrawal is nothing but a psychic condition that foreran drug use, and remerges in a post-detoxification drug-free condition [228; 230; 242].

Secondary withdrawal has much in common with some frequent psychiatric disorders, in being only incidentally recognized in one special condition, drug-addiction, and in being disguised by the latter until detoxification is accomplished. Under these circumstances, addiction acts as a complication of another psychiatric disorder. The craving, which emerges in the absence of the drug, already exists, virtually speaking, before the addict-to-be has ever tried the substance. In other words, a psychiatric problem already exists — a problem that draws virtual benefits from the effects of the drug. When addicts-to-be meet the substance, their proneness to craving, based on the relief of psychopathological symptoms, develops into actual craving, and addictive behaviour follows.

Khantzian put forward the self-medication hypothesis of addictive disorders, with special reference to heroin and cocaine [170]. He suggested that the effects of substances interact with psychiatric symptoms, so compelling individuals to resort to substances themselves, as long as some kind of proneness exists. Subjects self-select which substance to use, on the basis of their personality structure and its impairments. Consistently with such a theory, antidepressant treatment should succeed in reducing the craving for heroin in heroin addicts [395]. As regards psychostimulants, sedatives and opiates, many observations have so far suggested that abuse is nothing more than an attempt to treat underlying mental discomfort. There is still disagreement, however, about whether an effective therapy against comorbid conditions (such as phobia or depression) is likely to control addiction too. Rounsaville and colleagues were the first to comment that their therapeutic results were consistent with Khantzian and Wurmser's hypothesis that heroin addicts resort to opiates in order to manage mental discomfort [319].

On the whole, they supported the idea that drug use is not the expression of a novelty-seeking attitude, a taste for euphoria or, alternatively, a self-injuring behaviour. In their view it looms as a self-medicating strategy against unpleasant feelings and emotions that lead to discomfort. That strategy is bound to fail, given the associated hazards and long-term complications, but substances can prove useful in handling what would otherwise be experienced as overwhelming and devastating.

To quote Silvestrini, who discussed the issue of addiction being secondary to some psychiatric disorder: **"**what is actually of great interest is not whether psychiatric illnesses are the cause or the consequence of substance abuse; but witnessing that addiction itself often counts for less than the underlying psychic phenomenon" [344]. The psychopathological substrate counts for more than its complication, in terms of etiopathogenesis, prevention and therapy. In particular, the risk of a relapse stems directly from the persistence of the substrate.

The role of subjective effects: the self-selection hypothesis

In illustrating his self-medication hypothesis, Khantzian puts forward the idea of the specificity of self-medicating effects, which, he argues, vary with the user's personality and the pharmacological properties of the substance.

One of the definitions given for temperament says that it is intended as "a way of being, thinking, reacting to circumstances and behaving towards other people, a way of responding to chemicals and, as well, to drugs of abuse"[344]. The effects of a drug depend both on its intrinsic properties, and on the users' reactivity. It is the combination between subject and substance that determines the substance's effects. Some individuals become addicted to the pleasurable effects of a substance, while others do not, in so far as they do not experience the same effects. The reasons for this difference are to be sought in differences in personality structure [170].

On the topic of psychostimulants, for instance, some argue that their analeptic properties are genuinely addictive, in so far as they make it possible to overcome the weariness and emptiness brought on by depressive states. It has, alternatively, been argued that the use of psychostimulants enhances self-esteem and assertiveness; and

that some appear to resort to cocaine in order to support a hyperactive lifestyle, as if to guarantee themselves total self-reliance.

Khantzian points out that addicts' memory of cocaine's subjective effects is an example of their hypersensitivity to overwhelming and intense stimuli, or to perceived alterations in their behaviour. Thus, they resort to their drug-of-choice in order to provide themselves with a quick buffer against discomfort.

Cocaine can produce different effects in different subjects. Subjects who experience paranoia after taking cocaine score higher on the Perceptual Aberration Scale and Magic Ideation Scale, two psychometric indexes of psychotic proneness. It follows that cocaine-induced paranoia is not just due to cocaine overdosing, but, rather, reflects a basic psychotic proneness, with respect to which subjects differ from each other [326].

Differences between the subjective effects of marijuana have also been investigated, in terms of genetic structure, on one hand, and environmental factors, on the other. Two typologies of acute reaction to marijuana have been defined: the first consists of unpleasant symptoms such as confusion, suspiciousness and agitation; the second comprises pleasant effects such as euphoria, creativity, talkativeness, extroversion and vigour. The typologies are consistent with patterns of marijuana use, as expected. Those who experience pleasurable effects after trying marijuana are likely to use it again [100; 264]. Those who had a bad first experience are less likely to repeat it. The subjective effects of marijuana are in line with the reinforcement of marijuana taking, and the latter correlates with levels of use. Subjects who have tried marijuana and then did not take it again describe acute effects as less pleasant, or neutral [100]; conversely, regular users describe acute intoxication as very pleasant. In conclusion, there appears to be a link between the quality of subjective effects, behavioural reinforcement and pattern of use.

Similar research into alcohol abuse showed that differences between alcohol-induced subjective effects are linked with different patterns of alcohol use. In an experimental context, subjects who show they like alcohol better than placebo report greater alcohol-induced euphoria and vigour, whereas those who like alcohol as much as placebo report blunter sensations of the same kind. Again, subjective effects condition substance use [85].

Sensation-seeking behaviour and impairment of gratification: what is too little or too much?

Sensation-seeking behaviour and novelty-seeking attitudes have become increasingly common phenomena among adolescents and young people. Excitement may certainly be considered a basic need of normal adolescence, but increasing numbers of young people seem to be taking dangerous, often self-destructive, experiences to an extreme, at the expense of access to more usual sources of stimulation and of experiences embodying ordinary gratification. Unpleasant feelings, such as boredom or emptiness, may drive young people to new forms of excitement through dangerous living, involving, for instance, unsafe kinds of sexual intercourse, breaking the rules, or anything else which calls up strong, intense emotions. Excessive stimulation is sought to remove a

sense of emotional emptiness. According to Zuckerman, sensation-seeking individuals are keen to experience strong emotions at any cost and by any means, to the point that intense stimulation becomes a basic personality need [411]. Similarly, Cloninger identified novelty-seeking attitudes as a temperamental trait [61; 62].

Zuckermann suggests that sensation-seeking behaviour can be explained through the variability of basic arousal, with special reference to its level of activity and reactivity. Optimum arousal should correspond to an optimum level of gratification; when one falls below that optimum threshold, sensation-seeking behaviour is elicited as a way to cope with the loss of gratification. Through sensation-seeking behaviour, an attempt is, he argues, made to restore the lost level of gratification. Zuckermann notes how crucial the intensity of desired stimulation is to the dynamic of sensation seeking; it turns out to depend, symmetrically, on the intensity of the lack of gratification [410; 411].

On genetic grounds, a link has been reported between sensation-seeking behaviour and the D4-dopamine receptor gene [29]. On one hand, this evidence indicates that sensation seeking is structurally determined; on the other, it suggests that sensation-seeking behaviour in an expression of dopaminergic functioning, which is thought to be the anatomical basis of gratification. The novelty-seeking dimension, which resembles sensation seeking, is itself related to the dopaminergic system. Subjects with novelty-seeking traits have higher dopaminergic reactivity, as shown by the increased secretion of growth hormone or the increased inhibition of prolactine secretion after bromocryptine administration [117]. It has also been argued that risky experiences constitute a non-chemical form of stimulation resorted to in order to counter depressive lapses [99; 375].

Sensation-seeking behaviour is one among a series of personality risk factors listed for substance abuse. The novelty-seeking dimension, as defined by the Tridimensional Personality Questionnaire, is also predictive of substance use; it helps to discriminate between abusers and non-abusers, and relates to early-onset abuse [145]. Other markers are social deviance, low self-control, low harm avoidance, greater self-reliance, and intolerance to frustration [35]. Apart from these features, sensation-seeking behaviour may be viewed as a feature of hyperthymia or cyclothymia. Sensation seeking does, in fact, appear to be in line with mood elation, and it may be that the need for stimulation in bipolar individuals during states of mood elation stems from a structurally based, state-dependent, especially intense reactivity to pleasurable stimuli. Another possibility is that, during depressive states, the same subjects are driven to seek the same kind of stimulation by a strongly imprinted recollection of previous pleasurable experiences. On that interpretation, sensation seeking acts as a way to compensate for a lack of gratification.

The psychology of addiction: evolution of theoretical models.

Psychodynamic theories

The earliest observations on the dynamics of addiction to psychoactive substances deal with the issue of narcissism, understood as a behavioural orientation towards the self as the main source of gratification. Narcissism is viewed as favouring a pathological development of the Ego, characterized by a regressive evolution towards the oral

stage, to which the subject appears to stay attached. Glover [123] also recalls a model of dynamic self-adaptation to conflicts, focusing on regression, while Rado [295] formulates the new concept of pharmacothymia . Glover recognizes the core of alcohol dependence in a regressive dynamic in which individuals seek refuge in a world of fantasy. The path towards psychosocial impairment starts with object achievement frustration, so that the Ego is resorted to as the easiest source of gratification. The perpetuation of alcohol consumption works by attaching the subject to this narcissistic method of escape. A vicious circle moving from self-punishment by alcohol consumption to negative feedback from the environment, leads to a new self-injuring drive and then a new episode of alcohol consumption. In this way each episode becomes part of an ongoing expression of the same maladaptive strategy.

Rado thought that addiction to psychoactive substances was a specific disorder, and christened it pharmacothymia; an issue crucial to pharmacothymia was what he called tolerance to euphoria. The pathogenesis of pharmacothymia started from a stage at which substances are used to control some underlying psychic discomfort of a depressive (anti-euphoric) type. In the next stage, a vicious circle is established by which forms of negative feedback from the environment renew the drive towards drug taking. As to the nature of pharmacothymia, Rado agrees that narcissism lies at its core.

Tiebout was later to revise Pharmacothymia, using a different descriptive approach [365]. He focused on what he calls the barrier, an unconscious defensive instrument against psychic discomfort, feelings of emptiness, vulnerability and panic anxiety. In non-alcoholics, barriers are incomplete and adaptive, but barriers in alcoholics-to-be are sturdier, because of an underlying mental disorder, and they cause discomfort (due to insufficient self-shielding). Alcohol consumption generates strength, fulfilment and vitality, by replacing anxiety and impotence. Alcohol becomes an instrument to challenge barriers, and reflects the discomfort that lies underneath, in line with Rado's theory. On therapeutic grounds, only once barriers have been neutralized, can alcohol be recognized as harmful. It is up to the therapist to guide the patient towards the neutralization of barriers, through recognition of their defensive role, the underlying discomfort and the secondary role of alcohol use. Later on, Krystal and Raskin argued that addicts suffer from a lack of self-care and are unable to handle their own feelings towards themselves and others, because of thick, rigid defensive structures, which are expressed through behaviours such as denial and detachment [195].

In the same period, other authors supported the idea of narcissism and other forms of psychic dysfunction as a source of anxiety when adolescents look towards adult roles [54;115]. In contrast with previous theories, the focus is placed on the Ego rather than on the object of addiction (Ego-psychology vs. Id-psychology). Moreover, researchers' attention shifts from the concepts of drive and conflict, on to the wider and more complex concept of Ego structure and the management of affects, behaviour, and the relationship with the outer world. The suggestion that substance abuse stems from underlying psychopathology received fresh support during the epidemic era of drug addiction, starting in the early Seventies, from Wurmser and Khantzian [169;402]. Alongside

the theories of Glover and Rado on alcohol dependence, Wurmser regards addiction in general as a kind of narcissistic disorder. Addiction develops through various stages, starting with interpersonal failure, and proceeding through an overactive affective drive in reaction to a feeling of emptiness. The search for gratification is then bound to head towards the Ego, and psychoactive substances are one of the means by which this affective regression can be accomplished. According to Wurmser, substance use is to be read as a regressive dynamic, in line with what Tiebout had already suggested. The novel aspect of Wurmser and Khantzian's view on addiction was that they regarded substances as a means of progression, that is, as instruments to counter regression. In other words, substances provided a compensation for the psychic discomfort that had led to regression.

Khantzian later properly formulated the self-medication hypothesis, partly anticipated by Kohut [181], as follows. Khantzian's view highlights the compensatory role of substance use. Addiction is interpreted as being due to insufficient self-care, and abused substances compensate for structural shortfalls in personality. In psychodynamic terms, such personality shortfalls are thought to stem from a narcissistic impairment of interpersonal relationships. Khantzian stresses the importance of relapses in the interpretation of addiction's pathogenesis and, at a later stage, in the definition of therapeutic targets. In fact, as long as any therapy must be conceived as consistent with the nature of the disease to be treated, treatments for addiction should aim at countering relapse-proneness to drug use, which is the distinctive feature of drug addiction [170]. One implication of Khantzian's self-medication hypothesis is the concept of self-selection (as had actually been anticipated by Wieder and Kaplan, who had called it the drug-election phenomenon, and by Milkmann and Frosch, under the name of elective abuse). The effects of abused substances must be potentially self-medicating with respect to the underlying psychopathology, and this is the key that makes them appealing as a means of self-medication. In psychodynamic terms, it can be said that the choice of a drug mirrors a preference in self-defensive style [162; 246; 385].

Beyond psychodynamics

In the Seventies, psychoanalytic views underwent revision, in response to increasing knowledge about the pharmacology of abused substances. The authors of that period hypothesized that addiction originates in a combination between environmentally-induced affective disorders, personality shortfalls and the addictive power of certain substances. On the other hand, behaviourism put forward a different but not incompatible interpretation of alcohol dependence: substance use is the outcome of an inability to cope with awkward situations. The therapeutic key to an escape route from the vicious circle of addiction is to learn how to rearrange correct coping strategies. The method consists in simulating exposure to the key stimuli, which would usually elicit a pathological reaction, so allowing the therapist and the patient to work together in solving the problem. Patients should learn how to think out a different coping strategy, and the therapist helps them to put it into practice [25].

Recent discoveries in the neurobiology of reinforcement, addiction and tolerance

have raised some doubts about the validity of the self-medication hypothesis. In any case, Khantzian had already revised his theory by resituating it within a wider biopsychosocial model, where abused drugs play the role of self-medicating instruments, only to become impossible to handle at a later stage. The fact is that the addictive property of certain drugs does not appear to be necessarily centred on a self-medicating dynamic, according to which substances counter some psychic discomfort; or on the elicitation of pleasurable subjective effects. In fact, the essential nature of addiction should, rather, be recognized in the power to reinforce appetitive behaviour. For instance, the anxiolytic effect of diazepam in anxious subjects does not necessarily mean that diazepam will be craved for at higher and higher doses. If the self-medication hypothesis was correct, the therapeutic potential of anxiolytics on a substrate of anxiety should by itself predict the development of an addiction to anxiolytics. Subjects challenged with subliminal doses of cocaine or placebo, in a double-blind choice system, turned out to develop a significant blind-preference for cocaine, though no subjective euphoric effects were ever reported [105]. In other words, the relationship between psychic functioning and substances may not fully account for subjective effects. Such evidence is in contrast with Khantzian's line of reasoning in the self-selection hypothesis [25; 170; 372].

Addiction and Bipolar Spectrum

The PISA-SIA (Study and Intervention on Addictions) Group of the Department of Psychiatry of the University of Pisa, Italy, has, over the last few years, built up an evidence-based theory according to which bipolarity is a risk condition for heroin addiction, and drug addiction in general.

Psychiatric comorbidity influences the beginning, the clinical course, and the prognosis of drug addiction disorders as well as the compliance of addicted patients [237- 239; 372]. Generally speaking, as many as 50-60% of drug addicts can be labelled as dually diagnosed (Mood Disorders, Anxiety Disorders, Chronic Psychosis, Alcoholism, Aggressive Syndromes, Personality Disorders, Somatoform Disorders) [142; 276; 321]. The most frequent form of comorbidity is certainly that with Mood Disorders. One out of three heroin addicts suffers from some comorbid mood disorder [93; 200; 304; 324; 332; 352; 383; 386]. On the elation side, manic syndromes seem to be quite rare, while hypomania occurs as index episode in as many as 0.9% of cases, and as lifetime diagnosis in as many as 7% [251; 252; 320]. One may wonder whether opiate addiction may be considered a form of vicious self-medication practice. Opiates do not seem to induce depression; conversely, they soothe depressive feelings. If that is correct, heroin is not taken to produce euphoria, but to fight dysphoria; as time goes by self-medication practice would gradually come to resemble the condition of diabetes, where subjects crave for sweet food: just as diabetics who overeat are at risk from metabolic coma, drug addicts lose control over their behaviour as addiction sets in.

As mentioned above, the PISA-SIA Group suggests a different point of view: the subjects who are most prone to risky behaviours are those who are at risk of drug-addiction. Among risk-seeking subjects, the diagnosis of a syndrome belonging to the

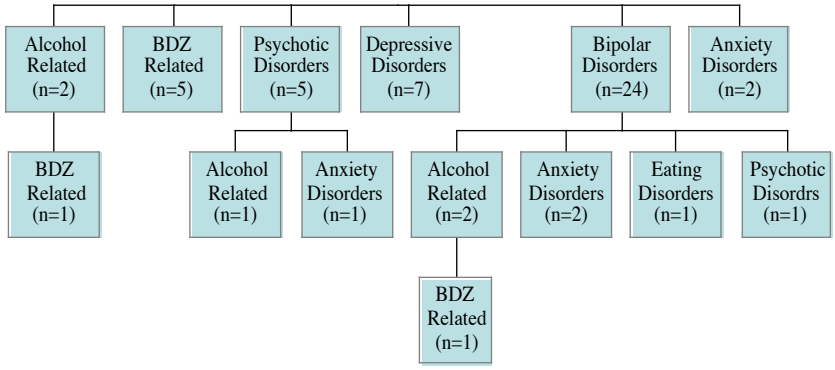

Figure 2.
Psychiatric comorbidity in heroin addicts.
Pisa Methadone Programme (1993-2001)

bipolar spectrum is the rule.

The evaluation of data gathered at the PISA-Methadone Maintenance Treatment Programme from 1993 to 2001, revealed that half of the patients treated suffered from psychiatric comorbidity. The commonest forms were Bipolar Disorder I (55.6%), Unipolar Depressive Disorders (13.4%) and Psychotic Disorders (11.2%). 20% of all these subjects were affected by dependence on alcohol or benzodiazepines. Both of these two forms of dependence are considered to constitute a dual diagnosis, as they are thought to develop on the basis of untreated or mistreated psychiatric disorders (Bipolar Disorder or Panic Disorders). The high prevalence of Bipolar Disorders can be accounted for by the fact that most patients were enrolled in a psychiatric setting [224]. In any case, bipolar subjects have been shown elsewhere to be a category at significant risk of substance abuse [41; 144; 251; 391].

In our data 28% of bipolars, 33% of psychotics and 11% of subjects with anxiety disorders displayed one or two further psychiatric conditions (Figure 2). Between 1988 and 1993, other patients were enrolled for the PISA-Naltrexone Maintenance Treatment Programme. 65% of these were not mentally ill. The most frequent disorders were Bipolar II, Disorder (51.8%) and Major Depression, single episode (26.9%). Unipolar Recurrent Major Depression was rare, and it is, anyway, an unstable diagnosis, often shifting through time to Bipolar Disorder II [214] (Figure 3).

Thus, the type of treatment in which subjects can be retained appears to reflect the severity of the addictive pathology. Bipolar I patients usually suffer from such a severe addictive disease, and, beyond that, such a severe mood disorder, as to require methadone treatment. Conversely, Bipolar II patients are less severely affected both as regards their mood disorder and their addiction. That is why they can successfully receive naltrexone treatment, which, as a rule, is suitable for subjects who are not

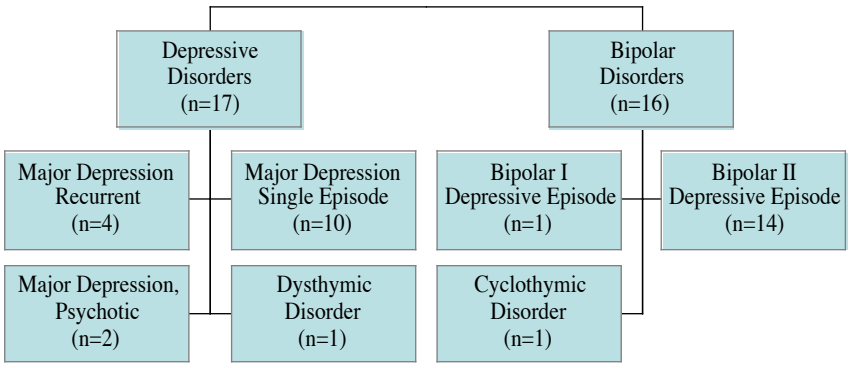

Figure 3.
Mood disorders in heroin addicts. Pisa Naltrexone Programme (1988-1993)

severely addicted, and mostly display low-grade or no craving [231; 301; 342]. In the light of this evidence, we conclude that unipolar recurrent major depression is not likely to be the most frequent diagnosis among heroin addicts. It follows that heroin addiction might no longer be viewed as a vicious self-medicating practice. There could be a link between bipolar disorder and addiction: bipolar disorder can be considered a risk factor for substance abuse. In fact, bipolar subjects often engage in law-breaking, sexual promiscuity and impulsive behaviours. These subjects may therefore be those most likely to seek out heavy drugs.

Consistently with this view, the evidence of proneness to substance abuse is distributed over the whole bipolar spectrum. In fact, substance abuse is more likely not only among subjects with axis I bipolar disorders, but also among subjects whose affective temperaments themselves constitute a risk condition for the development of major bipolarity; higher risk eventually emerges too in the case of cluster B personality disorders, which are characterized by a wide symptomatological and clinical overlap with bipolar syndromes. Lastly, on the same hypothesis, the personality features which have repeatedly been considered as signs of bipolarity, such as Cloninger's novelty seeking, should also indicate a greater likelihood of substance-related problems. Proneness to substance use should be understood as aspecific, as an equivalent to risky behaviour, and the same is true of those who take various classes of psychoactives, such as cannabinoids or stimulants.

Some heroin addicts not suffering from any major mood disorder can be assessed as having affective temperaments. Comparing heroin addicts with controls chosen from the same environment, using the TEMPS-A (a self-evaluation rating scale for affective temperaments by Akiskal & Mallya [8]), it was found that the cyclothymic profile was that best represented among heroin addicts. Addicts scored an average of 8/17 (47.05%)

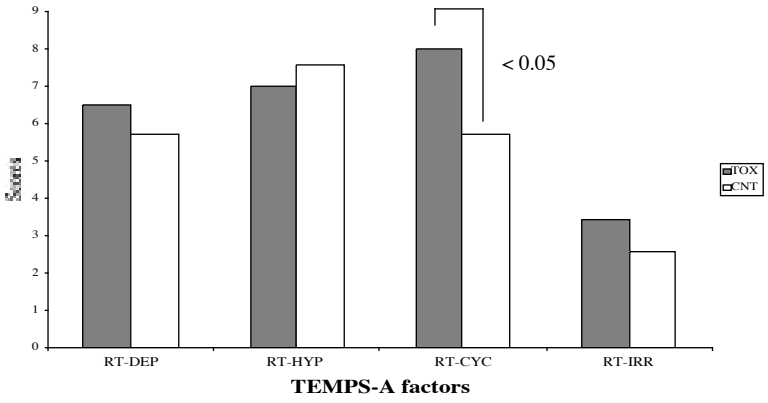

Figure 4
Comparison between 36 heroin addicts and 41 controls recruited from the same environment, along the TEMPS-A (a self-evaluation rating scale for affective temperaments by Akiskal & Mallya)(from Pacini, 2000)

on the cyclothymic scale (vs. 6/17, 35.29%) [214]. In other words, heroin addicts fitted the cyclothymic profile better than controls (Figure 4). Among these patients, cyclothymic and irritable temperaments were most frequently the dominant ones [271]. A dominant hyperthymic temperament means a higher probability of alcohol abuse in those with a dominant depressive, cyclothymic or irritable temperament (temperamental dominance depends on the synopsis of scores on various scales, so that the temperament for which a subject has the highest divergence above the sample mean is said to be dominant). When accounting only for extreme affective temperaments, which are ranked just below major affective states, in terms of symptom weight, the only difference assessed was that along the scale for irritability. Extreme temperament is recorded when subjects score above a certain threshold, corresponding to the +2SD deviance threshold with respect to the average score for the general population.

Hyperthymic and irritable temperaments were found to be at risk of substance use in a large sample of 1010 mentally healthy individuals, evaluated along Akiskal & Mallya's TEMPS-I and a questionnaire on substance-use habits. The higher the score is on the hyperthymic scale, the greater the risk of alcohol abuse.

The same link also seems to involve cannabinoids[218]. Chronic psychotic patients, cannabis abusers vs. non abusers, were compared in terms of their clinical features and diagnostic subgroups (affective vs. schizo-like). Cannabis use was further classified into past only or enduring (past and present). Cannabis users displayed a lower grade of affective flattening and higher levels of violence, and they most commonly belonged to the affective cluster. The most frequent diagnosis among cannabis users was bipolar disorder I, the present phase being manic, depressive or mixed. In line

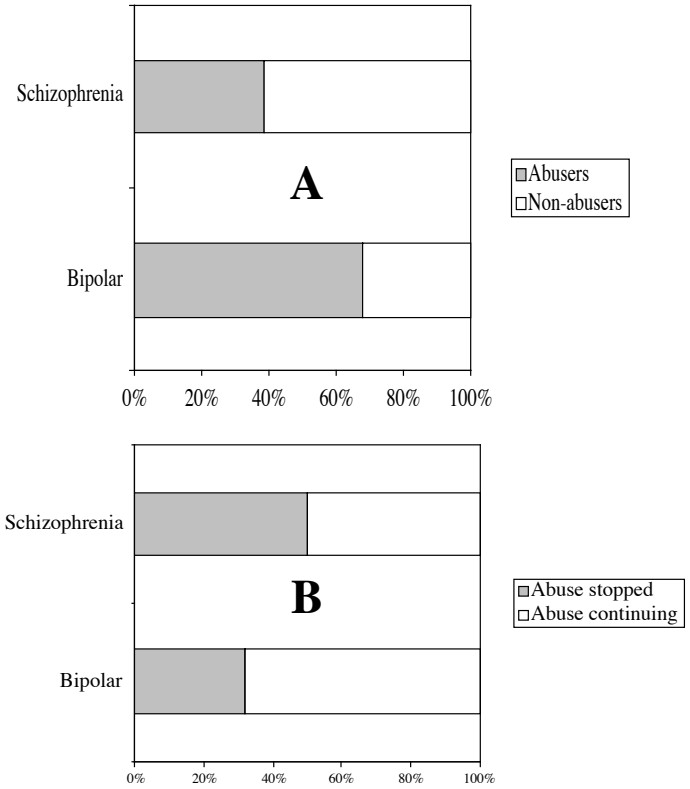

Figure 5.
A. 111 in-patients with psychotic episode. Diagnostic clusters in cannabis abuse
B. Diagnostic clusters in 66 cannabis abusers inpatients with psychotic episode who stopped or are continuing abuse after psychosis

with what has already been reported for heroin abuse, cannabis use is more likely among bipolar patients than among schizophrenics. Moreover, bipolar disorder is the most likely diagnosis in patients with a history of cannabis use. Bipolar patients are therefore the ones who tend to persist in their use of cannabis, even beyond acute psychotic episodes (Figure 5).

Alcohol abuse is a long-known form of compliance with social phobia. It was, in fact, noted that alcohol-abusing social phobics differ from non-abusing peers in their familial antecedents of bipolar disorder, type II. This provides further evidence of a connection between bipolars and substance abuse[281].

Extremely high proneness to risky behaviours persists in addicted patients, too. Bipolar addicts, in fact, seem to be at higher risk than ordinary addicts for HIV-infection. Historically, male gays and drug injectors have had the highest risk of infection, but heterosexuals are at considerable risk too. HIV-positive patients with a history of major depression were compared with HIV-negative peers, in an attempt to account for the

presence of bipolar disorders. A family history of alcohol or some other kind of abuse is more frequent among HIV-positive patients, as well as a lifetime history of bipolar II disorder (78%), possibly combined with a cyclothymic or hyperthymic temperament (52% and 35%, respectively). Otherwise, no differences emerge for clinical features such as the source of infection (drug injection, gay sex, or other). Provokingly, these data suggest that premorbid hyperthymic and cyclothymic traits may put subjects at risk from the dangerous behaviours (needle exchange and sex trading) that are specifically related to HIV infection [280] .

On these bases, against which no evidence has been reported so far, it can be hypothesized that bipolarity is a risk factor for dangerous behaviours. Temperamental profiles, whether of dominant or extreme type, do represent risk conditions for substance use in non-clinical groups. On clinical grounds, bipolar I and II disorders are the most frequent dual diagnosis conditions among heroin addicts and chronic psychotic cannabis users. One way of distinguishing heroin addicts from controls is along dimensions of temperamental bipolarity. A further suggestion is that, on genetic grounds, bipolarity, antisocial attitudes and substance abuse may all derive from the same substrate.

Treatment of Personality Disorders during Methadone Maintenance

Treece and Nicholson verified that some personality features indicate a need for higher methadone stabilization dosages, whereas others tend to lower methadone dosages. Methadone-treated patients and street addicts were classified in three groups, according to the cluster of their personality disorder, plus a fourth category for addicts with a non-pathological personality. Street addicts had been enrolled by means of a newspaper ad. The A-cluster featured schizoid, schizotypical and paranoid personalities characterized by loneliness, isolation and oddity. The B-cluster comprised borderline, narcissistic, histrionic and antisocial personalities, which were regarded as displaying dramatic, overemotional, eccentric styles. Antisocial personality disorder was displayed by 75% of the subjects. The C-Cluster was actually excluded, because it featured only two subjects. Methadone dosages turned out to be higher in the A- and B-cluster groups than in the non-pathological group [368].

A case can be illustrated as an example of a dual diagnosis of personality disorder and heroin addiction: it was that of a 29-year-old white male addict, of middle class origins, diagnosed as suffering from chronic depression and schizotypical personality disorder, and treated with 100 mg/day methadone. At the age of 18 he started displaying depressive features, isolation and antisocial behaviour. He first tried narcotics during his military service. He used marijuana, hallucinogenic drugs, amphetamines and barbiturates occasionally, but in high amounts; his use of heroin quickly became massive and regular. He underwent methadone maintenance at 23, after four unsuccessful detoxification programmes, but continued to abuse alcohol and anxiolytic drugs even after 14 months of treatment, while displaying low self-esteem, flattening of emotions and stereotypical speech, thought inconsistency, lateness, repetitiveness, and lying [368].

The PISA-SIA Group verified that methadone dosages depend on the grade of psychopathology and aggressiveness at treatment entrance [225]. A sample of 20 subjects was

divided into two clusters according to the baseline SCL90-score (high psychopathology vs. low psychopathology). All subjects had been abstinent from various substances for a long time and had achieved a satisfactory level of psychosocial adaptation, after a treatment period of variable length (1-96 months). Stabilization dosages ranged from 7 to 80, averaging 39±23 mg/day. A higher degree of psychopathology corresponded to higher stabilization dosages (60 mg/day vs. 30 mg/day on average, the latter corresponding to a lower degree of psychopathology); similarly, higher aggressiveness accounted for higher stabilization dosages (50 mg/day vs. 30 mg/day for mildly aggressive subjects). Neither psychopathology nor aggressiveness appeared to vary with treatment duration. Methadone-sensitive psychopathology appeared to comprise depression, phobic anxiety, paranoia, somatic features and psychotic symptoms, the latter two showing the strongest correlations. As regards aggressiveness, methadone dosage seemed to be related to unexpressed aggression, irritability and violence, the strongest correlations emerging for the latter two. In conclusion, the higher the level of psychopathology and aggressiveness at treatment entrance, the higher the methadone dosage required for stabilization.

Conclusions

To conclude, it remains controversial whether a personality can be defined on the basis of proneness to drug-addiction alone, that is, a toxicophilic personality. The data gathered so far have failed to support the original hypothesis made by Felix, according to which drug addiction was itself a specific personality disorder. Most studies have examined groups of substance abusers, in an attempt to determine what personality type had forerun the development of drug abuse. The personalities of addicts were assessed in terms of personality features or dimensions [102; 242]. Reviews on the issues of pre-alcoholic and pre-narcotic personality have failed to identify any distinctive feature, nor has any personality substrate been ascertained in defining a risk condition for future drug use [70; 71; 242; 371; 372] . However, some DSM-III, IIIR and IV personality disorders tend to be common among subjects with substance use disorders. Such personality disorders feature the same characteristics or symptomatological clusters as those emerging as a trend among addicts along the MMPI analyses.

We suggest that the issues of personality and addiction can best be discussed separately for each of the phases of addiction: first contact with substances, continuation of use, full-blown addiction. It is necessary to distinguish between personality factors that lead towards substance use, those that favour ongoing use, and those that eventually prompt addiction.

Moreover, relationships between personality factors and substance use should be investigated separately for different classes of substance. In fact, despite the importance and crucial role of the addictive potential displayed by some substances, it is unlikely that different subjective effects do not interact with different personality substrates.

The Clinical and Therapeutic Aspects of Mood Disorders in Addicted Patients

Epidemiology

Depression as a syndrome is certainly a common psychiatric issue among heroin addicts (see table 2 for details). According to several studies, one out of three heroin addicts can be diagnosed as depressed [93; 200; 304; 324; 332; 352; 383; 386], and lifetime evaluations have revealed prevalence rates varying between 60% and 90% [43; 141; 155; 172; 240].

Personality disorders are very commonly associated [76; 151; 171; 270; 290; 320; 396], but de-

Table 2
Epidemiology of Mood Disorders in Heroin Addicts

Diagnosis	*%*	*Studies*
Major depression:		
Index episode	33	Wieland and Sola, 1970; Lehman and De Angelis, 1972; Robins, 1974; Weissman et al. 1976; Rounsaville et al. 1979; Dorus and Senay, 1980; Steer and Kotzer, 1980; Senay, 1981
	42	Brienza et al., 2000
Lifetime	60-90	Hendriks, 1971; Khantzian and Treece, 1979; McLellan et al., 1980; Jainchill et al., 1986; von Limbeek et al., 1992
Atypical depression	12..4	Rich et al., 1989
Non-bipolar depression	13.4	Maremmani et al., 2000; 2000a; 2000b
Manic episode	<0.1	Rounsaville et al., 1982a
Manic episode after MM	0.015	Gold et al., 1982
Hypomanic episode:		
Index episode	0.9	Rounsaville et al., 1982a
Lifetime	7.0	Rounsaville et al., 1982a
Cyclothymia	5.5	Mirin et al., 1988; Mirin and Weiss, 1991
Bipolar I-II	5.5	Rounsaville et al., 1982a; Mirin et al., 1988; Mirin and Weiss, 1991
Bipolar I	55..6	Maremmani et al., 2000; 2000a; 2000b
Bipolar II	51.8	Maremmani et al., 1994

Table 3
Depression and the natural history of heroin dependence

Diagnosis	*%*	*Studies*
Before treatment:		
Street-life	14	*See MM studies*
	54	Brienza et al., 2000
Treatment seeking	34	*See above*
During treatment:		
Drug-free	46	Dorus and Senay, 1980
	30	Clerici et al., 1987
MM, index episode	12.6	Chatham et al., 1995
	17-23	Rounsaville et al., 1980; 1981; 1982; 1982a; 1983; 1983a; 1985; 1986; 1987; Rounsaville, 1985; Rounsaville and Kleber, 1986; Humeniuk et al., 2000
MM, lifetime	48-70	*See above*
During detoxification	62	Dackis and Gold, 1983
After detoxification	25	Dackis and Gold, 1983

pressive syndromes mostly belong to the area of mood disorders [5; 26; 43; 55; 75; 169; 171; 172; 233; 249; 254; 287; 307; 320; 340; 378; 394].

An index episode of moderate depression characterized one patient out of three, among those entering methadone treatments [93; 192; 383], and similar rates are provided by surveys among large groups of subjects treated in drug-free settings . For instance, depression was assessed in as many as 30% of patients who followed drug-free rehabilitation programmes in therapeutic communities in a totally drug-free regimen [59]. Correlations between depression rate and the natural history of heroin dependence are reported in table 3.

Depression or dysthymia often reaches a level of 50%, and 60% has been recorded when lifetime prevalence is considered [171; 172]. Major depressive episode follows detoxification treatments at a rate of 25% [74], whereas as many as 62% of methadone-maintained subjects develop one major depressive episode during, or shortly after, methadone tapering.

According to Rounsaville [310- 317; 320; 320; 323; 325] , index and lifetime prevalence rates for major depression among heroin addicts vary between 17% and 23%, and between 48% and 70%, respectively. Subjects who spontaneously enter methadone treatment are more likely to display major depression (34% vs. 14% among untreated subjects). Depression is found in over 50% of street addicts[43].

As regards mood elation, full-blown manic episodes are quite unlikely (0.9% of the Yale Study population) [321]. On the other hand, hypomanic features occur as often as 7%, and as many as 5.5% of these addicts can be assessed as suffering from bipolar I

or II disorders [320]. Interestingly, 3 patients among the two hundred examined developed manic episodes after methadone discontinuation [124]. Similar results are provided by another study, which reported rates of 12.4% for major depression, whether typical or atypical, and 5.4% for bipolar disorders, including cyclothymic disorder [251; 252] .

Original data from a PISA-SIA Group study suggest that the rate of bipolar II disorder is far higher, at least among non-psychiatric patients. Interestingly, only 20% of patients who had initially been classified as suffering from Major Depression, Single Episode, without psychiatric antecedents, maintained the same diagnosis through time. 7.5%, on the other hand, had been through Major Depression, Single Episode, and were in remission at the time of the study. 2.5% were assessable as Recurrent Major Depression. The remaining 37.5% of Major Depressive Episodes were actually part of pictures of either bipolar I (2.5%) or bipolar II (35%) disorders, on the basis of a history of mood elation episodes, whether spontaneous or iatrogenic. Both cyclothymic and dysthymic disorders proved to be infrequent; psychotic episodes, whether mood-congruent or incongruent, were uncommon, too. Melancholic depression was unlikely. By contrast, 87.5% displayed significant hyperthymic (62.5%) or dysthymic (25%) temperamental features, so documenting the prevalence of the bipolar spectrum [214].

In a different study performed by the same team, 45 consecutive heroin addicts were assessed for the presence and quality of concurrent psychiatric disorders, which were divided into four major clusters: affective, anxious, psychotic and polyabuse. The affective clusters comprised Bipolar I Disorder, Depressive Phase (55.5%), Dysthymic Disorder (13.3%); the anxious cluster (4.4% of the total) included Panic Disorder with or without agoraphobia, and Obsessive-Compulsive Disorder; psychotic syndromes (11.1%) and impulse control disorders were classified together in the psychotic cluster; polyabuse comprised cases of anxiolytic drug (4.4%) and/or alcohol dependence (11.1%), and received as much attention as dual diagnosis, accepting the interpretation that polyabuse is the result of an underlying panic or social phobic disorder [212; 213; 224].

Further data are needed to definitively assess the actual prevalence of bipolar disorders compared with unipolar ones among heroin addicts. The low occurrence of full-blown mood elation appears to be inconsistent with the well-known euphoric effects of opiates. On neurochemical grounds, an increase of endorphins has been documented during manic states; similarly, on clinical grounds, data have been reported that allow antimanic properties to be attributed to the opiate antagonist naloxone [377]. The same agent is consistently ineffective in depressed patients. In psychodynamic terms, it may be noted that the denial of sorrowful aspects of reality, the emphasis on factual and emotional contingency and an attitude of onnipotence, all of which are outcomes of heroin use, resemble the psychological features of manic states, though definite manic themes or full-blown manic behaviours may be missing.

Assessment and evaluation of depression in addicted patients

An evaluation of depressive features in addicted patients should always take into account the relationship that links depressive symptomatology with addictive states.

Dysphoria, for instance, may be a salient item either in opiate intoxication or withdrawal [255; 394]. Research has investigated the possible impact of addiction on spontaneous depressive states, in an attempt to distinguish substance-induced features (such as apathetic mood or exhaustion), or withdrawal-related items (such as sleep or appetite disorders), from others, which are closer to the core of an independent depressive disorder (such as chronic dysphoria or hopelessness) [316] . Generally speaking, the three nuclear features of depression as an illness are anedonia, psychomotor excitement or inhibition and suicidal thoughts. Anedonia, according to Rounsaville, clinically resembles hypophoria, which Martin singled out as a prominent mood feature among heroin addicts [229]. Hypophoria seems to be crucial, first in initiating substance abuse, and, again, as part of the secondary withdrawal syndrome, which can persist for years or become important after years of abstinence, by acting as a significant risk factor for relapses into addiction. Separately, a minority of depressed addicts display suicidal thoughts, so suggesting that suicidal thoughts develop independently of drug addiction and other widely represented depressive features among heroin addicts. The prevalence of depressive features among heroin addicts cannot be explained merely as being due to intoxication or withdrawal conditions [340]. The average severity of the symptoms displayed is comparable with that of non-addicted depressed patients who would like to commit, or who attempt, suicide [249]. In conclusion, the relationship between heroin addiction and depression appears to be quite a complex issue.

Several authors recommend observing patients over a drug-free period, before assessing any psychiatric comorbidity or resorting to specific therapeutic instruments. In fact, mood and anxiety symptoms can often be explained in terms of states of intoxication or withdrawal. In alcoholics, for example, the drug-free observation of abstaining alcoholics is recommended for as long as four weeks before judging any comorbid condition to be present, and, therefore, starting the patient on some psychotropic treatment [204]. A hypothesis of dysthymia requires a 6-month long observation period for correct evaluation**.** As a rule, when a family history of psychiatric disorders is found in subjects with a doubtful diagnosis, psychotropic treatment provided in line with current clinical judgment is appropriate [253; 254; 267; 268].

Family History of Mood Disorders

Up to 19% of cocaine abusers and 7.5% of opiate abusers have a first-level family history of mood disorders [382]. First-level relatives of cocaine abusers are at greater risk of both Unipolar and Bipolar Disorders, compared with the relatives of non-abusers [382]. Siblings of heroin addicts whose parents have suffered from depression are characterized by a high rate of mood and/or anxiety disorders.

Siblings of depressed heroin addicts are more likely than siblings of non-depressed addicts to develop antisocial personality disorder and display poorer social and intellectual functioning.

In the PISA-SIA Group sample of heroin addicts, a first- or second- level family history of psychiatric illness was found in as many as 70%. Of that 70%, 30% did not

suffer from any axis I psychiatric disorder but displayed an affective temperament (hyperthymic or depressive). The remaining 40%, besides having a family history of psychiatric illness, were themselves affected by a major psychiatric disorder [214].

Studies on monocorial twins have mostly focused on alcohol-related problems: twins score the same as regards the prevalence of alcohol-related issues, concurrent abuse/dependence of other substances, and forerunning (childhood and adolescent) or present antisocial conduct. In monozygotic twins, a family history seems to carry weight for the co-occurrence of major depression and alcoholism, but not for other kinds of abuse. Some authors point out, however, that the possible discrepancy between the environmental backgrounds of the monozygotic and dizygotic twins examined limits the reliability of results [134; 165; 286].

Primary or secondary nature of comorbid mood disorder in relation to addiction

The higher incidence of mood disorders among heroin addicts does not seem to be attributable to heroin abuse. In fact, the recurrence of depressive episodes is common throughout the history of addicted patients, even when those episodes forerun the onset of substance use. During methadone treatment, depression is still common, though less so than in untreated addicts [82]. A group of addicts examined using the Beck Depression Inventory displayed depressive features in 60% of cases when entering methadone treatment, but only half that proportion (30%) while on methadone. Among methadone-maintained subjects, depression mostly occurs within the first two months; from then on, the occurrence rate falls progressively, so suggesting that most cases of depression develop in reaction to a severe addictive condition, rather than being opiate-induced. However, the presence of depression in heroin addicts seems to have a negative prognostic meaning. Patients who are depressed when entering treatment are those that will display enduring psychostimulant abuse while on treatment, even at a six-month term [178]. The likelihood for the onset of major depression after methadone discontinuation has been estimated as being as high as 4% [124]. It must be remembered that, before psychotropics were developed, laudanum used to be resorted to for the treatment of depression, with results that were especially satisfactory in cases of agitated depression [373]. Electro-convulsive therapy produces a release of endorphins, both in animal and human models [152]. A higher methadone dosage is required to achieve stabilization in addicted patients with comorbid mental diseases (mostly corresponding to mood disorders) [224].

It can be awkward to discriminate between drug-induced symptoms and primary psychopathology, because a considerable overlap is found, even on pathophysiological grounds, between substance abuse and mood disorders [87]. Cholinergic and aminergic systems influence mood, feelings and psychomotor activity, so that mood disorders themselves may be supposed to stem from an abnormal interaction between these systems, as well as a state of cholinergic-muscarinic hypersensitivity [87]. Presumably, drugs prescribed for the treatment of mood disorders are able to counteract that abnormality. Accepting this point of view, drug abuse may be read as an attempt at self-medication

directed at autonomous psychiatric disorders.

Several factors make it difficult to distinguish heroin-induced mood disorders from autonomous equivalent pictures. These are: the wide symptomatological overlap between mood disorders and substance use disorders, the awkwardness involved in obtaining clear and exhaustive information about past psychopathology and past patterns of substance abuse, and the differences between treatment settings and populations from which data are gathered (drug-free outpatient services, methadone clinics or treatment centres, therapeutic communities and emergency units) [59; 87; 208].

Impact of comorbid mood disorders on the natural course of heroin addiction

Depressed addicts report a higher rate of recent alcohol and opiate use than non-depressed peers. Consistently with this, psychosocial and legal problems arising from substance use are more severe among depressed addicts. Several studies have found that depression is often associated with recent stressful life events, familial disharmony, financial troubles, and working and legal problems [316]. The combination of depression and maladjustment is likely to push addicts towards some request for treatment, whereas troubles related to substance abuse alone are not likely to promote treatment-seeking behaviours [316]. It is when legal and psychosocial trouble is brought about that addicts become motivated strongly enough to ask for medical intervention. Addicted patients entering treatment, an event that usually marks a critical phase in addictive history, have higher levels of depression than peers already under methadone maintenance [185; 292]. DeLeon called this depressive syndrome of the addict as "circumstance-related depression" [83; 84]. It is interesting to note that no correlation has been found between levels of cannabis consumption and the severity of the depressive symptoms displayed.

Dysphoria can be a crucial issue in leading addicts to ask for treatment. As regards therapy, data are available that indicate the possible effectiveness of antidepressant pharmacotherapy and psychotherapy in depressed addicts.

According to data gathered by the PISA-SIA Group, no difference emerges between addicts with or without comorbid mood disorders as regards somatic issues, typology of lifetime abused substances, number of past treatments, or clinical aspects of the addictive disease (e.g. patterns of drug use, periodic abstinence and addictive dynamics). Addicts with mood disorders do, however, display poorer psychosocial functioning, but it should be recalled that depression itself, even without concurrent substance abuse, is associated with psychosocial deterioration and the impairment of free time. As far as family adaptation is concerned, it is addicts who have no comorbid mood disorders who appear to do best. In fact, depression seems to favour family relationships, or, rather, to improve them with respect to the standards of addicted patients. In other words, the disruptive potency of addiction is witnessed by the corrective effect of comorbid depression, which actually adds to the damage.

Addicts with mood disorders report a less satisfactory sexual life, consistently with the nature of the disease, and greater number of legal problems. Addicts with an index episode of depression tend to receive greater therapeutic care (with several therapeutic

approaches combined), at least at the beginning [185; 292]. As for the chronology of addiction, it took less time for heroin addicts with mood disorders to develop their addiction: in fact, although they are quite old when first using the substance, they start regular substance use earlier. In addition, heroin addicts with comorbid mood disorders prove to have been addicted for a shorter time when they first ask for treatment [143].

Substance use among Bipolar Patients

Evidence has progressively increased that lifetime heroin use is not uncommon among bipolar patients [40; 41; 144; 251; 341; 360; 391]. In fact, heroin use occurs as often as 20% during depressive episodes, and up to 25% during manic episodes [97]. Yet some studies report lifetime heroin use in patients with a history of mania to be far lower, no more than 5% [247].

The association between mood disorders and substance use has been observed for over 2000 years. Plato pointed to alcohol as being one of the causes of mania [6]. Soranus, around 100 A.D., stated that the excessive drinking of alcohol often provokes manic states [408]. Around 90 A.D., Aretheus noted that mania, which he describes as a transient delusional condition, can be produced by the excessive consumption of wine or opium[384]. Early in the twentieth century, Kraepelin asserted that alcohol abuse, which can be observed in as many as 25% of patients suffering from manic-depressive psychosis, is the outcome of a state of psychomotor excitement [190].

The use of cannabinoids may elicit psychotic syndromes with excitement and hypomanic features, which tend to achieve resolution more rapidly than they do in spontaneous psychotic states [309]. Cases of hypomania have been described as due to the combination disulfiram-marijuana [197], and manic syndromes have been documented when marijuana abuse followed the consumption of prescribed fluoxetine [358].

Among cannabis-abusing chronic psychotics, bipolar disorders are much commoner than schizophrenia. On clinical grounds, cannabis-abusing bipolar psychotics show higher levels of aggressiveness and a lower degree of emotional flattening [213]. A strong relationship has been reported between cocaine abuse, attention-deficit disorder with hyperactivity, and bipolar disorders [65; 387]. Hypomanic features are often observed in cocaine abusers [201]. Cocaine is the second most commonly abused substance among bipolar patients (30%), after alcohol (80%), and followed by sedatives-hypnotics (21%) and opiates (13%) [126]. Mood disorders are a risk factor for substance use and abuse, especially in forms of bipolar disorders that are distinguished by their early onset and the recurrence of mixed-manic episodes or states.

Addiction and Suicide

In addiction treatment the first objective is prompt intervention when a patient displays homicidal behaviours and/or suicidal thoughts, and/or is pharmacologically unstable. The first two situations require immediate hospitalization in a psychiatric department. The third can sometimes be managed in non-psychiatric hospital departments. Alcohol-related mood alterations and depressed mood are strong predictors of

Table 4
Heroin Addiction and Suicidality

Diagnosis	*%*	*Studies*
Drug (ab)use and dependence in general population	11-18	Robins, 1974
Drug (ab)use and dependence in patients who committed suicide		
Before 1970's	5	Dorpat and Woodhall, 1960; Barraclough et al., 1974
During 1980's	58	San Diego Suicide Study, 1989 Pages et al., 1997
<30 years old	67	San Diego Suicide Study, 1989
> 30 years old	46	San Diego Suicide Study, 1989
>40 years old	14	San Diego Suicide Study, 1989
Suicide in general population	0.3E-4 0.82E-4	Miles, 1977; Humeniuk et al., 2000
Suicide in heroin addicts	3E-4 8.2E-4	Galanter and Castaneda, 1985
Suicidal thoughts in heroin addicts	31-75	Deykin and Buka, 1994; Rossow and Lauritzen, 2001
Suicidal attempts in heroin addicts	7-25 28-61	Ward and Schuckit, 1980; Stimmel et al., 1983; Galanter and Castaneda, 1985; Krausz et al., 1996 Deykin and Buka, 1994
Heroin addicts who attempted suicide		
History of depression	87	Murphy et al., 1988
Atypical depression	29	San Diego Suicide Study, 1989
Brief depressive symptoms	100	Hasin et al., 1988
Heroin addicts who committed suicide	92	San Diego Suicide Study, 1989
Polyabusers	12.6	Kosten, 1988; Bukstein et al., 1993; Chatham et al., 1995; Mezzich et al., 1997; Mino et al., 1999; Hill et al., 2000
Social maladjusted		
Pure heroin addicts	8	Flower et al. 1986

suicidal acts. Only after these conditions have been checked, can any treatment for addiction be started.

The epidemiology of suicide in drug addiction is reported in table 4.

90% of addicts with a history of suicidal acts also have a history of depression [262].

According to the San Diego Suicide Study ("SDS Study") [303], heroin addicts are at greater risk of suicide when they have concurrent mood disorders, 29% of which correspond to atypical depression. Transient depressive features are quite frequent too in patients diagnosed as "pure addicts" (on average they display 4.1 depressive symptoms): addicts' suicidal behaviours may therefore be equivalent to full-blown depressive states, with rapid onset and intense symptomatology, but lasting for too short a time (under 15 days) to meet the diagnosis of Major Depressive Episode [139]. In any case, addiction itself carries a high risk of suicide. The relationship between alcoholism and suicide has been known for a long time, but recognition of the link between suicide and opiate addiction is quite recent [23; 92]. Studies performed before the Seventies reported a suicide rate as low as 5%, probably due either to a defective surveying methodology or the low degree of severity of the incipient phenomenon. The SDS study, surveying 283 consecutive cases of suicide in San Diego County between 1981 and 1983, reported a 58% prevalence rate of alcohol or substance-related problems[303], which is far higher than that of the general population (11-18%) [304]. The suicide rate among addicts (between 8.2 and 30 per 100,000) was 11 times higher than in the general population [109; 147; 245]. The lifetime prevalence rate for suicide attempts varies from 7 to 25% among addicts [109; 356; 380]. Addicts usually first commit or attempt suicide below the age of 40 — a younger age than that for alcoholics or the general population[371]. 50% of addicts first commit or attempt suicide at an age below 28 [34]. Again the SDS study reported that 67% of young people (below 30 years of age) who committed suicide were heroin addicts, whereas suicidal addicts were only 46% of older-than-30 suicide committers and 14% of older-than-40 ones. Early psychosocial difficulties, as witnessed by living in institutions, fostering families, a diagnosis of attention deficit disorder with hyperactivity, a positive family history for suicide, alcohol dependence and depression, all seem to be risk factors for suicidal acts among heroin addicts, especially for those displaying prominent disruptive behaviours [232; 299; 356]. Polyabuse, especially of sedative-hypnotics and alcohol, is also a risk factor for suicide among heroin addicts, due to either narcotic potentiation or aggressive discontrol [106; 232; 356]. Suicidal heroin addicts recorded a recent use of 3.6 different substances on average; 84% had been using alcohol, heroin and psychotropics together, while only 8% had been pure drinkers, and 8% had been be pure opiate addicts [106]. Suicidal thoughts may be present in non-depressed addicts too, especially when addiction is combined with a lack of family support, severe psychosocial maladjustment, and polyabuse [248]. As regards polyabuse, it should be pointed out that the abuse of cannabis or hallucinogenic drug carries a lower risk of suicide than combined alcohol, heroin, cocaine and tobacco abuse [68; 366]. Features of suicidal heroin addicts vary according to gender: female suicidal addicts tend to abuse prescribed medications, display borderline features, have a history of past suicide attempts, and declare suicidal intentions. In dual diagnosis suicidal addicts, the axis I comorbid disorder usually foreruns addiction [288].

As regards which kind of mood disorder is at greatest risk of suicide, it can be noted that bipolar I patients, unless a record of mixed episodes is prominent, display a ten-

dency to be at high risk of polyabuse but are unlikely to commit suicide. By constrast, depressed and dysphoric patients, whether non-bipolar or bipolar II or bipolar I with mixed features, are suicide-prone [366].

On therapeutic grounds, an effective antidepressant treatment lowers the likelihood of suicide among depressed heroin addicts [130]. According to the observations of the PISA-SIA Group, naltrexone-treated patients seem to be at higher risk of suicide, whereas methadone treatment appears to offer some protection against it [250].

Heroin addiction and its consequences on mood

Opiates usually produce mood disorders during intoxication, while chronic opiate use induces a fall in CNS noradrenergic firing. Unlike other abused substances, opiates are very unlikely to cause psychotic symptoms. Substance use during manic episodes may depend on loss of inhibition, impulsiveness, impairment of judgment or lack of caution. Patients with mixed episodes are twice as likely to use substances than normal subjects. The switching phase can be intensely unpleasant and lead to substance use as a form of self-medication.

Taking the opposite view, some authors judge that mood liability develops as a consequence of CNS neuroadaptation to chronic exposure to heroin. The leading hypothesis is that heroin-induced depression stems from functional alterations in the endorphinergic, noradrenergic and hypophysis-adrenal gland system. Adaptation to the protracted use of heroin may continue for several months after detoxification, and come to underlie what is clinically described as hypophoria [229]. Since 1942, detoxified heroin addicts have been described as showing a "protracted withdrawal syndrome", or a "post-withdrawal syndrome", which features chronic residual and often invalidating withdrawal symptoms [227; 228; 230; 272]. The clinical picture is dominated by an organic mood syndrome, which is sensitive to methadone and represents the crucial risk factor for relapse into heroin use. Dysphoria, in fact, is usually associated with an increase in craving and substance-seeking behaviours. Relapse into heroin use followed by a soothing of dysphoria works to refuel the vicious circle of addiction, even when other features of early or protracted withdrawal are absent. Mood disorders also develop during opiate detoxification. Depression seems to occur more frequently among addicts who have gone through methadone tapering (60%) than among those entering methadone treatment after heroin discontinuation (25%) [74]. This can easily be explained by considering that addicts with mood disorders tend to join methadone treatment programmes, as this is the only treatment that has proved effective in restoring the heroin-related opioid imbalance and controlling the associated psychopathology. So it is quite likely that mood alterations, which led subjects to undergo methadone treatments, will re-emerge after therapeutic stabilization has been achieved.

Treatment of Mood Disorders in heroin addicts

The reduction of opiate use may itself induce the onset of psychiatric disorders (mania, depression, psychosis) that put the subject at risk of a relapse into heroin use.

When mood disorders are unrelated to substance abuse, psychiatrists should be careful about using agents associated with abuse liability, and take into account possible interactions with other psychotropics (e.g. benzodiazepines). MAOIs (Monoamine Oxidase Inhibitors) should be avoided, so as to prevent interactions with cocaine, heroin or other psychotropic drugs [174; 177; 397]. Generally speaking, rapidly acting benzodiazepines (diazepam, alprazolam) should be avoided, as they have a high addictive potential. Slowly acting benzodiazepines (oxazepam, clorazepate), which ensure a lower abuse liability, are safer to use, at least in selected patients and under medical supervision. Any other psychotropic should be evaluated by urinalysis. In methadone-maintained patients who are dependent on heroin and BDZ, clonazepam, a long-lasting, potent and slow-acting benzodiazepine, which is therefore free of addictive properties, can be resorted to as a replacement for other compounds [132; 331].

One frequent complication of opiate addiction is dependence on alcohol, cocaine or other substances. 60% of methadone-maintained patients were abusing cocaine when they entered treatment. Cocaine abuse is found in as many as 40% of heroin addicts, alcohol abuse is problematic in 15% to 30% of cases, and BDZ abuse is quite common [11; 16; 20; 354]. No comparable data on naltrexone-maintained patients are available. Even so, it does seem that polyabuse is common among patients who enter naltrexone treatment without fitting it, but who refuse or are denied better-fitting options due to environmental pressure or cultural bias [211].

Special care is required when treating addicts suffering from additional psychiatric disorders, as intervention on heroin addiction alone, even when successful, cannot be expected to resolve the abuse of other substances. Such patients require closer monitoring (daily alcohol test, twice-a-week urinalyses), more frequent counselling sessions, direct access to self-help groups (e.g. Alcoholics Anonymous) and specific pharmacotherapy (e.g. disulfiram) [357].

Two studies have shown that high dose methadone treatment, when combined with frequent medical controls, is likely to favour a decrease in cocaine use. As a rule, patients addicted either to heroin or other substances, CNS depressants in particular, should be stabilized on methadone and gradually detoxified from other substances. Attempts to treat all different kinds of abuse at once are bound to fail. The recommendation is that abuse issues should be faced one by one [357].

Antidepressants

Despite the frequency of depressive disorders among heroin addicts, few reports are available in the literature on the use of tricyclic antidepressants in these patients. When doxepine was administered at doses ranging between 25 and 150 mg once a day in the evening, an improvement in the data on anxiety, depressive features and anxiety-related insomnia [351] was documented. Amitryptiline partly controls withdrawal symptoms in abstaining volunteers [351]. In a double-blind, placebo-controlled study of doxepine in depressed addicts, a significant improvement was documented along the Zung and Beck Hamilton rating scales. Although a lot of probands dropped out, retained subjects showed a decrease in craving [399]. Later studies performed on methadone-treated

subjects failed to show any greater improvement for imipramine-treated subjects (doses ranging between 150 and 225 mg/day) vs. placebo, but a general decrease in depressive symptoms was documented [178]. The conclusion could be drawn that methadone treatment accounts for the improvement of depressive symptoms, no further advantage being provided by imipramine. In cases of severe depression, the parentheral administration of clomipramine (25-50 mg) ensures fast and significant improvement, showing impressive results after just one week of treatment [82]. The natural course of depressive symptoms after methadone initiation is marked by a gradual decrease in severity that continues through the first eight months [93;318;340;359;386]. Tricyclic agents should therefore be resorted to only when depression shows no significant improvement in response to methadone treatment, and when, consequently, the estimated risk of relapse stays high [93; 318; 340; 359; 386]. Caution is also needed in the light of several cases of tricyclic abuse that have been documented in the literature [66; 355]. According to the PISA-SIA Group, a dose of 150 mg/day is effective in treating most of the cases of depression in heroin addicts. Tricyclics can be used alongside methadone tapering, at the end of a successful programme, or to favour abstinence in drug-free subjects in the first six months after the successful accomplishment of a programme, due to their property of controlling mild withdrawal symptoms (enduring insomnia or protracted withdrawal states).

On the whole, clinical trials on the effectiveness of tricyclic antidepressants have provided ambiguous results. This may be partly attributed to the difficulty of retaining abstaining addicted patients in any unspecific treatment. To sum up, it may be said that trials on doxepine have agreed in showing its efficacy in methadone-maintained patients, at doses ranging between 25 and 100 mg. Otherwise no significant efficacy has been ascertained for either imipramine or desimipramine. However, desimipramine blood levels are higher than expected in methadone-maintained subjects.

As regards SSRIs (Selective Serotonin Reuptake Inhibitors), their effectiveness and safety have been documented by the PISA-SIA Group on subjects displaying intermittent depression while maintained at average methadone doses of 100 mg/day. It must be remembered, though, that SSRI bioavailability rises in methadone-maintained patients. In fact, both fluoxetine and fluvoxamine may cause methadone blood levels to increase significantly (by up to 200%, in the case of fluvoxamine) [153]. Sertraline increases methadone blood levels during the first two weeks of administration [256]. Methadone doses should therefore be pondered carefully, especially if SSRIs are added on during the induction phase. Interestingly, fluvoxamine has proved useful in improving the bioavailability of methadone over a 24-hour period, in high dose-treated patients, who report withdrawal symptoms before each new administration (probably due to a fast metabolism). Patients who show an unsatisfactory response to 100-150 mg/day methadone can definitely benefit from the addition of fluvoxamine [33; 81].

MAOIs' stimulating properties, which have been documented in depressed non-addicts too, make them unfit for use with heroin addicts, due to their abuse proneness. Moreover, the likelihood of cheese-effect accidents is supposedly too high in patients such as addicts, who are known to have hardly any control over their consumption of

chemicals, food or alcohol. In prognostic terms, the presence of affective symptoms predicts poorer control over abuse conducts, heavier psychosocial impairment, and a greater suicidal risk.

Mood-stabilizing drugs

Bipolar syndromes are probably the most frequent psychiatric disorders among heroin addicts. As mentioned above, 39 out of 40 consecutive heroin addicts entering methadone treatment were diagnosed as suffering from bipolar I or bipolar II disorder, or displayed hyperthymic temperament, or else had a family history of bipolarity [214]. The use of mood stabilizers is appropriate in patients with bipolar disorders or borderline personality disorder, which are both categories that often involve substance abuse. However, neither lithium nor carbamazepine has been clearly shown to be suitable for heroin addicts with bipolar disorders [256]. Moreover, it should be recalled that the normalization of basal mood does not ensure control over true addiction, once the revolving door phase has been entered. Mood stabilization may be crucial for the control of substance use in the honeymoon phase, or in subjects who can stay persistently abstinent after the accomplishment of detoxification. Bipolar abusers have a poorer outcome than non-abusing peers. Their response to lithium is predictably poor, whereas better results can be expected if anticonvulsants, especially valproate, are used. However, lithium may reasonably be attempted in bipolar cocaine addicts [72; 113; 269].

Lithium-methadone interaction have been suggested on an experimental basis, but has not yet been clinically confirmed [157;158]. Fenythoin, carbamazepine and phenobarbital strongly decrease the bioavailability of methadone, so causing opiate withdrawal [256]. Valproic acid and the latest anticonvulsants do not seem to have this effect.

Opioidergic agents

Agonists

Antidepressant properties have been reported for opiates, so suggesting that opioid use may develop as a form of self-medication for depressive symptoms, on one hand, and to support the endorphinergic hypothesis of dysthymic disorders, on the other. The administration of opioids to depressed patients has showed some efficacy, though failures have been reported too. In two trials, beta-endorphins were successful in treating depression in a few non-addicted depressed patients (there were 2 responders in one trial and 3 — out of 6 — in another) [12; 180]. The efficacy of beta-endorphins was confirmed vs. placebo, whereas no greater efficacy over placebo was documented for morphine or methadone, on non-addicted depressed patients [116]. In opiate addicts, higher methadone doses (over 100 mg/day) are needed to stabilize patients with prominent features of depression and aggressiveness at programme entrance [225]. In a two-year follow-up, methadone maintenance seemed successful in achieving major mood stabilization in bipolar I patients [212]. Though contrasting data do exist [98; 285], some neurobiological observations are consistent with that orientation. Opioid receptors and endorphins are highly concentrated in hypothalamic and limbic areas, as both are involved in the physiology of affective states; and opioid systems have been shown to interact with

Table 5
Pharmacological interactions and dosages in methadone maintained heroin addicts with mood disorder psychiatric comorbidity in the experience of the PISA-SIA Group

	Dosages (md/daily)		
	Min	*Mean*	*Max*
Bipolar patients			
Methadone (stabilization)	50	120	320
Carbamazepine	400	510	800
Valproic acid	318	480	1000
During depressive phase			
Fluoxetine*	10	20	40
Fluvoxamine*	50	120	200
Paroxetine	20	28	40
Sertraline*	25	100	200
Citalopram	5	20	60
During manic phase			
Haloperidol*	3	7	9
Clozapine	25	50	100
Risperidone*	1.5	4.5	6
Olanzapine	5	10	20
Quetiapine	100	200	300
Monopolar depressive or dysthymic patients			
Methadone (stabilization)	60	120	200
Imipramine	50	80	150
Clorimipramine	25	35	50
Trimipramine	25	75	150
Fluoxetine*	20	30	40
Fluvoxamine*	100	150	200
Paroxetine	20	30	40
Sertraline*	50	100	200
Citalopram	10	20	60

**Use caution during the methadone induction phase. Re-evaluate methadone dosage if patient is already in treatment.*

catecholaminergic systems, which are themselves involved in the pathophysiology of depressive disorders. This is in agreement with Extein's hypothesis that "a decrease in endorphinergic activity may be the pathophysiological basis of depression" [99].

Table 5 shows pharmacological interactions and dosages in heroin addicts with mood disorder psychiatric comorbidity as recorded in the experience of the PISA-SIA Group.

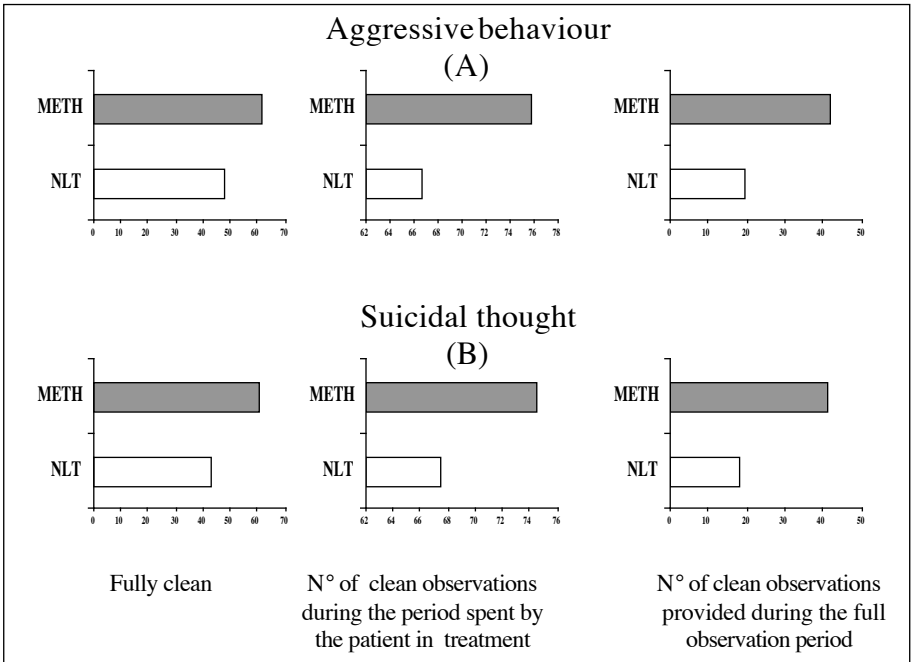

Figure 6.
Naltrexone Maintenance (n=63) vs. Methadone Maintenance (n=91).
A-Absence of aggressiveness (668 observations)
B-Absence of suicidal thoughts (670 observations)

Antagonists

Although opiates are known to produce euphoric states, and spontaneous states of elation are associated with high CNS levels of endorphins, a low incidence of manic states has been reported among heroin addicts. Naloxone, an opiate antagonist which has no apparent effect on depressed patients, has proved to have antimanic properties [377]. It has been hypothesized that naltrexone has a negative influence on basal mood, on the basis of observations on addicted or non-addicted patients. One bulimic patient treated with naltrexone developed panic attacks [220]. Of 80 naltrexone-maintained patients who were also receiving psychosocial treatment, 13 experienced an overdose accident during the first year of treatment. Four overdoses were lethal, including one case of suicide. Of nine non-lethal overdose cases, four were classified as attempted suicide [250]. Unpublished data gathered by the PISA-SIA Group indicate that naltrexone treatment is less effective on the aggressive behaviour and suicidal thoughts of heroin addicts

Table 6
Treating mood disorders in heroin addicts
PISA-SIA (Study and Intervention on Addictions) Group recommendations

A. Remember that antidepressant pharmacotherapy alone does not extinguish addictive behaviour in heroin addicts
B. Apply antidepressant properties of long-acting opiates
C. Use over-standard doses of methadone (up 120 mg/day)
D. Remember that antidepressant medications (especially SSRIs) increase methadone blood levels
   a. Use SSRIs in rapid methadone-metabolizer patients
   b. Use caution during MM induction phase
   c. Do not use SSRIs during patients' detoxification
E. Remember that craving increases during manic phases. Avoid switching antidepressants. Prefer anticraving antidepressants (fluoxetine or sertraline) in depressed heroin addicts
F. Avoid MAOIs because of their interaction with cocaine (disulfiram effect)
G. Avoid BDZ for treating comorbid anxiety (use anxiolytic properties of long acting opiates)
H. Use clorimipramine plus methadone to reduce the latency of antidepressant effect
I. Use tricyclic antidepressants after opioid detoxification for at least six months to reduce post-detoxification hypophoria
J. Consider the possibility of tricyclic abuse (especially amitriptiline) and tricyclic withdrawal syndrome
K. Use mood stabilizers in bipolar heroin addicts, but remember that mood stabilizing therapy alone does not extinguish addictive behaviour in heroin

(Figure 6). This flaw emerges most clearly in long-term treatment programmes. By contrast, bipolar patients with a low craving for opiates are those who seem to benefit from naltrexone maintenance, as witnessed by the satisfactory retention rate among this subgroup compared with uncomplicated addicts or non-bipolar addicts. The use of fluoxetine as add-on to naltrexone maintenance has been shown to improve patients' outcome, so suggesting that naltrexone has an anti-reward property, which is specifically reversible through fluoxetine's antidepressant effects [216; 226].

Table 6 shows the PISA-SIA Group recommendations for the treatment of mood disorders in heroin addicts.

The Clinical and Therapeutic Aspects of Anxiety Disorders in Addicted Patients

Most addicted patients display symptoms of anxiety at some time during their addictive history [77-79; 135; 154; 184; 192; 197]. In alcoholics, as much as 50-70% of that symptomatology can be described as generalized anxiety, panic disorder and phobic syndromes. The occurrence of anxiety features is even more common among specific groups of cases featuring withdrawal or intoxication syndromes, where that frequency rises to 80%. From an etiopathogenetic viewpoint, a genetic link between anxiety and addictive disorders has been postulated; some authors have interpreted that link as depending on a self-medicating dynamic. Although it is hard to tell whether anxiety is of a primary type, or springs from a substance abuse/addiction course, it can be agreed that comorbid anxiety disorders in alcoholics or drug addicts deserve specific clinical attention and therapeutic intervention.

Epidemiology

According to the 1994 National Comorbidity Survey, 24.9% of the general population is affected by some anxiety disorder, whereas alcohol dependence only occurs in 13.7%. Alcoholics or drug addicts with comorbid panic-agoraphobic disorder or social phobia display severe anxiety, and the degree of severity of their anxiety symptoms appears to strengthen their drive towards alcohol consumption. In this context higher anxiety levels are predictive of heavier drinking or drug taking. The rate of anxiety disorders among addicted patients does not exceed that expected for the same disorders in the general population. Moreover, the rate of comorbidity for alcohol or drug dependence among people affected by anxiety disorders is not particularly significant, if compared with that for the general population. Consistently with this, the risk of alcohol abuse/dependence developing among social-phobia patients is high only in a subgroup showing features of bipolarity, type II.

Anxiety symptoms are the rule during stimulant intoxication or CNS depressor withdrawal, due to an increased release of catecholamines. The administration of sodium lactate is effective in eliciting panic attacks not only in patients suffering from panic disorder, but also in alcoholics. Moreover, lactate serum levels increase during alcohol intoxication in alcohol-dependent individuals. Anxiety symptoms forerun the onset of alcohol abuse in as many as 40% to 60% of alcoholics with comorbid anxiety disorders. On the other hand, it is far more common to recognize alcohol disorder as the background for many anxiety disorders. It is still controversial whether, once detoxification has been achieved, anxiety symptoms can be expected to shoot up or, conversely, dwindle. Certainly, anxiety disorders that have a favourable outcome are expected to take quite a long time to achieve resolution.

In monocorial twins born of alcoholics, anxiety is marked only among subjects who drink heavily, so suggesting there may be a link between the degree of exposure to alcohol and the likelihood of developing clinically relevant anxiety. It has not so far been demonstrated, however, that a high risk of drug addiction or alcohol dependence correlates with a correspondingly high risk of anxiety disorders. The risk of alcohol

dependence in subjects with panic disorder, phobias or generalized anxiety does not differ from that of the general population. Lastly, one possibility not to be ignored is that the development of anxiety disorders in alcohol-dependent individuals is itself the sign of a genetically determined proneness to anxiety that is independent of alcohol abuse.

Heroin addicts very commonly report anxiety-like symptoms, and several studies have reported features of anxiety and neuroticism as being strongly represented among them, but only a minority of patients can actually be diagnosed as affected by any anxiety disorder, outside the context of opiate withdrawal [77- 79; 135; 154; 184; 192; 197]. At least one anxiety disorder affects up to 12% of patients, with a lifetime prevalence of only 6% [320; 324]. Average rates for phobias are very low, though the range is between 1% [307] and 9.5% [186].

Clinical pictures that resemble episodes of panic disorders are not infrequent during methadone maintenance or methadone tapering, with a recorded frequency of between 1% and 2% [124;197;251]. In such cases, scholar phobia and separation anxiety are commonly reported as early precursors of current full-blown anxiety. These data indicate that the spontaneous panic disorder of heroin addicts might actually be the result of an opioid dysfunction, with a consequent lack of endorphinergic inhibition on the ascendant noradrenergic firing [124].

As regards obsessive-compulsive symptomatology, the only data available are those in the Yale study by Rounsaville and coll., who report an index and lifetime rate of 10% and 20%, respectively [320]. DOC-affected patients tend to concentrate their negative expectations on an object that becomes their feared object, and they structure their daily life around an avoidant attitude. Similarly, though not symmetrically, drug addicts structure their lives around the compulsive pursuit of a single object, the drug, and concentrate the whole body of meanings and expectations of their own existence on it. In this way the drug may be viewed as an invulnerable defender against underlying phobic preoccupations. Wurmser put forward the suggestion that "in most addicts, a phobic core can be identified, which can be typically described as the phobia (and desire at the same time) of being trapped, captured, enchained within boundaries, institutions, jail, either physical restriction or affective ties". The drug would then gain the value of a counterphobic shield: it is compulsively craved for as strongly as the phobic object is avoided [403].

Clinical pictures

Any of the DSM-IV anxiety disorders can become manifest during a phase of intoxication or withdrawal, whatever the substance abused. The most common pictures are those typical of phobias, panic disorders and generalized anxiety. DSM-IV indicates syndromes such as substance-induced anxiety disorders, and states that prominent symptoms comprise free anxiety, panic attacks, obsessions and compulsions. The onset of symptoms can come less than one month after an episode of intoxication or withdrawal, and may endure for months, so causing significant psychosocial and

working impairment, as well as difficulties in managing private life. Comorbid anxiety disorders sometimes represent a true dual diagnosis, but their features are not distinguishable from drug-induced ones. Despite this, DSM-IV provides useful criteria for drawing a distinction: the likelihood of an anxiety disorder being primary rises when anxiety symptoms forerun the onset of substance abuse; when symptoms endure far beyond an episode of intoxication or withdrawal; or when they exceed what might be expected from the severity of the toxic state. Lastly, a history of anxiety disorders unrelated to any condition of abuse/dependence makes a diagnosis of primary anxiety disorder more likely.

Treatment of Anxiety Disorders in Addicted Patients

Apart from conditions of intoxication or withdrawal, the treatment of anxiety in addicted patients does not differ from the treatment of simple anxiety syndromes. Anti-anxiety agents are indicated for patients who continue to display anxiety even when receiving effective treatment for their addiction. Target symptoms should be always defined and monitored, and treatment should not necessarily be thought of as chronic. This is particularly true of benzodiazepines, which are useful only to the extent to which they prompt patients' acceptance of other treatments. Agents such as alprazolam, lorazepam or diazepam should be avoided, because of their strong abuse liability. Diazepam is one of the most popular abused psychotropics among heroin addicts, not only due to its property of soothing some of the opiate withdrawal symptoms: as addicts themselves report, it is often used to maintain euphoria, or to reproduce a heroin-like euphoria when taking methadone [175], if heroin itself produces few strong sensations, or else to make a subject feel "high"[398; 399]. Clonazepam, on the other hand, has proved suitable and safer, and can be used in dosages of up to 0.50 mg three times per day, when required. These findings are consistent with the data provided by animal studies, in which diazepam has proved to heighten the effects of opiates [339]. At high doses, diazepam is mostly used to buffer withdrawal symptoms, or to improve the course of rapid detoxifications, or to prolong abstinence after detoxification has been completed.

During methadone treatment too, diazepam abuse is a common finding, more so than among alcoholics [47; 47; 175; 178; 194; 194; 328; 351; 398; 399]. The percentage of methadone-maintained subjects using benzodiazepines is as high as 10-20%, reaching a maximum of 30%, as reported by some authors, if benzodiazepines or hypnotics have been used during the previous week [47; 149; 355]. According to the Treatment Outcome Prospective Study, between 5% and 16% of methadone-maintained subjects have been using benzodiazepines weekly or less often [159]. Regular diazepam use is common too, as assessed by random urinalysis: 20% of patients turned out to be high-rate diazepam users (with more than three positive urinalyses over a 6-month period) and 46% were defined as low-rate users (with at most one positive result) [138]. It is doubtful whether benzodiazepine use should be read as an attempt to deal with anxiety, or actually looms as a form of addiction. Lately, the problem of benzodiazepine withdrawal has been regarded with increasing concern, and cases of symptomatic withdrawal have been documented for

dosages even lower than those taken on average by methadone-maintained patients [390]. Benzodiazepine-abusing methadone patients may display oversleeping, ataxia, speech difficulties, and even anger attacks [175]. Through time, diazepam addiction has partly replaced the already recognized phenomenon of dependence on hypnotics, which are often carelessly prescribed by G.P.s for insomnia. Diazepam abuse can sometimes produce states of altered, dreamlike states of consciousness, which addicts may experience as optimum conditions for engaging in illicit behaviours.

Dreadful accidents may happen in those circumstances, so the prescription of benzodiazepines to addicts should only be allowed when strictly necessary, and addicted patients should never be given free access to them. In particular, it is harmful to encourage addicts to decrease their methadone dosage and use benzodiazepines to compensate for the difference: not only will patients' clinical conditions not improve, but they will also be put at risk of developing a polyaddictive disease [222].

No matter what the dynamics may be that underlie benzodiazepine use, it can certainly be expected to worsen an addict's already delicate conditions, especially if heavy, regular use is initiated. That is why clinicians agree that the anxiety of agonist-maintained addicts should be dealt with first by regulating the agonist dosage, then, if necessary, by counselling facilities, relaxing techniques or environmental intervention.

The findings emerging from the PISA-SIA Group experience indicate that the average methadone dosage needed to stabilize heroin addicts with a dual diagnosis of

Table 7
Pharmacological interactions and dosages in methadone-maintained heroin addicts with psychiatric anxiety comorbidity in the experience of the PISA-SIA Group

	Dosages (md/daily)		
	Min	*Mean*	*Max*
Panic disorder patients			
Methadone (stabilization)	80	85	90
Imipramine	25	30	50
Fluvoxamine*	50	100	150
Paroxetine	10	20	30
Sertraline*	50	100	200
Citalopram	10	20	40
OCD patients			
Methadone (stabilization)	80	100	110
Clorimipramine	75	150	300
Fluoxetine*	20	30	40
Fluvoxamine*	150	200	250
Sertraline*	50	100	200

**Use caution during the methadone induction phase. Re-evaluate methadone dosage if patient is already in treatment*

anxiety disorder is lower (80 mg/day) than the average required to stabilize other types of dually diagnosed addicts, or even uncomplicated patients (100 mg/day) (Table 7). Consistently with such observations, naltrexone has been shown to elicit anxiety in non-addicted, as well as addicted patients [220].

The anxiety disorders of heroin addicts can also be treated successfully with antidepressant drugs and buspirone [112]. Tricyclic agents and SSRIs are effective in controlling both anxiety and depressive symptoms, and are suitable for long-term treatment programmes. Imipramine and nortriptiline may cause sedation and hypotension.

The Clinical and Therapeutic Aspects of Psychotic Disorders in Addicted Patients

Previous suggestions [27] about a possible causal relationship between the chronic use of morphine and the onset of a psychotic picture failed to be confirmed by later studies [182;283]. Data on the comorbidity of substance use disorders strengthen the assessment that the likelihood of a schizophrenic spectrum diagnosis among heroin addicts on methadone maintenance is low. In the Yale study, only 3.4% of patients were diagnosed as affected by schizophrenia (0.2%) or schizoaffective disorder (3.2%), so raising doubts about the reliability of previously reported prevalence rates [317], which ranged between 11% and 19% in different surveys [59; 115]. Moreover, the major studies [19; 261; 307; 346] that have investigated the prevalence of substance use disorders in populations of schizophrenics have reported heroin use as being found in 2-6.9% of subjects, a range that falls below its prevalence among the USA general population, which is estimated to be as high as 9% in the latest NIDA survey[265]. Apart from this, the prevalence of amphetamine and hallucinogenic drug abuse turned out to be greater among schizophrenics than in the general population — 25% vs. 15% and 20% vs. 15%, respectively [19; 329].

Some authors [329; 346] speculate that schizophrenic patients self-select pro-dopaminergic substances, as likely to be effective in alleviating their negative symptoms, comprising spontaneous or iatrogenic depression and extrapyramidal effects deriving from neuroleptic medications. The dopamine-wasting effect of psychostimulants may itself lead to the persistence of abuse behaviours, given the need to maintain a normal dopaminergic firing level. This mechanism resembles cocaine-induced dopaminergic stress, through which a dopaminergic hypofunction perpetuates the tendency to resort to cocaine.

However, patients whose clinical picture mostly consists of negative symptoms are unlikely to possess the drive and psychomotor arousal that are needed to engage in drug seeking and drug consumption [91]. It has also been hypothesized that methadone, due to its antipanic, antipsychotic and anti-anxiety properties, which are common to natural opiates, may be effective in stabilizing patients' proneness to psychotic outbursts. Thus, the low occurrence in methadone-treated patients of psychotic outbursts, which are partly forestalled by opiate-agonism, may mask the underlying presence of schizophrenic-like conditions [30; 168; 234; 261; 300; 302; 404].

Despite the advances in knowledge about the opiate and opioid receptor systems, the relationships between opiates and psychotic disorders are far from being clarified. The use of opiate-antagonists in psychotic disorders has been proposed on the basis of evidence of higher levels of endorphins in the CNS fluid of schizophrenic patients, and their tendency to dwindle as treatment proceeds. Even so, the administration of naloxone to schizophrenics led to significant improvements only in one subgroup of patients. Catatonic schizophrenia has proved to be the type most likely to respond to opiate-antagonists, consistently with the well-known observation that the administration of beta-endorphins induces catatonic-like behavioural changes in the rat, which has led to their being called "endogenous neuroleptics" [377]. Some authors argue that neither opiate

agonists nor antagonists should be considered antipsychotic agents [156], whereas others have provided evidence to support the antipsychotic effectiveness of opiate agonists [30]. It is mostly believed that the antipanic, antipsychotic and antiaggressive properties of opiates make them appeal to psychotic subjects [234; 300; 302; 401]. In general, the hypothesis of a direct involvement of neuropeptides in the pathophysiology of psychotic disorders [273] is supported by the following evidence, as well as by longstanding reports on the antipsychotic effects of heroin: methadone maintenance is responsible for the prevention of psychotic relapses in individuals with a history of psychotic episodes forerunning the addictive phase. In the same subjects, the gradual subtraction of methadone along a methadone-tapering schedule was followed by psychotic relapses [202; 274]. These clinical phenomena are consistent with the antidopaminergic activity of methadone, as witnessed by the increase in serum prolactine after its administration [125]. The use of methadone has been proposed as a treatment in cases of schizophrenia which have turned out to be resistant to traditional medications, and in cases of the early development of dyskinesias, when neither treatment discontinuation, nor its continuation with the same psychotropics is recommended [191]. Clouet has been a prominent supporter of this view: "the majority of neurophysiological, neurochemical, and behavioural studies is compatible with the hypothesis that both neuroleptic and opiate-agonists are useful in the treatment of psychotic disorders, as both classes produce overlapping changes in the activity of CNS dopaminergic pathways" [64]. In any case, the similarities between opiates and neuroleptics are certainly partial, since opiates, unlike neuroleptics, may elicit pleasurable subjective effects, rather than the reverse, whereas neuroleptics are not characterized by any specific or striking effects on aggressiveness. The partial overlap of clinical effects suggests that a different mechanism is operative with opiate agonists compared with neuroleptics. Although opiates are not thought to favour the onset of psychotic disorders, and the occurrence of the latter is unlikely among opiate users, authors have reported psychopathological similarities between the dynamics of addictive and psychotic thought. The addicted patient resembles the psychopathic one because in both the Ego fights the Super-Ego in an attempt to undermine its control; an analogy with a psychotic mental structure can be recognized in a shared hostile attitude towards the outer world. To quote Wurmser [404], "In the compulsive use of drugs the Ego struggles to deny not only values, authority and responsibility (i.e. the Super-Ego), but also the lines drawn between objects, the boundaries of time, the external-internal dichotomy, the defining limits between social realities and conceptions." Addictive diseases display a kind of aggression against the syllogistic foundations of rational thinking which resembles that of psychosis. From a comparison between addiction and psychosis — Wurmser concludes — the only difference to emerge, apart from the different attitude of the Super-Ego, is of a quantitative kind.

Stimulants, cannabinoids, hallucinogenic agents and psychotic disorders.

A different point can be made regarding other non-therapeutic substances. Mescalin, psylocibine and LSD are straightforward psychotomimetics and hallucinogenics, because

they can bring on psychopathological syndromes displaying the same features as those of spontaneous psychotic disorders. Amphetamines and cocaine and, to a lesser extent, cannabinoids may produce a range of thought or sensorial-perceptive alterations which can reach the same degree of severity as full-blown psychotic states [24; 67; 121; 137; 140; 164; 350; 361]. These effects are wholly consistent with the specific action of these substances on the dopaminergic system, which is known to be hyperactive in the brain of acute schizophrenics. Substance-induced acute psychosis is usually short-lasting. It is not uncommon, however, to witness the persistence of psychotic symptoms, along the course of a schizophrenic-like prognosis. Different interpretations of such pictures are plausible: they might apply to individuals who abuse drugs as a result of their previous psychopathological condition; or else, to prone individuals who leap into a full-blown disorder due to an aspecific excitatory effect of substances — an effect shared with stressful events; lastly, the substance could be directly and specifically responsible for the onset of a psychotic picture in low-risk populations.

Substance Use Among Psychotic Patients

The prevalence of substance abuse among psychotic patients varies over a wide range, between 10% and 70%, [88; 258] but it appears that 47% of schizophrenics, on average, display lifetime alcohol or substance-related disorders, meaning a relative risk 4.6 times greater than that of the general population [297], where substance use disorder occurs as often as 16% [46; 89; 297]. Over 70% of schizophrenic patients are heavy tobacco smokers [46; 94]. Young age, male sex, low educational level [258], and a family history of substance abuse are predictive of a higher risk of addiction [88]. Schizophrenic patients with a history of substance abuse stand out in displaying an earlier age of onset, better pre-morbid global functioning and adaptation, higher occurrence of positive symptoms, frequent need for medical intervention due to intoxication or psychiatric symptoms, shorter overall symptom-free time, and worse response to typical antipsychotic drugs [88; 161]. Up to 50% of subjects admitted to in-patient treatment who have proved unresponsive to standard treatments, report concurrent substance abuse [406]. On the other hand, drug-abusers also suffering from mental illness are those most likely to be offered treatment facilities [400; 406]. As regards the occurrence of complications and psychosocial adjustment, substance-abusing schizophrenics show less compliance with treatment programmes, a higher risk of medical events (including HIV-related issues), and a higher frequency of suicidal acts [161; 261]. The destructive influence of substance abuse is also significant for these patients in terms of a sharp fall in their level of social functioning, and a sharp rise in levels of poverty, wandering and homelessness, violence and familial maladjustment [261]. However, when interventions succeed in keeping substance abuse under control, substance-abusing schizophrenics follow a more favourable disease course than that of their non-abusing peers [193].

Various hypotheses have been formulated to explain the relationship between substance abuse and schizophrenia. According to the "liability" model, in particular, non-psychotic abusers may become schizophrenic as the result of the toxic action of

abused psychotropic substances on their brain functioning. A higher incidence of schizophrenia among non-psychotic abusers than in the general population goes to support this hypothesis [193]. Another theory hypothesizes that schizophrenics tend to resort to substances as a result of their condition itself, or their exposure to neuroleptic medication, as a form of self-medication against disease-related or treatment-related negative symptomatology [38;163;170;207]. The high occurrence rate of drug abuse might alternatively be a consequence of a cognitive impairment typical of schizophrenia, which consists in an incapacity to anticipate the consequences of one's choices [63]. This interpretative model does not fit the fact that drug-abusing chronic psychotics display higher levels of psychosocial functioning, or the observation that their involvement in sensation-seeking behaviours suggests an absence of major cognitive impairment [88; 369].

Comorbid mood or anxiety disorders are common among schizophrenics, and antidepressant treatments are effective on them [69; 347]. Dysphoria is a major, though not the only, drive towards substance use among schizophrenic patients. Substance use among schizophrenics cannot, in fact, always be justified in terms of dysphoria: some authors provide evidence that the number of depressive symptoms weakly influences the risk rate for alcohol, cannabinoids abuse or polyabuse [39; 348]. Conversely, others have reported the association between depressive and anxiety disorders to be quite strong. In abusers, depression can develop during a period of abusing practice, or may simply be a response to the interruption of drug abuse. However, it is not uncommon to find that depression among schizophrenic patients, when it is responsive to antidepressants, develops into an alcohol-free condition [69]. Pharmacotherapies for the control of dysphoric mood may be as useful in treating drug-abusing schizophrenic patients as they have proved to be with non-psychotic cannabis and cocaine abusers [347]. Other medications, such as BDZs, high dose glycine or anticonvulsants, may also be useful in treating comorbid anxiety in schizophrenics. Nevertheless, the administration of BDZs in dually diagnosed patients should always be pondered carefully, because of their intrinsic addictive potential. Novel antipsychotics may contribute to the reduction of dysphoria in dual diagnosis patients. Studies on olanzapine, risperidone, quetiapine and clozapine agree in suggesting a significant anxiolytic effect [49; 345].

Drug-abusing schizophrenics do not have a drug of choice, and the pattern of their choices among the various available substances is similar to that in the general population [88; 329]. In other words, no specific relationship is likely to stand between schizophrenic symptomatology and the choice of abused substances; but this choice does tend to reflect the rate of consumption of that substance in the subject's environment. The abuse of at least one substance is quite likely (three times more likely for alcohol than for other substances), and the less addictive a substance is in the general population, the more likely it is to induce addiction among chronic psychotics (relative risk is as high as 6 times that in the general population for psychostimulants and hallucinogenic drugs). When changes in the popularity of a substance coincides with changes among the same cohort of psychotics, this is mostly due to a change in its availability. On the whole, chronic psychosis does favour the onset of addiction to various different classes of psy-

chotropics, with no particular selectivity, thus making what are normally less addictive substances as addictive to these psychotics as others substances. Schizophrenia does not differ from other psychiatric diseases in the typology of abused substances, or the quality of experienced effects, whether positive or negative ones [89; 259; 259; 260]. As regards the subjective evaluation of the drives to use substances, surveys on the question of the reason patients give for resorting to substances suggest no peculiarity: schizophrenics use substances for the same reasons as other subjects, that is, to "be high" or to avoid "feeling down", to "feel better", to "enjoy" and "to buffer depression" [90]. Polyabuse is the most frequent substance use pattern among schizophrenic abusers. Alcohol is the most abused (37%), and a lifetime diagnosis of alcohol use disorder is frequent too (22-47%). Cannabinoids come second (23%), followed by stimulants and hallucinogenic agents (13%) [42]. Other substances, such as opiates or sedatives-hypnotics, are far less common [94; 193]. The ECA study did not report any relationship between the typologies of abused substances and psychiatric diagnoses [297].

Substance-Induced Psychotic Disorders

Positive urinalysis screening for substances is required for the diagnosis of any acute psychotic syndrome as substance-induced. Taken alone, however, no clinical criteria can authorize such a diagnosis, nor can causal relationships be assessed between possibly abused substances and psychotic outbursts on the basis of clinical examination. Comparisons between urine-positive and urine-negative acute psychotics do provide statistically significant differences, but these are clearly insufficient to justify a conclusion in single case contexts. Acute substance-induced psychoses are characterized by hallucinations that are irregularly associated with delusions, and, less often, match delusional themes. As for the typologies, visual hallucinations and persecution delusions are prevalent. Delusions are more common in cocaine-induced acute psychoses, whereas isolated hallucinations, occasionally coupled with delusions during acute phases, are more typical of cannabinoid or psychotomimetic intoxication. Even with the substances which are least likely to induce delusions, the dominant type is a delusion of persecution.

Cannabis-Related Chronic Psychosis

Cannabis-related acute psychosis mostly looms as one cannabis-induced psychotic outburst in already psychotic individuals. This aetiological interpretation requires the symptoms to improve spontaneously in a substance-free condition [345; 374]. If psychotic symptoms endure in a substance-free condition, a suspicion is raised that a psychotic proneness is the ground on which psychotomimetic drugs trigger an actual disease. For individuals who were heavy cannabis users before the onset of their chronic psychosis, it can be hypothesized that psychotomimetic drugs are capable of producing chronic psychotic disorders, which are influenced by, but do not depend on, concurrent or enduring abuse. At present, we can define cannabis-related chronic psychosis as a kind of chronic psychosis that appeared concurrently with the heavy use of cannabis, and

then continues despite patients' cessation of cannabis use [345; 350]; or that appears in past regular cannabis users when cannabis use has been over for some time. With psychotic symptoms set in the context of current use, no relationship has been reported between psychosis and recent variations in consumed amounts: psychotic onsets have been documented during periods when consumption was heavier than usual, lighter than usual or with constant doses. The remission of psychotic symptoms in a cannabis-free condition undoubtedly implies a favourable prognostic meaning. However, primary psychotic disorders also benefit from the discontinuation of concurrent cannabis use, since these kinds of disorder, though substantially independent of substances as regards their pathogenesis, are certainly exacerbated by the use of psychotomimetics. Some Indian authors report that as many as 34% of psychotics who have a history of cannabis use can be classified as primarily cannabis users and secondarily psychotics, on the basis of the chronological sequence of the two phenomena [57]. In any case, the onset of chronic psychosis has been found to be more likely among currently non-psychotic cannabis users than among currently non-psychotic patients who do not use cannabis. The elicitability of psychotic symptoms in some cannabis-takers only, and not in others, suggests differences in psychotic proneness between individuals. Nevertheless, the familial occurrence of chronic psychotic disorders in the siblings of psychotic cannabis users is definitely low. In general, some cannabis-using psychotics can be considered to have become psychotic as a result of taking cannabis, whereas for some others it is more likely that cannabis has had a powerful influence in producing psychotic symptoms because of a basic psychotic proneness.

Features of chronic psychoses and points of clinical discrimination

Most cannabis-related acute psychoses only take a short time to improve, and relapses are only likely if there is later recurrent drug taking. On the other hand, a small subgroup of cannabis-positive acute psychotics follows an unfavourable course, characterized by chronicity, the recurrence of acute episodes and unresponsiveness to antipsychotic treatments. It has been pointed out that in these patients cannabis may elicit an intensification of psychotic proneness to a higher level or degree of relevance, or actually induce a psychotic disease by acting as an aetiological agent. No acute-phase clinical criteria have been agreed on as useful in identifying cannabis-related chronic psychoses, nor have any acute-phase features been recognized as predictive of the later course. Most studies have only described the psychotic symptoms which appear to be associated with recent cannabis consumption, and none of them have so far dealt with the differences between acute, subacute and chronic forms. Generally speaking, no evident differences can be expected. At present, therefore, a diagnosis of cannabis-related psychosis is made in cases of relapsing-remitting psychosis, even when these are currently cannabis-unrelated, if there is documentation to show that the onset of psychosis followed an episode of cannabis consumption. Some features have been singled out as being specific to cannabis intoxication, but none have proved useful in discriminating between cases according to their future course, whether briefly

remitting versus chronic relapsing, or persistent schizo-like. Cannabis-related psychotic outbursts are characterized by markedly odd behaviour, a higher level of aggressiveness and psychomotor excitement, better insight, fluctuating consciousness, greater anxiety, vivid visual hallucinations, and elated rather than blunted affect [24; 31; 50; 150; 213; 309; 343; 350; 361; 363; 364; 374].

Cocaine-related chronic psychosis

Acute psychosis has been documented in chronic cocaine users with no previous Axis I disorder, after an average of three years of continuous use. Such episodes usually achieve resolution spontaneously as long as cocaine use does not persist, and is not prolonged after the so-called crash phase, which is distinguished by psychomotor depression and oversleeping. The chronic use of cocaine or amphetamines has also been associated with chronic psychotic disorders, which continue along an independent course, displaying chronic psychotic symptoms with no co-occurring cognitive deficiency. The risk of developing chronic psychosis does not vary with the pattern of cocaine use. Other factors are therefore likely to be involved, such as those associated with the premorbid personality [164; 291; 326; 327].

Treatment for psychoses in addicted patients

Antipsychotic agents

Both typical and atypical antipsychotics have been evaluated in dually diagnosed psychotics. If it is to be comprehensive, any evaluation of antipsychotics must take into account their impact on drug-related issues: on one hand, abused substances may have psychotomimetic properties; on the other, the persistence of, or relapses into, drug-taking are both predictive of an unfavourable course.

Typical antipsychotics (TAs) offer little help to dual diagnosis psychotics [37; 44; 88; 345; 345; 400; 406]. Substance use is common among schizophrenics treated with TAs, and it shows no reduction during treatment; in fact, a tendency towards an increase in consumption during treatment has emerged for some substances, such as nicotine [235; 236]. Psychotics who are also abusers show a less favourable response to TAs, presumably due to the pro-psychotic effects of persistently abused substances, which limit the incisiveness of that treatment. When substance use foreruns a psychotic outburst, agents such as haloperidol or perfenazine can be expected to prove less effective than would otherwise be the case.

Since both TAs and abuse substances act on the CNS dopaminergic system, it can be hypothesized that special phenomena may intervene in the relationship between the pharmacodynamics of the specific agent and its impact on the course of psychoses, when substance abuse co-occurs [37; 345]. At clinically effective dosages, it has been shown that TAs turn off the mesolimbic dopaminergic firing, which is the known substrate for the reinforcing effects elicited by many abused substances, such as cocaine. Cocaine itself and alcohol are the two most frequently abused drugs among psychotics. Several addictive substances induce an increase in the levels of omovanillic acid (OVA), an index of dopaminergic activity, and enhance the release of dopamine in the nucleus accumbens,

which is the terminal of the dopaminergic mesolimbic pathway [243]. On this basis, it is plausible that the use of substances is effective in reversing the dopaminergic blockade induced by TAs. On one hand, this is consistent with the relapse-provoking role of drug use; on the other, it suggests that treated psychotics may resort to substances to counter the blunting effect on emotional life brought about by the mesolimbic antagonism of TAs. In a highly tolerant mesolimbic system, like that of abusers, which is more sensitive to lack of stimulation than that of normal individuals, the administration of TAs is likely to elicit an intense and intolerable hypophoria, followed by compensatory behavioural activation towards sources of reward. For individuals who have already learned to achieve rewards by substance use before treatment, resorting to available substances would automatically ensure compensation. The abuse-enhancing effect of TAs would be directly related to the antidopaminergic potency of the specific compound. Consistently with that, the use of desimipramine as adjunct to a TA for cocaine-abusing psychotics has been reported to reduce cocaine use, which does not happen with the same agent among non-psychotic cocaine abusers. In other words, TAs appear to enhance drug abuse in a way that is reversible by desimipramine, which is effective on drug abuse to the extent to which it counteracts the mesolimbic dopaminergic antagonism achieved by TA.

Clozapine, which possesses low specificity on dopaminergic receptors, showed a poor capacity to reduce dopaminergic transmission in animal models, when compared with TAs. Again in animal models, clozapine, unlike other antipsychotics, has been shown to decrease cocaine consumption, when a fixed dose schedule is used, and to lengthen cocaine-free periods, when an increasing dose schedule is used. On clinical grounds, clozapine has revealed anticraving properties. Firstly, the responsiveness of psychotic patients to clozapine is independent of concurrent substance use, in a way that is not attainable with TAs, which, as a rule, prove to be less incisive in substance-abusing individuals. Some authors have even suggested that substance-abusing psychotics may display a better response to clozapine than non-abusers [9; 45; 205].

In dual diagnosis schizophrenics, clozapine treatment reduces nicotine use. In fact, switching from haloperidol to clozapine lowered nicotine consumption, whereas haloperidol had caused it to increase. The clozapine-related reduction in nicotine use is dose-related [236]. Alcoholics treated with clozapine are likely to have stayed abstinent (50%) throughout the first year after discharge from hospital. Two psychotics with alcohol dependence, treated with 500 mg/day clozapine, were shown to have stayed abstinent in the long term [107; 108].

The interpretation of clozapine's effects on drug and alcohol use is not clear, though: in some contexts, a primary anticraving effect seems to loom, whereas in others it seems plausible that drug use leads to a reduction because in its case there is no need for self-medication brought about by an antidopaminergic blockade, such as that which has to be dealt with in the case of TAs [170; 210]. Abusing schizophrenics, in fact, report "negative symptoms", anxiety and mood especially, to a lesser extent, whereas counteraction by dopaminergic substances ends up by exacerbating psychotic symptoms, so unfavour-

ably affecting the course of the illness, and impairing the efficacy of antidopaminergic antipsychotics (i.e. TAs). A vicious circle is set up comprising negative symptoms and treatment by TAs, the use of dopaminergic substances, psychotic relapses, and then the potentiation of TA treatment to achieve a wider antipsychotic defence spectrum.

In dually diagnosed patients, TA-induced hypophoria could be the key to an explanation of the dynamics between antipsychotic treatment and the course of concurrent substance abuse. The frequency of depressed mood symptoms among TA-treated psychotics and their partial reversal following drug-taking are consistent with this explanatory model. The novelty-seeking dimension of Cloninger's Tridimensional Personality Questionnaire, which implies a higher risk for substance-related behaviours, has been recently associated with the D4 receptor subtype. Agents acting as D4 antagonists may reduce drug-seeking behaviour, whereas D2 antagonists (such as TAs) appear to increase them, especially in individuals who are highly positive to D4. In reality, clozapine's profile is distinguished by its higher specificity for D4 receptors (higher D4/D2 ratio) [193]. Risperidone, which has the highest specificity for D4 receptors, has not yet been evaluated on this issue.

Methadone and antipsychotics

The concurrent use of antipsychotics in methadone-maintained psychotics can be considered acceptable and helpful [58;176]. When combined with methadone, low dosages of TAs such as chlorpromazine, flufenazine and haloperidol are needed in controlling psychotic symptoms [351]. One problem is that antipsychotics are quite likely to be poorly tolerated by heroin addicts. Usually, TAs are not abused, but, if they are, patients should to be urged to comply. Depot preparations make it possible to skip the limitations posed by non-compliance and concurrent methadone treatment seems to act as a shield against extrapyramidal side-effects. Table 8 shows the methadone and antipsychotic dosages needed for psychotic heroin addicts. Clinicians should be particularly careful during the

Table 8
Pharmacological interactions and dosages in methadone-maintained heroin addicts with psychosis and violent behaviours in the experience of the PISA-SIA Group

	Dosages (md/daily)		
	Min	*Mean*	*Max*
Methadone (stabilization)	30	140	290
Typical antipsychotics (haloperidol equivalent)*	3	7	9
Clozapine	100	150	300
Olanzapine	10	10	20
Risperidone	2	4	6
Quetiapine	25	50	100
Valproic acid	80	100	110

**Use caution during the methadone induction phase. Re-evaluate methadone dosage if patient is already in treatment*

Table 9
Treating Psychosis in Heroin Addicts
PISA-SIA (Study and Intervention on Addictions) Group Recommendations

A. Apply antipsychotic properties of long acting opiates
B. Use the patient's greater compliance during methadone maintenance or buprenorphine maintenance to reduce the risk of psychosis crises
C. Add-on low doses of typical or atypical neuroleptics (in combination with mood stabilizers). Take advantage of methadone and/or neuroleptic blood level increases
D. Prefer clozapine-like neuroleptics
E. Consider the possibility of withdrawal psychosis. Reintroduce methadone or buprenorphine
F. Add neuroleptics with caution in low tolerance psychotic MM heroin addicts. Use caution also during the MMTP induction phase.
G. Avoid low potency neuroleptics in MM heroin addicts (higher dose = greater metabolic interference = greater blood level increases)
H. Consider the use of I.M. antihistaminics for agitated psychotic MM heroin addicts.

induction phase, in order to minimize the narcotic mutual potentiation of antipsychotics and opiates, especially when TAs are used. As a rule, the recommendation is to avoid administering antipsychotics until the steady state has been reached with methadone. In the meantime, the sedative action of methadone itself can be resorted to. In addition, the use of benzodiazepines cannot be recommended. In cases of severe psychomotor excitement requiring neuroleptic administration, limited amounts of neuroleptics can be used, as long as they are under medical control, and as long as neuroleptic doses are not taken late in the evening. Antihistaminic agents are a valid and suitable alternative option for achieving sedation in psychotic heroin addicts.

Disulfiram

Disulfiram counteracts alcohol consumption regardless of the presence of psychotic symptoms. The reduction of alcohol abuse is bound to have a positive impact on the course of psychosis itself, because alcohol is known to worsen psychotic symptoms. In subjects treated with high-dose disulfiram, however, psychotic symptoms have been reported to deteriorate [42; 193]. Schizophrenic alcoholics have been reported to benefit from disulfiram treatment to the same extent as non-psychotic alcoholics. In particular, alcohol abuse in schizophrenics seems to show an excellent response to the clozapine-disulfiram combination [42].

In conclusion, disulfiram is useful in psychotic alcoholics at a dosage of 250 mg/day: at this dosage, the likelihood of an iatrogenic worsening of psychotic effects carries less weight than the impact of ongoing alcohol use in causing exacerbation and in harming the overall course of the illness.

Disulfiram has also been shown to be useful in treating cocaine dependence in methadone-maintained opioid addicts [282].

Desimipramine

Desimipramine has been used at doses of 100-150 mg/day in cocaine-addicted psychotics, as an adjunct to antipsychotic treatment. In these patients, that combination achieved a good level of control over cocaine craving. The same agent, when tried on non-psychotic cocaine-addicts, failed to show any definite efficacy [2; 4]. Anticraving dopaminergic agents must be avoided during acute psychotic phases, because of the risk of exacerbating psychotic symptoms, as well as the uncertainty of their impact on substance abuse. In stabilized chronic psychotics, our anecdotal evidence suggests that ropinirole, up to 1.5 mg/day, can lead to a reduction in craving, with no concurrent psychopathological destabilization.

Table 9 shows the PISA-SIA Group recommendations for the treatment of psychotic heroin addicts.

The Clinical and Therapeutic Aspects of Aggression and Violence in Heroin Addicted Patients

Assessment of the role of opioids in modulating aggressive behaviour is no easy matter, as most studies on the subject actually deal with animal models, where acts of aggression result in defensive behaviour (a physiological form of response to threats from outer) against preying. These studies have provided a variety of evidence, allowing the following conclusions to be drawn [120; 136; 335- 337; 381]:

1. Several areas of the brain that are related to the production and modulation of defensive behaviour are crowded with opioid receptors and enkephalin-binding axon terminals. These areas comprise:
   a) the nucleus proprius of the terminal stria and the nucleus accumbens, as modulators of defence [15; 127; 128; 133; 257; 296; 334],
   b) the periacqueductal grey substance, which produces/enhances defence [18; 333; 338].
2. The peripheral administration of naloxone heightens or elicits defensive behaviour and aggression. On the other hand, naltrexone failed to modulate defence in monkeys, while its administration to mice caused aggressive outbursts to dwindle in frequency. Most of the evidence indicates that the role of opioid modulation differs with the typology of aggression that is being considered [36; 101; 160; 293; 294; 305; 362; 392].
3. Naloxone-challenged cats showed greater proneness to defensive behaviours, in terms of a lowered threshold and a shortened latency of reaction. The effects measured depended on time and administered dosage. Interestingly, in the same model preying behaviours showed they had acquired a longer period of latency after naloxone administration [335].

Violence of addicted patients: a consequence or a sign of adjunctive disease ?

The data in the literature on the relationship between aggression and the opioid system mostly come from animal studies, due to the limitations placed on experimentation with humans. Despite this problem, the role played by opioids in regulating human aggression can be investigated through the natural model provided by opiate-addicted patients.

On one hand, the exposure to opiates is responsible for acute neurochemical and behavioural alterations (tolerance), which are expressed through withdrawal phenomena overlapping with those induced experimentally on animals. On the other hand, enduring exposure to some opiates produces stable behavioural conditioning, which is a crucial aspect of the clinical picture of addiction. Such behaviours are likely to be due to the impairment of normal opioid functioning. Investigations into the dynamics of opioid alteration in addicted patients, and into the links between aggression and other addictive features, may therefore lead to a better understanding of the ways opioids function in non-addicted humans.

Opiate use does not produce a uniform degree of social impairment. In fact, different social typologies of heroin addicts have been described, as follows. The severest

form of psychosocial maladjustment is found in those called "street junkies": they are often polyabusers, and insist on receiving prescriptions for any substance that may be useful to them in soothing withdrawal symptoms or substituting heroin. These addicts commonly commit crimes in order to obtain their daily supply of heroin. On the other hand, the so-called "stables" accept social rules and regulations, and do not form groups with other addicts. In some cases they have good jobs and do not get into legal trouble. The antisocial types are wholly submerged in the clandestine world of addiction. As a rule, they live outside the limits of the law and engage in criminal activities. Their aggressiveness is also likely to exceed any drug-related need, as if they were driven by a wish to cause others harm. Addicts who live in "two worlds" may resort to crime and have relationships with other addicts, but, at the same time, they are able to keep a lawful job. They are, in fact, the most dangerous type of heroin addict, since they may harm themselves or others while at work, due to opiate intoxication or withdrawal. Lastly, the so-called "loners" are not involved in drug-related activities, have no stable job, and often live on help from others rather than personal resources. They often suffer from severe mental illness [198].

The entire range of aggressive behaviours can be observed among heroin addicts. It would be interesting to determine whether aggressiveness actually implies being unusually prone to substance abuse, as an aspecific index of psychopathology; or whether, conversely, the self-medicating effects of opiates on aggression favour the transition from use to abuse and eventually to addiction. Once addiction has set in, aggression may represent a tolerance-related phenomenon, and express one facet of primary or secondary withdrawal. The fact that aggression is only relevant in metabolically impaired addicts, incidentally suggests that opioids may exert physiological control over the levels of aggressiveness in humans.

The PISA-SIA Group [7] evaluated heroin addicts classified according to the level of aggression severity (high vs. medium) (Figure 7), concluding that the severity of aggression is related to the severity of addiction itself, rather than to other drug-related issues. Aggressiveness in addicted patients is best seen as an expression of acquired tolerance to opiates, rather than as a personological, temperamental feature but it is a feature with further implications. What it does imply is:

1. A severer form of the intoxication-to-abstinence circle, whether assessed by self-evaluation or observer examination.
2. A higher level of psychopathology, especially as regards the symptoms that are typically related to opioid impairment (anxiety, depression and psychoticism).
3. An earlier age of first contact with the substance and an earlier age at which substance use becomes a habit. The combination of these two parameters defines a new index, which we have called "latency of addiction"; it is inversely correlated with the degree of cerebral resistance to opiate exposure. In comparisons between subjects who habitually consume the same amounts of heroin, the more aggressive ones have a shorter latency of addiction, indicating that they take a shorter time to reach a condition of cerebral metabolic impairment after repeated exposure to

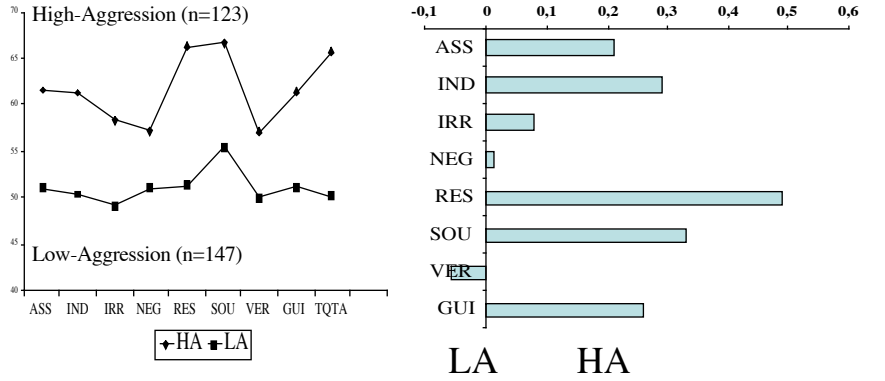

Figure 7.
High-Aggression Heroin Street Addicts . Discriminant analysis (n=270)

opiates.

4. A higher score on the Harm Avoidance scale of the TPQ. Harm Avoidant subjects tend to overrate the negative and unfavourable side of events, and their behaviour displays avoidance stereotypes. Cautious, preoccupied, pessimistic, introverted, shy, feeble subjects record high scores on Harm Avoidance. Low scores, on the other hand, indicate a positive attitude, assertiveness, extroversion, faithfulness and high energy levels. The biological basis of Harm Avoidance, according to Cloninger's theory, is that a hyperfunctioning serotoninergic system corresponds to low Harm Avoidance and vice versa. Harm Avoidance itself seems to be one of the results of addiction: the negative, fearful part of craving, through repeated experience or anticipation of withdrawal, may induce persistent conditioning of the addict's behaviour. Addicts with intense craving — a sign of their metabolic impairment — hardly respond even to the highest heroin doses or to average methadone doses, and are likely to become so strongly harm-avoidant as to be conditioned by harm-avoidance in every aspect of their life.
5. A higher degree of withdrawal severity.

Opiates as antiaggressive agents

The top priority of intervention on addicted patients is to control possibly homicidal or suicidal patients, and metabolically impaired ones. In the first two cases, hospitalization is required; whereas the latter can sometimes be successfully treated with an outpatient regimen.

On therapeutic grounds, antidepressant treatments do buffer the risk of suicide in addicted patients. In our experience this risk appeared to be higher among naltrexone-treated patients, and lower in methadone-maintained ones. A series of studies indicates

that opiate agonists are likely to be effective in controlling concurrent psychopathology and aggression in opiate-addicted patients. In our clinical practice we examined over 600 street addicts on heroin who asked for treatment. Of these, 30% reported suicidal thoughts, though a high degree of severity was only recorded in 1% of cases. Anger and hostility were found in as many as 40%, but were displayed in severe form in only 4%. Violence occurs most often among non-depressed addicts and phobic addicts. Suicidal thoughts and aggression are quite common among street addicts applying for treatment from the PISA MM treatment programme; our view is that these subjects may have such a highly impaired opioid function that it can no longer be controlled even by the highest heroin street doses. In fact, in our personal experience, most heroin addicts search for treatment when they cannot find enough money to ensure their daily heroin supply. We examined heroin addicts, not necessarily seeking for treatment, and compared them to controls. Heroin addicts show the highest levels of aggression on all scales, especially physical violence, rancour and suspiciousness. The range of aggression severity is wider among heroin addicts, so that a subgroup of addicts turns out to be less aggressive than the average for controls, whereas another group shows a level of aggressiveness that is far above the same average. The sample can be divided into two subgroups of about equal size. One group is characterized by a degree of aggression lower than +1SD (with respect to the control group): we infer that these addicts are still able to find enough heroin to buffer their needs. The other group proves to be highly aggressive, especially in terms of violence, unexpressed hostility, rancour, suspiciousness and guilt: these subjects are likely to suffer from extreme opioid impairment, which cannot be compensated by any amount of heroin, not even the highest available. These patients are, in fact, characterized by their high scores on Harm Avoidance, more severe withdrawal and psychopathology, a prevalence of male subjects and a shorter latency of addiction. In our clinical practice, violent behaviours also occur during treatments (in as many as 40% of all subjects examined). Irritability, in particular, is common (80%). The lowest levels of aggression are displayed by subjects in Therapeutic Communities and on naltrexone treatment, while methadone-maintained subjects are more aggressive. However, the average methadone dose in the group used for comparison was 30 mg/day, far below optimum therapeutic dosages, which range between 80 and 120 mg/day. We suppose that such aggression is likely to depend on undermedication, consistently with the observation that subjects displaying more severe psychopathology (depression, anxiety, paranoia and somatic symptoms) and aggression at treatment entrance turn out to need higher stabilization dosages [221]. In particular, an inverse correlation was found between violent behaviour and methadone dosage. It has also been demonstrated that dual diagnosis heroin addicts need higher stabilization dosages (150 mg/day on average) than heroin addicts with no additional psychiatric disorder (whose average dose is 100 mg/day). As long as adequate dosages are used, retention rates do not vary with the presence or absence of dual diagnosis [224]. In fact, even if there is a trend towards a lower retention rate for dually diagnosed subjects during the early period of treatment, this trend seems to show a cross-over

pattern after the first three years, so that dual diagnosis addicts are more likely to have been retained in treatment after three years. Bipolar patients are an exception to this rule, as they continue to show a lower retention rate [212].

Further information about the relationship between opiates and aggression comes from our clinical observations on agonist- or antagonist-maintained populations. When addicts were compared in terms of features of aggressive behaviour by repeated monthly evaluations, significant differences emerged between methadone and naltrexone-treated patients. Methadone-treated patients displayed lower levels of aggression and self-injuring behaviour. Subjects did not differ in the assessment made of their aggressiveness at the beginning of treatment, but methadone-maintained patients proved to be less aggressive at the end of the observation period. The unsatisfactory effects of naltrexone in controlling aggressiveness were also documented in a sample of bulimic patients, who received naltrexone alone or naltrexone plus fluoxetine, in a three-month monthly cross-over protocol [219]. Within the same study, a case was reported of a bulimic patient who developed panic attacks in the early phase of treatment with naltrexone [220]. Naltrexone may also be responsible for the opioid-like discomfort observed in naltrexone-maintained patients: in fact, the addition of fluoxetine to naltrexone succeeds in improving the retention rate of naltrexone-maintained subjects. We have suggested that fluoxetine is effective in overcoming some of the naltrexone-induced resistance to retention in naltrexone treatment [226].

In our opinion, then, the opioid system may be closely involved in the control of aggressiveness. Indeed, when addicts who take enough heroin are given enough agonist to balance their opioid tolerance, they do not display aggressive or suicidal behaviours. Aggressiveness, whether as self-injuring behaviour or as outward violence, only characterizes addicts whose opioid tolerance has become unbalanced by a high level of opioid stimulation. Among non-addicts, violent or suicidal individuals may be marked out by a primary imbalance of their opioid system. Consistently with this hypothesis, a higher level of endorphins was documented in autistic subjects, and was not balanced by a corresponding tolerance to opiates [388]. In fact, the administration of opioid-antagonists to autistics was not followed, as in drug addicts, by any withdrawal symptoms [183; 275]. Aggressive subjects may constantly display a subnormal functioning of their opioid system, similar to what addicts end up by suffering from, due to chronic exposure to toxic opiates. On clinical grounds, the aggressive behaviour of heroin addicts mostly looms as a sign of metabolic impairment. Aggressive heroin addicts require higher methadone dosages than their non-aggressive peers, and if aggressiveness is a problem during agonist-treatment, an increase in dosage is probably needed.

Traditionally, drug addicts have been thought to be essentially psychopaths — violent individuals who unconsciously long for death. This view appears to be incorrect: aggressiveness can best be considered as a sign of addictive disease, and deserves more appropriate medical intervention than stricter repression and social stigma.

As a fall in levels of aggressiveness follows adequate methadone treatment, it can be hypothesized that some addicts-to-be resort to heroin as a means of self-medica-

tion, rather than to seek euphoria. According to Khantzian [170], aggressive symptoms are among the features that may be found in the habit of self-medication.

Opiate agonists display an antiaggressive action both against self-injuring behaviour and against outward violence. Interest has been raised on this issue because of the lack of antiaggressive medicines, on one hand, and the frequency of aggressive syndromes among psychiatric patients, on the other. Apart from clozapine [56;376], in fact, antipsychotic agents show a poor capacity to control aggressiveness outside a psychotic condition. According to Khantzian, we may state that in normal conditions, and during the course of development, the brain produces endorphins not only to control pain, but also to maintain affective balance and well-being. Endogenous opioids may be crucial to the modulation of human aggression, which may be essential to survival but is also devastating when it becomes uncontrolled. By studying the role and function of endorphins in mental activities, a better understanding can be achieved of how to increase energy and activity without eliciting aggression, and about how abnormality and dysfunction of the opioid system may be related to destructive expressions of human aggressiveness [170].

The Clinical and Therapeutic Aspects of Alcoholism in Heroin-Addicted Patients

Several data from the literature define the relationship between depressive states and alcohol abuse, though controversy continues about the dynamics that link different kinds of depressive syndromes and alcohol-related problems. Most authors agree in considering heavy drinking as an equivalent, or a masked form, of depression [284]. Patients who continue to drink, despite severe or advanced somatic consequences, display a peculiar form of depression [284]. Alcoholism stems from depressive states, which are mostly of minor severity and a disguised kind [379]. Other studies have described a significant association between bipolar disorders and alcohol abuse. According to Kraepelin, as many as 25% of bipolar patients abused alcoholic drinks [189].

Several authors conclude that alcohol abuse mostly characterizes depressive states, and is resorted to as a way to elate mood and soothe pain, whereas alcohol use during states of mood elation is a sign of excitement and impulsiveness [41]. DSM has suggested a close link between cyclothymia and alcohol abuse. Chronic depression too has been associated with alcohol abuse. It is not surprising, therefore, that alcohol use, which can stand as an addictive disease itself in some cases, is often found combined with substance abuse in general. Studies in the literature have increasingly reported an association between heroin and alcohol abuse [11; 17; 21; 22; 52; 73; 131; 148; 188; 251; 325; 330]. Alcohol abuse seems to be related to polyabuse, and mainly affects young addicts; among these, lifetime rates for alcoholism range between 10 and 75%. The National Drug Alcohol Collaborative Project (NDACP) reported a rate of 43% for combined alcohol-heroin use in a sample of over 1500 heroin addicts [52]. Heroin was the first substance to be abused in 99% of cases. Rounsaville reported a lifetime and index prevalence of alcohol dependence of 13% and 34%, respectively [322]. Californian addicts have been reported to abuse alcohol at a rate of 53-75%, and 11% have been admitted to hospitals for alcohol-related somatic matters. Alcohol abuse occurs as often as 10-20% among street addicts, and up to 27% among methadone-maintained subjects [11;131]. Some authors have tried to explain the increase in alcohol use during methadone treatment programmes, concluding that methadone-maintained addicts may abuse alcohol in order to counter the opioid-normalizing effect of methadone, and to go beyond the methadone-heightened opioid threshold [11; 131; 393]. When the correlation between alcohol use and heroin use among methadone-maintained addicts was examined in a large sample of heroin addicts, it was pointed out that alcohol use during methadone treatment seems to be the result of an automatic behavioural pattern, according to which alcohol use tends to rise as street-opiate use falls, and the reverse [11]. Furthermore, Rounsaville, who supports this theory, also reports that alcohol use is mostly found in addicts who had once abused alcohol, so displaying a relapse into a previous alcohol-related disorder [322].

On the basis of their clinical experience, Maremmani and Shinderman suggest that the use of alcohol, benzodiazepines and other types of drug in heroin addicts may be correlated with a condition of opiate dependence improperly compensated by street heroin or by substitution treatment dosages. Thus the search for an appropriate metha-

done dosage during methadone maintenance is crucial not only because it raises the retention rate for patients within the treatment group, so allowing an improvement in social rehabilitation, but also because it lowers the risk of polydrug abuse [222].

Heroin addiction, alcoholism and self-help groups

Anonymous or Self-Help groups are known to be a valid instrument in the treatment of alcohol dependence. The most active self-help groups are Alcoholics Anonymous (AA) and Club for Alcoholics in Treatment (CAT). As regards AA, which is best represented in the USA, but is also active in Italy, American authors note that, despite official guidelines laid down by the national committee (General Service Office for AA), stating the full compatibility of methadone treatment with AA activities, methadone treatment is often quickly eliminated, if not completely neglected [3]. Progress has certainly been made in the field of self-help with the formation of institutional groups, which follow a well-defined, constant method and are directed by operators skilled in their specific task. Particularly interesting results have been achieved by the CAT organizations, started in Zagabria in 1964, by applying Hudolin's thought [146]. They aim to provide members with a structured programme for the treatment of alcohol dependence. However, cultural bias should be neutralized, if the aim is to combine a self-help approach with methadone treatment; secondly, some changes should be made. For instance, CAT operators often reject the concept that alcohol dependence is a disease, preferring to speak of behavioural disorder. The concept of metabolic disease must, in any case, be accepted in order to get patients into a successful treatment and avoid any discrimination taking place. In fact, any refusal of this approach can be interpreted in terms of social and historical trends, and has no clear correspondence with the theoretical system of self-help interventions. Hudolin himself stated that the first crucial step is to approach subjects as patients, a status they should be acknowledged as possessing if they are to receive appropriate treatment rather than blame. Nevertheless, self-help groups continue to judge it necessary to look beyond that concept, so as to avoid useless in-patient treatment and overtreatment by medical means; integrated approaches, they insist, should be preferred, to provide the best fit with each individual lifestyle. Scientifically speaking, these views appear to be meaningless, and they can be used as a basis for the proliferation of gratuitous belief and unskilled intervention due to the neglect of scientific principles. Another point made by most CAT operators is that, by defining alcoholics as suffering from an illness, an excuse for controlled drinking may be introduced; this, they suspect, may result in contacts between people and alcohol being favoured, which is the origin of the whole problem. This statement cannot be wholly agreed upon, especially from an alcoholic's point of view. The true problem is a different one — the widespread lack of medical approaches to alcohol dependence, which leads to the view that any chemical compound, except for hepatoprotective preparations, is inappropriate. The conceptualization of alcoholism as a pathological state does not mean systematically referring alcoholics to in-patient treatments, to the detriment of integrated approaches. As long as the specific dynamic of this type of

disorder is well understood, both kinds of approach can be applied, since both are supposed to contribute to a satisfactory outcome. The principle that a drug-free condition is to be achieved before any treatment approach is initiated should be looked at again. It has been widely accepted that disulfiram-treated patients are expected to meet no difficulty when enrolled in self-help programmes. Misunderstandings are, however, common when dealing with methadone-treated patients who continue to abuse alcohol, or apply for self-help programmes while taking psychotropics for anxiety or mood disorders. Though CAT operators receive a thorough training in how to deal with relapsing behaviour as a crucial aspect of addictive diseases, they often regard a drug-free state as the only satisfactory outcome. If gammahydroxybutirrate (GHB) meets raised expectations, this view will turn out to be a misconception. A drug-free condition was originally conceived by Hudolin himself, within his hypothesis of an environmental approach, not as the ideal outcome, but as a way to achieve the true objective — the reversal of a dysfunctional lifestyle. That objective implies that a drug-free condition is perfectly compatible with pharmacotherapy, whether aversion therapy or some other form. It will be enough to know which drug to choose for a given phase of the disease: benzodiazepines or GHB for withdrawal, serotoninergic agents to favour enduring abstinence, GHB to control craving, whether alone or associated with SSRIs, and acamprosate as an anti-craving agent in detoxified patients.

Psychopharmacotherapy of heroin addicts with alcohol dependence.

Alcohol undoubtedly has a negative influence on the outcome of a methadone maintenance programme. It implies a more severe cognitive and behavioural disturbance, a higher prevalence of psychiatric disorders, and a lower degree of compliance, which often conditions an operator towards a quicker, premature tapering of methadone [86; 307]. Moreover, alcohol dependence has more serious somatic consequences (e.g. chronic hepatic failure), which can lead to premature death or may favour overdosing accidents, due to interference with the methadone metabolism [118]. Since both addictions need to be treated at the same time, disulfiram was tried first on methadone-maintained patients,

Table 10
Pharmacological interactions and dosages in methadone-maintained alcoholics heroin addicts in the experience of the PISA-SIA Group

	Dosages (md/daily)		
	Min	*Mean*	*Max*
Methadone (stabilization)	240	310	380
GHB	10	27	30
Clonazepam	2	5	9
Trimipramine	50	70	100

**Use caution during the methadone induction phase. Re-evaluate methadone dosage if patient is already in treatment*

but, though the complete safety of the combination was ascertained [53;203;367], its efficacy is still controversial, as disulfiram is mostly equivalent to placebo [203]. The decrease in alcohol consumption appears to depend on a subject's compliance with the combined treatment; this depends in its turn on the level of the subject's awareness of the severity of the problem [203]. It is awkward to get addicted patients to take disulfiram daily: as an alternative, subcutaneous implantations can be resorted to, as long as patients consent; or else, methadone administration may be allowed, but only as long as compliance with disulfiram treatment is shown. Another strategy is not to provide patients with methadone if there is a positive result to the screening test for alcohol on the breath (revealing alcohol use during the previous 12 hours) or abnormally high alcohol blood levels. This procedure does not guarantee that patients will abstain from alcohol after their methadone has been administered. Table 10 reports the feasible combinations of psychotropics with methadone, as observed by the PISA-SIA Group.

The combined use of methadone and disulfiram should be limited to the most severe cases, or at least to cases in which non-compliance has hampered the feasibility of other treatments. Apart from such cases, different pharmacotherapies, supportive approaches or psychosocial treatment should be used.

Naltrexone, though useful in pure alcoholics, is unsuitable for alcohol-dependent heroin addicts. During naltrexone treatment, in fact, substance abuse (like benzodiazepines and stimulants) has been reported to increase [211]. One possible explanation is the following: heroin is capable of inducing a strong craving, which reinforces heroin taking. Naltrexone blocks the heroin-induced reward, so leading craving to extinction, but at the same time, it ends up by intensifying the hypophoria caused by lack of opioid stimulation. Naltrexone-treated subjects may therefore resort to alcohol or BDZ to soothe late withdrawal symptoms and naltrexone-enhanced hypophoria.

GHB for alcohol-dependent heroin addicts

GHB is a general anaesthetic drug which is no longer used for its original purpose. GHB has several pharmacological properties: at anaesthetic dosages, it causes an increase in dopamine levels in several cerebral areas, which follows a widespread inhibition of CNS neuronal activity. Lower dosages seem to selectively raise dopamine transmission in the mesencephalic ventral tegmental area [103; 104; 173; 209; 370]. Some of GHB's pharmacological properties are particularly interesting: it binds to many different sites, none of them associated with GABA-A receptors, whereas it does bind to GABA-B receptors; it substitutes for ethanol in rats; moreover, it has been proved to decrease ethanol consumption in alcoholics [110; 111; 119].[217; 223]. Hence, GHB may be used in alcohol-dependent heroin addicts, and be added on to methadone even when it is administered at high dosages, like those needed to control heroin use.

It is worth mentioning the case of a female heroin addict displaying alcohol dependence, who became stabilized on methadone when treated at the PISA-SIA Group. F.M. was a 31-year-old unemployed woman, with a 10-year history of heroin addiction, at that stage a polyabuser and HIV-positive. She had been treated with 10 mg/day methadone

at a Local Service, and was drunk with alcohol when first observed at the PISA-SIA Group Service. She was judged to be one of the most severe cases ever observed. After 24 days of treatment, she had cut down on her alcohol consumption by 70%, and her CGI score of 3 indicated a mild form of disease, so recording a major therapeutic gain combined with the absence of major side-effects. She was given GHB at an average dose of 27 cc/day (min. 20, max. 30), together with methadone at an average dose of 27 mg/day (min. 10, max. 30) and clonazepam, on average 4.75 mg/day (min. 2, max. 9). Trimipramine, 100 mg, was also used in the evening to control insomnia. During the subsequent phases of stabilization and maintenance, GHB dose was gradually increased up to 60 cc/day, to be maintained for at least one year. Maintenance lasted 7 years, until the patient passed away due to AIDS. At the time she died, she was receiving methadone, 40 mg/day, while GHB, previously given at 10 cc/day, had recently been tapered off.

Final remarks and recommendations

Our chief recommendations include increasing the probability of enrolment, raising heroin addicts' compliance and taking a global approach to the disease. It is very important to achieve rapid, complete control of acute phases. This becomes possible if the patient can be detoxified or if methadone treatment can be initiated in line with the patient's opiate tolerance. After this phase it is necessary to stabilize residual symptoms (in the subacute phase) and maintain achievements in the long term (case management). It is generally possible to achieve detoxification in psychostimulant, hallucinogenic drug or cannabis abusers before any psychiatric treatment is started, but, if concomitant heroin addiction is present, patients must been directed towards methadone treatment. The prescription of abuse-liable psychotropics, such as BDZs, must be assessed with great caution. For heroin addicts with multiple drug abuse, it is reasonable to perform detoxification from different substances one by one, during methadone maintenance.

Some misconceptions have been spreading among medical operators, who are often called to deal with dual diagnosis patients. The first is that dually diagnosed heroin addicts are unresponsive to standard treatments for heroin addiction. The second is that these addicts are, on the whole, non-compliant. The third is that they are expected to have a less satisfactory outcome.

During our many years of clinical experience we have observed that the rate of survival-in-treatment is significantly higher among dually diagnosed methadone-maintained patients than among uncomplicated heroin addicts. The lower dropout rate observed among our dual diagnosis patients cannot be interpreted as a difference in the success rate for completion of the programme, since this is the same regardless of the presence or absence of dual diagnosis. Rather, the lower dropout rate brings with it the benefits of a higher rate of retention in treatment. Dually diagnosed subjects display a greater degree of compliance with methadone treatment, which allows them to control their addiction and their psychopathology at the same time. This fact is testified by the high values recorded by them on the social adjustment index utilized (DSM-IV GAF) and by the absence of hospitalization episodes throughout the treatment period in patients

who had previously been hospitalized many times.

In conclusion, we can state that dual diagnosis addicts should in all cases be treated for their addictive disease by using adequate methadone dosages, which can be expected to be higher than those required to treat uncomplicated addicts, while considering stabilization as a medium-term goal. Some dual diagnosis patients may benefit from the treatment that is targeting their addictive problem, thanks to its effects on their mental disorder too. Opioid agonists should be reconsidered, as not only possessing an anticraving activity, but also as being able to act as psychotropic instruments in treating mental illness, with special reference to mood, anxiety and psychotic syndromes. Lastly, dually diagnosed addicts can be expected to benefit from the facilities offered within integrated programmes to the same extent as uncomplicated addicts, as long as programmes are based on adequate dosages that are administered for a sufficient length of time.

Appendix A. Methadone Treatment in Dual Diagnosis Patients. The PISA-MMTP

In this section, we report clinical information about methadone treatment for dual diagnosis patients, on the basis of our personal experience in the PISA-SIA Group.

Methadone maintenance took root in the Sixties and continues to be the most widespread treatment solution for opiate addiction. It starts with an induction phase, through which dosages are gradually increased to reach an optimum value. Methadone Maintenance then follows, consisting in the administration of a constant methadone dosage. At the same time, medical facilities, rehabilitative interventions and counselling are available too. When this technique is properly applied, patients' conditions, which are bound to be displayed in a critical form at treatment entrance, will significantly improve as maintenance goes forward.

Initial methadone dosages are used to soothe withdrawal symptoms (early induction). As soon as withdrawal has been buffered, proper induction can be started, with the aim of identifying a therapeutic dosage value, which is expected to vary between individuals. For non-dual diagnosis patients, initial dosages range between 20 and 40 mg/day, and early induction takes no longer than 24 hours. Actual induction, which allows a therapeutic dosage level to be reached, lasts no longer than 5-10 days. The following stabilization phase, during which an optimum dosage is sought, and after which that dosage is stably administered as the maintenance dosage, is usually complete within a month. During the maintenance phase that follows, behavioural and psychosocial readjustment are allowed to develop, on the basis of what has been achieved during the previous phases. At this stage, opiate receptors are stably bound by the medication, so suppressing craving and addictive behaviours, on one hand, and compensating for the conditioning due to chronic opiate intoxication, on the other. Maintenance should continue for as long as patients show they are benefiting from it, and for as long as patients agree to stay in treatment. The best way of evaluating the therapeutic results is, in fact, the retention rate.

Independently of its essential target, methadone maintenance also plays an important role in social medicine. It can be crucial in limiting the spread of HIV infection among heroin addicts, but it can also improve mental health among opiate-addicted patients. In fact, dual diagnosis patients who are successfully treated by methadone maintenance tend to be retained in treatment longer than their uncomplicated peers.

In this appendix we have reported the guidelines for the treatment of dually diagnosed heroin addicts, as defined by the results from our ten-year naturalistic follow-up experience at the PISA-SIA Group. Reported indexes include first-day dosage, weekly dosage during the first month, and average dosage over the first four-month interval. Dosages are compared between dual diagnosis heroin addicts and uncomplicated peers. Moreover, stabilization dosage and the time taken to reach it are also accounted for: the term 'stabilization dosage' is used to refer to the minimum dosage administered for at least four months with constantly positive results. The outcome is evaluated as positive or negative according to two parameters — level of psychosocial adjustment, and recent

Table A1
First day, weekly first month dosages in dually diagnosed heroin addicts in the experience of the PISA-SIA Group

Time	*Uncomplicated heroin addicts*	*Dually diagnosed heroin addicts*
1st day	47±37	40±22
7th day	66±38	53±31
14th day	76±40	67±42
21st day	85±41	76±54
28th day	89±44	80±55

heroin use, as occurring more or less than twice in the previous two months.

Table A1 displays first-day and weekly dosages for the first month of treatment. Dual diagnosis patients need an average of 40 mg on the first day, like their uncomplicated peers. Highest first-day dosages for dually diagnosed addicts, of 80-100 mg/day, are slightly lower than those for uncomplicated peers (up to 200 mg). First-day dosages for dual diagnosis addicts, then, tend to be lower. During the first month of treatment dosages were increased by 40% in the first week, by a further 20% in the second week, by 10% in the third week and, lastly, by 5% in the fourth week. Again, dosages for uncomplicated addicts are slightly higher. Nevertheless, stabilization dosage is higher for dual diagnosis addicts (140 mg/day vs. 100 mg/day). In fact, the dosages required for dually diagnosed patients tend to continue to rise through the second month, but then stay the same throughout the whole of the rest of the observation period (Figure A1). On the whole, it can be said that uncomplicated addicts require higher induction dosages, but become stabilized at lower dosages. The time needed to reach stabilization is longer for dually diagnosed patients, an average of seven months vs. three among uncomplicated peers (Table A2). This gap is not fully justified by the fact that eventual stabilization dosages are higher, so dual diagnosis patients can definitely be said to proceed more slowly towards stabilization. Methadone tapering during treatment accomplishment does not proceed in divergent ways in the two groups, but it does take place more slowly in dual diagnosis patients. As for retention rates, it was noted that dually diagnosed patients experience a higher early rate of attrition, but no difference is left after eight months of treatment. First-day dosage is crucial for treatment retention: it is important to achieve complete control of withdrawal symptoms within 24 hours, by using a cumulative dosage of 80-100 mg when necessary, and as much as 200 mg in a few cases. If patients are left in a condition of partial withdrawal, it is quite unlikely that they will stay in treatment any longer. So, what precautions are needed, when the dosage exceeds 40 mg on the first day? As a rule, when withdrawal symptoms are assessable, 20 mg should be administered, and evaluation of withdrawal repeated after a couple of hours. If withdrawal shoots up again or persists, a further 20 mg should be

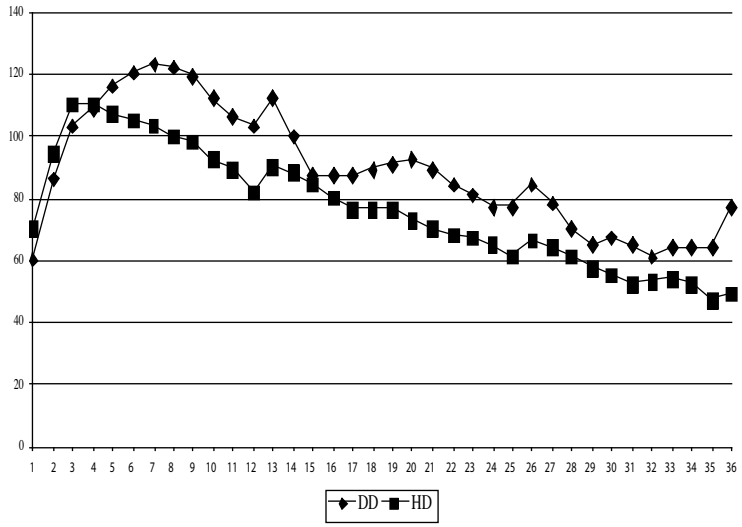

Figure A1. 36-month dosages in dually diagnosed patients in the experience of the PISA-SIA Group

Table A2.
Double diagnosis methadone-maintained patients.
Stabilization dose and time to reach it

	Dose (Mg/die)			*Dose (Mg/die)*		
Diagnosis	*Min*	***Mean***	*Max*	*Min*	***Mean***	*Max*
Heroin dependence	20	**105**	240	1	**3**	10
Alcohol-related disorders	240	**310**	380	3	**11**	20
BDZ addiction	80	**163**	400	2	**8**	19
Psychotic disorders	30	**140**	290	3	**13**	31
Depressive disorders	60	**130**	200	3	**6**	18
Bipolar disorders	50	**120**	320	3	**6**	22
Anxious disorders	80	**85**	90	2	**2**	3

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administered, and patients should be kept under observation for the next two hours. This procedure can be repeated until withdrawal is complete. The eventual cumulative dosage administered on the first day will be repeated through the following days (induction phase), until a steady state is supposedly reached (normally on the 3rd or 4th day). No differences due to the presence of absence of dual diagnosis are expected in these stages of treatment. In other words, the presence of dual diagnosis only seems to influence the management of the maintenance phase. From a clinical point of view, admission into methadone maintenance programmes should not depend on dual diagnosis. However, with the criteria currently being applied, dually diagnosed patients are likely not to be retained in treatment, since there is a trend to administer lower rather than higher methadone dosages. In fact, it must be recalled that dual diagnosis patients require higher dosages during the stabilization phase. If dually diagnosed patients display resistance to standard treatment, they are likely to be considered as non-responders, whereas they are simply not receiving adequate treatment. The time required to reach stabilization is longer for dual diagnosis patients, so it is important to monitor patients through quite a long period, before they can be expected to achieve stabilization. If these guidelines are applied, it is unlikely that an under-treated patient will be taken for a non-responder. Methadone tapering should only be considered after at least eight months, given that it has to be introduced very slowly with dual diagnosis patients. However, if tapering results in a worsening of psychosocial adjustment or a relapse into substance use, the previously used dosage should be restored, whatever the dosage level and whatever the tapering leap.

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5th ITALIAN METHADONE AND OTHER SUBSTITUTIVE THERAPIES CONFERENCE

1st "EUROPAD ITALIA" CONFERENCE

Centro Culturale "Luigi Russo"
Piazza del Duomo, Pietrasanta (LU), Italy, EU

December 4-6, 2003

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PROGRAMME

Thursday, December 4th, 2003: Public Theatre

Chairmen: I. Maremmani (Pisa) - R. Nardini (Pietrasanta)

16:00	I. Maremmani (Pisa)	*Opening ceremony and opening remarks*
16:15	WHO	Presentation of the WHO Report on "Neuroscience of Substance Use and Dependence"
17:00	M. Parrino (New York)	New directions in federal US policy in treating chronic opiate dependence
17:30	G. Di Chiara (Cagliari)	Neurobiology and neuropharmacology of methadone maintenance therapy
18:30	M. Farrel (London)	Delivering effective forms of agonist therapy: the challenge ahead
20:00		*Welcome Cocktail*
21:30		*"Paolo Picchio" award ceremony*

Friday, December 5th, 2003: Public Theatre

Chairmen: U. Corsini (Pisa) - A. Tagliamonte (Siena)

9:00	G.P. Guelfi (Genova)	Motivation to change, motivation to treatment
9:20	M. Reisinger (Brussels)	When maintenance treatment maintains the problem
9:40	M. Krausz (Hamburg)	Heroin-assisted treatment in Europe and the development of maintenance treatment in general
10:00	P. Quigley (Dublin)	Addressing problems of violence in the methadone treatment setting
10:20	G. Gerra (Parma)	Methadone vs Buprenorphine. Predictors of response
10:40	M. Torrens (Barcelona)	Psychiatric comorbidity in methadone maintenance treatment: implications in the outcome
11:00	J.J. Deglon (Geneva)	Clinical evaluation of patients with high dosage of methadone
11:20	M. Barra (Roma)	Some considerations about the treatment of heroin addiction
11:40	M. Lovrecic (Ljubljana)	Natural history of heroin addiction: Comparison between methadone maintained Italian and Slovenian heroin addicts
12:00	I. Maremmani (Pisa)	Methadone vs buprenorphine. The Italian multicentre observational study
12:20	R. Newman (New York)	Ethical issues in the field of addiction treatment
12:40		*Discussion*
13:00		*Break*

Chairmen: L. Tidone (Bergamo) - A. Vendramin (Padua)

15:00	A. Kantchelov (Sofia)	Motivational approach to Methadone Maintenance Treatment
15:20	L. Okruhlica (Bratislava)	Methadone dose and its correlation with concentration in plasma: lower versus higher doses
15:40	G. Perugi (Pisa)	Bipolar spectrum and heroin addiction
16:00	P.P. Pani (Cagliari)	The role of pharmacokinetics in the result of treatment
16:20	R. Mollica (Milan)	Tracking project: an update
16:40	E. Bignamini (Turin)	The function of psychotherapy in pharmacological therapy menagement
17:00	H. Waal (Oslo)	MMT policies in view of risk reduction versus treatment goal strategies
17:20	R. Nardini (Pietrasanta)	Methadone in jail
17:40	S. Dvoryak (Kiev)	Evaluation of effectiveness of drug treatment programmes in Ukraine
18:00	A. Kastelic (Ljubljana)	Methadone treatment in South-Eastern Europe
18:20	F. Starace (Naples)	Therapeutic interventions for drug dependence: the issue of compliance
18:40	M. Pacini (Pisa)	Methadone treatment for violent patients

Saturday, December 6th, 2003: "Sant'Agostino" cloister - "Luigi Russo" Cultural Centre		
9:00	Postersession	Committee: I. Maremmani (Pisa), R. Nardini (Pietrasanta), M. Reisinger (Brussels), M. Torrens (Barcelona), J.J. Deglon (Geneva), H. Waal (Oslo), A. Vendramin (Padua), L. Tidone (Bergamo)
	Chairmen: P.P. Pani (Cagliari), M. Lovrecic (Ljubljana)	
11:00		Poster awards and award-winning poster presentation
12:30	A. Tagliamonte (Siena)	Closing remarks

WORKSHOPS

A

Titolo: Il ruolo dei gruppi di autoaiuto nella tossicodipendenza da eroina

Sede: Saletta dell'Albergo Pietrasanta
Data: Mercoledi 4-12-2003
Orario: 15:00-19:00
Linguaggio: Italiano
Partecipanti: Max 50
Iscrizione: gratuita, preiscrizione obbligatoria
Conduttore: R. Nardini (Pietrasanta)

B

Titolo: Corso di perfezionamento sul trattamento metadonico

Sede: Saletta dell'Albergo Pietrasanta
Data: Giovedi 4-12-2003
Orario 10:00-16:00
Linguaggio: Italiano
Partecipanti: Max 30
Iscrizione: € 40.00
Relatori: I. Maremmani (Pisa), P.P. Pani (Cagliari), M. Pacini (Pisa)

C

Title: Brief Motivational Interventions for Methadone Maintenance Treatment

Motivation is a key component to change in substance abuse treatment as well as in methadone maintenance. Over the last decade effective strategies, brief interventions and structured approaches have been developed to enhance client motivation; subsequently clinicians' interest in motivational interventions substantially increases. Surprisingly, it seems that these are still not sufficiently incorporated in MMT practices. This intensive workshop is designed to sensitize participants to the power of motivational enhancement strategies, to provide them with the taste and understanding of the spirit of the motivational style of being with clients and to enrich their clinical skills with a method directly applicable in MMP daily work.

Venue: "Dell'Annunziata" Room, "Sant'Agostino" cloister - "Luigi Russo" Cultural Centre
Time: Thursday December 4th 2003, 2-4 p.m.
Language: English
Format: intensive workshop, exploring well-balanced sequences of didactic segments, interactive parts, role play and short exercises
Purpose: to teach participants the basic skills of effective motivational interventions and methods for conducting brief interventions, specifically structured for routine practice in MMT.
Method: the basic training approach for teaching Motivational Interviewing as recommended by Dr. W. Miller and Dr. S. Rollnick and the international Motivational Interviewing Network of Trainers.
Content: basic concepts, philosophy, principles, strategies and techniques of effective motivational interventions, with strong emphasis on structured brief interventions for MMT, as well as the style and spirit of the counsellor-client motivational interaction.
Participants: 30-50 professionals in MMT and substance abuse treatment. Basic counselling skills and knowledge, as well as sufficient level of spoken English are definitely required as prerequisite for active participation.
Trainer: **Alexander Kantchelov**, M.D., Licensed Trainer in Motivational Interviewing, Member of the international Motivational Interviewing Network of Trainers, Senior Trainer at the South-East European Institute for Motivational Interventions and Behaviour Change, trained and has collaborated with Dr. Stephen Rollnick and Dr. William Miller, contributing author in "Motivational Interviewing – Second Edition", Guilford Press 2002.
Fees: *€ 25.00*
Certification: certificates for attendance are provided for all participants.

CALL FOR POSTERS

5th Italian Methadone and other Substitutive Therapies Conference - 1st Europad-Italia Conference
Pietrasanta (Lucca) Italy, EU - December 4-6, 2003

Europad will select posters to be presented during the 5th Italian Methadone and other Substitutive Therapies Conference - 1st "Europad-Italia" Conference. Please submit an abstract of your poster.

The abstract must be written in English. Type the abstract in one paragraph, single spaced, do not exceed one page (150-200 words). Keep within the indicated margins. The title should be written in CAPITAL LETTERS, followed by the name(s) and affiliation of the author(s). The name of the author presenting the paper at the Forum should be underlined. **Abstract should be faxed by October 1, 2003 to:**

EUROPAD - Icro Maremmani, President, c/o AU-CNS - Via XX Settembre, 83 - 55045 Pietrasanta (Lucca) - Italy - E-mail: maremman@psico.med.unipi.it Fax number **+39 0584 72081**

Electronic Submission: Please e-mail the abstract to maremman@psico.med.unipi.it as a text file, and also as a Microsoft Word, Rich Text Format, document as an attachment to the e-mail.
Please note that submission of paper does not constitute acceptance for presentation. All authors of posters accepted for presentation will pay reduced fees even after November 1, 2003.

The best three posters will receive an award of € 500.00 and be published in "Heroin Addiction and Related Clinical Problems". Award-winning posters will be presented (20 minute presentation) Saturday, December 6 (11:30 a.m.) at the "Sala dell'Annunziata" of the "Sant'Agostino" cloister of the Cultural Centre "Luigi Russo" in Pietrasanta.

TITLE Name(s) of the authors Institution, country	
Abstract	

INFORMATIONS

Official language
English. Simultaneous translation into Italian will be provided

Registration
Registration is required for all participants. All authors of posters accepted for presentation will pay reduced fees even after November 1st, 2003

Fees	Until November 1st, 2003	After November 1, 2003
Participants	€ 150.00	€ 175.00
Poster presenters	€ 150.00	€ 150.00
Students and fellows*	€ 75.00	€ 75.00
Dinner, December 5th	€ 40.00	€ 40.00

On-site registration will be charged 25.00 € extra
* Proof of student or fellow status should be sent with registration form and shown at the registration desk.
Daily tickets will be availabe on the spot at the registration desk for € 100.00.
Registration fees include: name badge, admission to all scientific sessions, programme and abstract book, welcome cocktail, coffee breaks and refreshments.

Payments
Payments can be made by:
- *Banker's draft* (Personal or Company cheques cannot be accepted)
- *Bank Account N° 9204.51 MP Siena AG Pietrasanta ABI 1030 CAB 70220*
- *By Credit Card (Visa, Master Card; Carta SI for Italian participants)*

Number															
Expiration date						Total €									

- As on site payments *Signature*_____

Family name _____

*First name*_____

*Mailing addr.*_____*Postal code* _____*Country* _____

Phone _____ *E-mail* _____

Date of arrival _____ *Date of departure* _____

Hotel Accommodation	*single/double*	*Phone*
*Hotel Byron**** (Forte dei Marmi) - 5 km distance*	€ 135/190	+39 0584787052
*Albergo Pietrasanta**** (Pietrasanta) - 500 m distance*	€ 100/150	+39 0584793727
*Versilia Holidays**** (Forte dei Marmi) - 2 km distance*	€ 73/114	+39 0584787100
*Albergo ALK*** (Mna Pietrasanta) - 3 km distance*	€ 55/60	+39 0584745880
*Hotel Ambasciatori*** (Mna Pietrasanta)- 3 km distance*	€ 65/90	+39 0584745872
*Hotel Esplanade*** (Mna Pietrasanta) - 3 km distance*	€ 50/50	+39 0584745883
*Hotel Palagi*** (Pietrasanta) - 500 m distance*	€ 75/90	+39 058471448
*Albergo Stipino ** (Pietrsanta) - 1 km distance*	€ 55/62	+39 058470249

For Hotel accommodation, please provide payment for only 1 night as reservation; you will pay the difference directly in the hotel. We will completely refund payments made up to November 1st; no refund is payable after November 1st

Please send the registration form to: AU-CNSonlus, via XX Settembre, 83 Pietrasanta, Lucca, Italy by fax +39 0584 72081

INFORMATION FOR CONTRIBUTORS

The Editor of *Heroin Addiction & Related Clinical Problems* welcomes contributions of original manuscripts that are not under consideration for publication elsewhere. The *Journal* publishes research reports, proposals, letters to editor.

Peer Review: All manuscripts, including those written at the invitation of the editor, are subject to peer review by at least two experts to determine the originality, validity, and significance of the submitted material. Authors will usually be advised within eight weeks on the decision on their manuscript. All reviewers will remain anonymous.

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Bibliography must be ordered by authors' names alphabetically. Start each reference with bibliography number; use these numbers, in parentheses, for in-text citations. Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in the text.

Please use the following guidelines for arranging references:

Journal article:

1. Dole V.P., Nyswander M.E., Warner A. (1968): Successful treatment of 750 criminal addicts. *JAMA* 206: 2708-2711.

Book:

1. Tagliamonte A., Maremmani I. (1995): *Drug Addiction and Related Clinical Problems*. Springer-Verlag, Wien, New York.

Book Chapter:

1. Dole V.P. (1995): Methadone Maintenance. Comes of Age. In A. Tagliamonte and I. Maremmani Eds: *Drug Addiction and Related Clinical Problems*. Springer-Verlag, Wien New York. pp. 45-49.

Journal names should be abbreviated as they appear in *Index Medicus*, journals not currently indexed there should not be abbreviated.

Submission Procedure: Submit the files to Icro Maremmani, MD, Editor, **<maremman@psico.med.unipi.it>** and a Cc copy to **<aucns@libero.it>**

Submissions should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the journal it is being submitted (Research Reports, Proposals, Letters to Editor);

Ethics of Experimentations: Authors must declare in the cover letter that their studies submitted to *Heroin Addiction & Related Clinical Problems* have been conducted in accordance with Declaration of Helsinki.